frontiers | Research Topics

Treatment over the lifespan in bipolar disorder

Edited by
Andreas Reif, Dina Popovic
and Janusz K. Rybakowski

Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-8325-3212-6
DOI 10.3389/978-2-8325-3212-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Treatment over the lifespan in bipolar disorder

Topic editors

Andreas Reif — University Hospital Frankfurt, Germany

Dina Popovic — Sheba Medical Center, Israel

Janusz K. Rybakowski — Poznan University of Medical Sciences, Poland

Citation

Reif, A., Popovic, D., Rybakowski, J. K., eds. (2023). *Treatment over the lifespan in bipolar disorder*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3212-6

Table of contents

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 15 April 2020
doi: 10.3389/fpsyt.2020.00250

Patterns in Psychiatrists' Prescription of Valproate for Female Patients of Childbearing Age With Bipolar Disorder in Japan: A Questionnaire Survey

Masumi Tachibana[1], Tasuku Hashimoto[1,2], Mami Tanaka[3], Hiroyuki Watanabe[4,5], Yasunori Sato[6], Takashi Takeuchi[7], Takeshi Terao[8], Shou Kimura[5], Akio Koyama[9], Sachie Ebisawa[10], Yuichiro Shizu[11], Teruyoshi Nagase[12], Junichi Hirakawa[13], Kotaro Hatta[14], Michiko Nakazato[1,15] and Masaomi Iyo[1]*

[1] Department of Psychiatry, Chiba University Graduate School of Medicine, Chiba, Japan, [2] Department of Psychiatry, Sodegaura-Satsukidai Hospital, Sodegaura, Japan, [3] Division of Clinical Study on Juvenile Delinquency, Center for Forensic Mental Health, Chiba University, Chiba, Japan, [4] Division of Medical Treatment and Rehabilitation, Chiba University Center for Forensic Mental Health, Chiba, Japan, [5] Department of Psychiatry, Gakuji-kai Kimura Hospital, Chiba, Japan, [6] Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan, [7] Department of Psychosomatic and Palliative Medicine, Tokyo Medical and Dental University Medical Hospital, Bunkyo-ku, Japan, [8] Department of Neuropsychiatry, Faculty of Medicine, Oita University Yufu, Oita, Japan, [9] Department of Psychiatry, Yurakucho Sakura Clinic, Chiyoda-ku, Japan, [10] Department of Psychiatry, Alba Mental Clinic, Shinjuku, Japan, [11] Shizu Clinic, Sakura, Japan, [12] Department of Psychiatry, Takatsuki Hospital, Hachioji, Japan, [13] Department of Psychiatry, Hirakawa Hospital, Hachioji, Japan, [14] Department of Psychiatry, Juntendo University Nerima Hospital, Nerima-ku, Japan, [15] Department of Psychiatry, International University of Health and Welfare Graduate School, Narita, Japan

OPEN ACCESS

Edited by:
Andreas Reif, University Hospital Frankfurt, Germany

Reviewed by:
Heinz Grunze, Paracelsus Medical Private University, Germany
Sarah Kittel-Schneider, University Hospital Würzburg, Germany

***Correspondence:**
Tasuku Hashimoto
t.hashimoto1109@gmail.com

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *09 December 2019*
Accepted: *16 March 2020*
Published: *15 April 2020*

Citation:
Tachibana M, Hashimoto T, Tanaka M, Watanabe H, Sato Y, Takeuchi T, Terao T, Kimura S, Koyama A, Ebisawa S, Shizu Y, Nagase T, Hirakawa J, Hatta K, Nakazato M and Iyo M (2020) Patterns in Psychiatrists' Prescription of Valproate for Female Patients of Childbearing Age With Bipolar Disorder in Japan: A Questionnaire Survey. Front. Psychiatry 11:250. doi: 10.3389/fpsyt.2020.00250

Background: Accumulating evidence has shown that valproate has the greatest teratogenic potential for increasing the risk of major congenital malformations, such as neural tube defects, cleft palate, and neurodevelopmental disability. Although valproate is a pharmacological option for acute mania and is used as a stabilization drug for patients with bipolar disorder, some global guidelines state that valproate should not be used for girls or women of childbearing age with bipolar disorder. We investigated patterns in psychiatrists' prescription of valproate for bipolar female patients of childbearing age in Japan.

Methods: From March to May 2018, we conducted a questionnaire survey among psychiatrists from all prefectures in Japan on psychiatric practice as it relates to major depression and bipolar disorder throughout women's life. The questionnaire had two parts: (1) assessment of participating psychiatrists' backgrounds and attitudes toward patients and (2) their patterns of prescription of psychotropics for female patients with mood disorders across generations and periods of pregnancy. Each question item had four response options: "not at all," "rarely," "sometimes," and "frequently." We examined patterns of prescription for childbearing-aged women (late adolescence/young adulthood aged 18–24 years, childbearing-age, older adults aged 25–49 years) and pregnant women.

Results: In total, 571 psychiatrists (427 males, 123 females, and 21 unknowns) responded appropriately to the questionnaire, including 320 who examined at least one or more late adolescence/young adulthood bipolar women. Approximately 70% of psychiatrists answered that they frequently or sometimes prescribed valproate for bipolar women of childbearing age [late adolescence/young adulthood: not at all, n = 23 (7.5%); rarely, n = 69 (22.5%); sometimes, n =116 (37.8%); and frequently, n = 99 (32.2%); childbearing-age, older adults: not at all, n = 13 (2.7%); rarely, n = 67 (13.8%); sometimes, n = 185 (38.1%); and frequently, n = 220 (45.4%)]. The proportion of general hospital psychiatrists who answered "not at all" or "rarely" to the frequency of their valproate prescriptions was higher than that of psychiatrists working in other medical facilities ($\chi^2(3) = 18.2$, $p < 0.001$).

Conclusion: Most psychiatrists frequently or sometimes prescribe valproate for women of childbearing age in Japan.

Keywords: bipolar disorder, childbearing-age women, congenital malformations, pharmacoepidemiology, pregnancy, valproate

INTRODUCTION

Bipolar disorder frequently emerges in the late teens and young adults (1–3) and its prevalence in males and females is the same (4). The nature, course, and prognosis of bipolar disorder include: (a) a tendency toward remission and recurrent mood episodes (5), (b) frequent comorbidities such as substance use and anxiety disorders (6), (c) decreased quality of life and neurocognitive functioning in various domains such as work and family life (7, 8), and (d) high mortality characterized by suicide (9, 10) and general medical conditions (11). Therefore, the burden of illness is serious in young bipolar patients that need continuous, ongoing management.

Pharmacological treatment plays a crucial role in the continuous management of patients with bipolar disorder. According to several worldwide guidelines (12–14), pharmacology may be in the form of therapies for any mood episodes, including mania and depression, and as continued treatment for the prevention of any episodes in the maintenance phase. However, among girls, women of childbearing age, and pregnant women with bipolar disorder, continuous medication is often difficult to successfully administer; hence, the pharmacological strategy for these patients must be different from that for other patients due to the risks of congenital malformations. Several guidelines for the management of bipolar disorder such as the National Institute for Health and Care Excellence: bipolar disorder: assessment and management [CG185] (NICE), last updated April 2018 (NICE 185 guideline) (15), and the International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017) (12) commonly state that valproate should not be used for women of childbearing age due to its teratogenic potential.

Although valproate is one of the pharmacological options for the treatment of acute mania and the stabilization in patients with bipolar disorder, accumulating evidence has shown that valproate, among other pharmacological treatments for bipolar disorder, has the greatest teratogenic potential as it increases the risk of major congenital malformations, such as neural tube defects, including spina bifida {odds ratio [OR] = 12.7 [95% confidence interval (CI), 7.7 to 20.7]}, and cleft palate [OR = 5.2 (95% CI, 2.8 to 9.9)] (16, 17), and neurodevelopmental disability (18, 19). The CINP-BD-2017 states that valproate is not suitable for women of childbearing age. The NICE 185 guideline (15) and the UK National Institute for Health and Care Excellence Clinical Guideline 192, antenatal and postnatal mental health clinical management and service guidance, last updated April 2018 (NICE 192 guideline) (20), also state that unless alternative medications are not suitable, women (including prepubertal young girls) or the women without a pregnancy prevention program certificate should not undergo valproate treatment. Moreover, in November 2014, due to the emerging findings that prenatal exposure to valproate lead to neurodevelopmental adversities such as intellectual disability (21, 22), the European Medicines Agency issued a warning on regulatory restrictions regarding the use of valproate on girls and women of potential childbearing age unless other treatments are ineffective or not tolerated.

Our recent study that investigated the top 11 most frequently prescribed anticonvulsants and lithium using the National Insurance claims database in Japan from April 2014 to March 2015, showed that valproate was the most prescribed major anticonvulsant for female outpatients of childbearing age, and was prescribed slightly lesser compared to same-aged men. However, this data preceded the publication of the above-mentioned guidelines (23). The results of our study raise concerns as to whether most psychiatrists or physicians in Japan properly prescribe valproate for childbearing-aged women, who must be cautioned with regard to its high teratogenic potential; and if they were asked adequate questions regarding their methods of contraception during treatment. Based on the findings of our previous study, we

hypothesized that most psychiatrists and physicians do not pay close attention to the possibility of pregnancy, or the method of contraception, when they prescribe valproate for childbearing-aged women. We also hypothesized that psychiatrists who pay attention to patients' reproductive potential in their clinical practice only very cautiously consider prescribing valproate to bipolar women of childbearing age.

The aim of this study was to identify psychiatrists' patterns of prescribing valproate for bipolar female patients of childbearing age (in their late adolescent years and late forties), compared to those who are pregnant, in Japan. We also investigated the relationship between characteristics and reproduction-related interviews in the consultation of psychiatrists and their frequency of valproate prescription. To assess this, this study was performed through a questionnaire survey about psychiatric practices in major depression and bipolar disorders throughout the stages of a woman's life; this was conducted among psychiatrists in all prefectures in Japan from March to May 2018. This study also examined the frequency of prescription of other mood stabilizers [carbamazepine, lamotrigine, and lithium, which has teratogenic effects in humans and potentially causes cardiac malformations, such as Ebstein anomaly (24)], antipsychotics, and antidepressants in bipolar women of childbearing age and in pregnant women; we compared them with prescriptions for valproate.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional study was conducted among psychiatrists who belong to the following associations: Association of Japan Psychiatric Clinics: Tokyo branch and Chiba branch, Association of Japan Psychiatric Hospitals: Ibaraki branch, Chiba branch, and Tokyo branch, JSGHP; Japanese Society of General Hospital Psychiatry in 2018.

A total of 1414 medical institutions (963 General hospitals, 343 mental clinics, and 108 psychiatric hospitals) were chosen from the list of cooperation associations and 4,816 questionnaires were mailed through the postal service between March and May 2018. There were 571 respondents (427 male, 123 female, and 21 unknowns; mean age = 45.9 years, SD = 10.8). Psychiatrists who did not see patients of childbearing age (18 to 49 years) were excluded. Of 571 respondents, 320 (56.0%) and 497 (87.0%) psychiatrists met the eligible criteria for evaluating the prescription pattern among female bipolar patients in late adolescence/young adulthood (ages 18–24 years) and in early or middle age, respectively. Of 571 respondents, 571 (100.0%) psychiatrists met the eligible criteria for evaluating the prescription pattern of female bipolar patients who were pregnant.

At the beginning of the questionnaire, we declared the objectives of the study and our commitment to confidentiality. Therefore, completing and mailing back the questionnaire were considered to reflect written informed consent regarding participation in this study. The questionnaire survey of this study was performed anonymously. The study's protocol was approved by the ethics committees of the Graduate School of Medicine and School of Medicine, Chiba University (20 November 2017).

Measures

Sociodemographic Characteristics and Prescription Patterns of Participants

The questionnaire was used to assess participating psychiatrists' backgrounds, attitudes toward patients, and prescribing behavior. Regarding psychiatrists' backgrounds, participants were asked about their demographic data, including sex, age, years of clinical experience, hospital facility, and the number of patients with depression and bipolar disorder they treat per month. Regarding attitudes toward patients, the psychiatrists rated how often they focused on problems specific to life stages when counseling their patients. The question was followed by four response options: "not at all," "rarely," "sometimes," and "frequently." In this study, we focused on measurements of psychiatrists' attitudes toward patients' fertility by asking how often psychiatrists inquire about the following: any menstrual disorder, whether patients wanted to bear children, methods of contraception, and feelings of rejection for medication during pregnancy and breast-feeding periods. In their prescribing behavior, psychiatrists were requested to indicate how often they prescribed 16 types of medicine, depending on the patients' life stages. The life cycle was divided into 7 stages depending on the age: ages 0–11 corresponded to childhood, ages 12–17 to pubescence, ages 18–24 to late adolescence/young adulthood, ages 25–49 to early middle age, ages 50–59 to late middle age, ages 65 and over to late adulthood, and the pregnancy period. The number of the questions was 326 in total, consisting of 35 questions on the psychiatrists' backgrounds including sociodemographic data, 67 on their attitudes toward patients, and 224 on prescribing behavior (**Supplementary Material**). In this study, we focused on childbearing age and the pregnancy period, and defined childbearing age as being from 18 to 49 years and considered it to correspond to late adolescence and early middle age stages.

The 16 types of drugs were of four categories: antidepressants, mood stabilizers, antipsychotics, and Kampo. A full list of the medications is as follows: antidepressants: selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, mirtazapine, tricyclic antidepressants, tetracyclic antidepressants. Mood stabilizer: lithium carbonate, sodium valproate, carbamazepine and lamotrigine. Antipsychotics: typical antipsychotic, atypical antipsychotic; risperidone, olanzapine, quetiapine, aripiprazole and others atypical antipsychotics. Kampo (herbal medicine).

Primary and Secondary Outcomes

The primary outcome was to identify the psychiatrists' patterns of prescribing valproate to female bipolar patients of childbearing age, compared to those who are pregnant, and the relationship between the psychiatrists' characteristics and reproduction-related interviews and patterns of valproate prescription. The secondary outcomes were to clarify the

frequency of the prescription of other mood stabilizers (especially lithium), antipsychotics, and antidepressants in bipolar women of childbearing-age and in pregnant women.

Statistical Analysis

We first performed chi-squared (χ^2) tests for categorized variables to analyze categorical data between the current and previous affiliations of psychiatrists (i.e., general hospitals or other medical facilities) and the frequency of prescription of valproate to female bipolar patients in late adolescence/young adulthood. Categorical data were compared using the χ^2 tests followed by a residual analysis for multiple comparison (25). Additionally, we calculated the partial correlations, controlling for sex, between years of clinical experience, valproate prescription, and psychiatrists' attitude toward bipolar patients of childbearing-age and pregnant women. For all tests, a two-tailed $p < 0.05$ was considered statistically significant. All analyses were conducted using SPSS 22 (Arbuckle, 2013).

RESULTS

Psychiatrists' Trends for Prescribing Psychotropic Drugs for Female Bipolar Patients of Childbearing Age

A total of 320, 497, and 571 psychiatrists participated in the assessment of prescription trends for late adolescence/young adulthood, early middle age, and pregnant female patients with bipolar disorder, respectively. The participants' demographic characteristics are shown in **Table 1**.

In general, the psychotropic drug we chose was mostly prescribed to female bipolar patients of childbearing-age than to pregnant patients. Among female patients of childbearing age, early middle age patients received more psychotropic drug prescriptions than late adolescence/young adulthood patients, as shown in **Table 2**.

In the questionnaire, the psychiatrists' answers regarding the prescription of valproate to late adolescence/young adulthood female patients with bipolar disorder were the following: 23 psychiatrists responded not at all, n = 23 (7.5%); rarely, n = 69 (22.5%); sometimes, n =116 (37.8%); and frequently, n = 99 (32.2%). Regarding the prescription of valproate to childbearing-aged, older female patients with bipolar disorder the answers were the following: 13 psychiatrists responded not at all, n = 13 (2.7%); rarely, n = 67 (13.8%); sometimes, n = 185 (38.1%); and frequently, n = 220 (45.4%). On avoiding prescription of valproate to pregnant patients: 387 psychiatrists responded "not at all" (75.3%) while 126 responded "rarely", "sometimes", and "frequently" (24.7%).

Regarding the prescription of lithium to late adolescence/young adulthood patients with bipolar disorder, 15 psychiatrists responded not at all, n = 15 (5.8%); rarely, n = 54 (17.5%); sometimes, n =125 (40.6%); and frequently, n = 111 (36.2%). Regarding the prescription of lithium for childbearing-aged, older female patients; 7 psychiatrists responded not at all, n = 7 (1.4%); rarely, n = 42 (8.7%); sometimes, n = 181 (37.3%); and frequently, n = 255 (52.6%). Regarding lithium prescription to pregnant patients: 382 psychiatrists responded "not at all" (74.0%), while 134 responded "rarely," "sometimes," and "frequently" (26.0%).

In addition, regarding the prescription patterns of other medications, including other mood stabilizers (lamotrigine, carbamazepine) and antipsychotics for pregnant women, more than half (55.6%) the psychiatrists responded, "not at all" or "rarely" (**Table 2**).

TABLE 1 | Social and demographic characteristics of participants (N = 571).

	n	(%)
Male	427	(74.8)
Female	123	(21.5)
Unknown	21	(3.7)
Age (years)		
Mean	45.9	
Standard deviation	10.8	
Years of clinical experience		
<11 years	181	(33.1)
11 years to under 21	180	(32.9)
21 years to under 31years	111	(20.3)
More than 30 years	61	(13.7)
Unknown	24	(4.2)
Facilities		
general hospital	307	(53.8)
psychiatric hospital	151	(26.4)
clinic	62	(10.9)
others	7	(1.2)
Unknown	21	(3.7)
Specialized clinical department		
Psychiatry (general)	537	(94.0)
Psychosomatic medicine	27	(4.7)
Child psychiatry	33	(5.8)
Others	7	(1.2)

Affiliation of Psychiatrists and Prescription of Valproate for Female Bipolar Patients in Late Adolescence/Young Adulthood

The χ^2-test showed that there were significant differences in the current affiliation of psychiatrists and valproate prescriptions to female bipolar patients in late adolescence/young adulthood, as shown in **Table 3** [$\chi^2(3) = 18.2$, $p < 0.001$]. The Haberman-type residual analysis showed that psychiatrists working for general hospitals reported that they prescribed valproate less frequently (with either "Not at all" or "Rarely" in the questionnaire) than that of psychiatrists working for other medical facilities and hospitals. Additionally, the psychiatrists working for general hospitals answered "frequently," regarding valproate prescription, were associated with significantly negative standardized residuals, which was less than psychiatrists working for other medical facilities or hospitals. However, in their previous affiliations, there were no differences between general hospitals and other medical facilities in terms of valproate prescriptions.

Partial Correlation Between Valproate Prescribing Action and Psychiatrists' Backgrounds

We calculated the partial correlations, controlling for sex, between years of clinical experience, valproate prescription, and psychiatrists'

TABLE 2 | Row point questionnaire answers of drug prescription for bipolar female patients.

	Childbearing age												Pregnant women (*N* = 571)					
	Late adolescence/Young adulthood (18-24 years; *N* = 320)					Childbearing-age, older adults (25-49 years; *N* = 497)												
	Not at all		Rarely		Sometimes	Frequently		Not at all		Rarely		Sometimes	Frequently		Not at all		Rarely		Sometimes	Frequently	
	n (%)							*n* (%)							*n* (%)						
Mood stabilizers																					
Valproate	23	(7.5)	69	(22.5)	116 (37.8)	99	(32.2)	13	(2.7)	67	(13.8)	185 (38.1)	220	(45.4)	387	(75.3)	79	(15.4)	31	(6.0)	16	(3.1)
Lithium carbonate	15	(5.8)	54	(17.5)	125 (40.6)	111	(36.2)	7	(1.4)	42	(8.7)	181 (37.3)	255	(62.6)	382	(74.0)	77	(14.9)	37	(7.2)	20	(3.9)
Carbamazepine	109	(35.9)	102	(33.6)	74 (24.3)	19	(6.3)	122	(25.5)	157	(32.8)	148 (30.9)	52	(11.9)	402	(77.9)	78	(15.2)	30	(5.8)	3	(0.6)
Lamotrigine	32	(10.5)	57	(18.7)	126 (41.3)	90	(29.5)	40	(8.4)	75	(15.7)	209 (43.6)	155	(32.4)	221	(42.9)	119	(23.1)	124	(24.1)	51	(9.9)
Antidepressants																					
SSRIs[a]	136	(44.2)	115	(37.3)	43 (14.0)	14	(4.5)	137	(28.2)	186	(38.3)	124 (25.5)	39	(8.0)	288	(55.7)	167	(32.3)	50	(9.7)	10	(1.9)
SNRIs[b]	108	(35.2)	120	(39.1)	63 (20.5)	16	(5.2)	184	(37.9)	173	(35.6)	96 (19.8)	32	(6.6)	323	(62.5)	152	(29.4)	34	(6.6)	8	(1.5)
Mirtazapine	122	(39.7)	117	(38.1)	55 (17.9)	13	(4.2)	168	(34.8)	167	(34.6)	121 (25.1)	27	(5.6)	324	(62.8)	146	(28.3)	39	(7.6)	7	(1.4)
Tricyclic antidepressants	233	(76.4)	61	(20.0)	10 (3.3)	1	(0.3)	341	(70.6)	106	(21.9)	33 (6.8)	3	(0.6)	455	(88.5)	53	(10.3)	5	(1.0)	1	(0.2)
Tetracyclic antidepressants	216	(70.4)	65	(21.2)	24 (7.8)	2	(0.6)	309	(63.8)	118	(24.4)	51 (10.5)	6	(1.2)	423	(82.1)	74	(14.4)	17	(3.3)	1	(0.1)
Antipsychotics																					
Risperidone	54	(17.7)	102	(33.4)	121 (39.7)	28	(9.2)	64	(13.3)	150	(31.2)	208 (43.2)	59	(12.3)	200	(38.8)	190	(36.8)	106	(20.5)	20	(3.9)
Olanzapine	20	(6.5)	79	(25.7)	144 (46.9)	64	(20.8)	20	(4.2)	93	(19.3)	242 (50.3)	126	(26.2)	161	(31.0)	180	(34.7)	144	(27.7)	33	(6.4)
Quetiapine	17	(5.5)	71	(23.1)	147 (47.9)	71	(23.1)	20	(4.1)	73	(15.1)	250 (51.9)	139	(28.8)	144	(27.7)	165	(31.8)	160	(30.8)	50	(9.6)
Aripiprazole	10	(3.3)	47	(15.6)	164 (53.6)	85	(27.8)	11	(2.3)	54	(11.2)	264 (54.8)	153	(31.7)	110	(21.3)	177	(34.3)	180	(34.9)	49	(9.5)
Other atypical antipsychotics	109	(36.2)	109	(36.2)	66 (21.9)	17	(5.6)	170	(36.1)	150	(31.8)	120 (25.5)	31	(6.6)	286	(56.5)	148	(29.2)	65	(12.8)	7	(1.4)
Typical antipsychotics[c]	171	(57.2)	69	(23.1)	42 (14.0)	17	(5.7)	229	(48.8)	124	(26.4)	85 (18.1)	31	(6.6)	342	(67.2)	114	(22.4)	43	(8.4)	9	(1.8)
Kampo medicine (Herbal medicine)	99	(32.7)	98	(32.3)	79 (26.1)	27	(8.9)	156	(33.0)	134	(28.3)	144 (30.4)	39	(7.8)	211	(41.1)	152	(29.6)	111	(21.6)	39	(7.6)

[a]*SSRIs, selective serotonin reuptake inhibitors (e.g., paroxetine hydrochloride hydrate, sertraline hydrochloride, escitalopram oxalate, and fluvoxamine maleate).*

[b]*SNRIs, serotonin noradrenalin reuptake inhibitors (e.g., duloxetine hydrochloride, milnacipran hydrochloride, and venlafaxine hydrochloride).*

[c]*Typical antipsychotics (e.g., Chlorpromazine hydrochloride, haloperidol, levomepromazine maleate, sultopride hydrochloride, timiperone, and zotepine).*

attitude toward bipolar patients of childbearing age and in pregnancy (**Table 4**). The psychiatrists' years of experience was found to be positively and significantly correlated with a valproate prescription in late adolescence/young adulthood (18-24 years) (r = 0.13, $p < 0.05$). Conversely, in childbearing-aged, older adults (25–49 years) and pregnant women, there is no relationship between the two variables. There is no relationship between the contents of reproduction-related medical interviews and valproate prescriptions in childbearing age or pregnancy. In addition, there were no relationships between reproduction-related medical interviews and prescriptions of other psychotropics in childbearing age or pregnancy.

DISCUSSION

In this study, three important findings about psychiatrists' prescription patterns of valproate for female bipolar patients of childbearing age in Japan deserve to be mentioned. First, this study demonstrates that 70% of psychiatrists responding to the questionnaire sheet answered that they frequently or occasionally prescribed valproate for women of childbearing age in Japan, although most answered that they did not prescribe for women who were pregnant. Specifically, 32% of psychiatrists answered that they frequently prescribed valproate for women aged 18 to 24 years, and 38% occasionally prescribed it for same-aged women. Thirty percent of psychiatrists answered they rarely prescribed valproate, or that they did not at all prescribe it. Second, psychiatrists affiliated with general hospitals answered that they tended to refrain from prescribing valproate for childbearing-aged women compared to those affiliated with other medical facilities such as psychiatric hospitals or private clinics. Third, the frequencies of reproduction-related medical interviews were not correlated with the tendency to prescribe valproate to women of childbearing age, although years of psychiatric experience was positively correlated with this.

This questionnaire study conducted from March to May 2018 reveals the possibility that more than half of psychiatrists frequently or occasionally prescribed valproate for women of childbearing age in Japan. This finding is consistent with our previous study investigating the frequently prescribed tablets for childbearing-aged outpatients in Japan (23). On April 6, 2017, in reference to pharmacological treatments of women in the perinatal period, the Japanese Society of Perinatal Mental Health published the Perinatal Mental Health Consensus Guide 2017 on the website (http://pmhguideline.com/, in Japanese only); stating that valproate should not be prescribed to women of childbearing age. However, the society is small due to the small number of psychiatrists. Additionally, there were only 20 regular members at that time, and midwives constituted a large proportion of the regular members of the society (over 100 people). In other countries, such as Finland (26), Ireland (27), and Germany (28), valproate prescription has slightly declined, although the data from these studies are not limited to pharmacological treatments of bipolar disorder. In the UK, at the same time as the last updated NICE 192 guideline, the Medicines and Healthcare Products Regulatory Agency in

TABLE 3 | Affiliation of psychiatrist and valproate prescription for female bipolar patients in late adolescence/young adulthood (18-24 years).

	Prescription of Valproate								χ^2	*p*
	Not at all		Rarely		Sometimes		Frequently			
Current Affiliation									**18.2**	**0.001**
General Hospitals										
Oserved [*n* (Row %)]	20	(11.3)	49	(27.7)	57	(32.2)	51	(28.8)		
Expected	14.3		37.5		65.1		60.1			
Adjusted standardized residual	**2.3**		**3.2**		−1.9		**−2.2**			
Other medical facilities										
Oserved [*n* (Row %)]	6	(4.2)	19	(13.2)	61	(42.4)	58	(40.3)		
Expected	11.7		30.5		52.9		48.9			
Adjusted standardized residual	−2.3		−3.2		1.9		2.2			
Previous Affiliation									5.3	0.2
General Hospitals										
Oserved [*n* (Row %)]	24	(8.1)	67	(22.7)	106	(35.9)	98	(33.2)		
Expected	23.9		63		108		100.2			
Adjusted standardized residual	0.1		2.3		−1.0		−0.9			
Other medical facilities										
Oserved [*n* (Row %)]	2	(7.7)	1	(3.8)	12	(46.2)	11	(42.3)		
Expected	2.1		5.5		9.6		8.8			
Adjusted standardized residual	−0.1		−2.3		1.0		0.9			

p value was calculated by the Chi-square (χ^2) tests.
Bold numbers are statistically significant.

TABLE 4 | Partial correlation between valproate prescription and psychiatrists' attitude toward bipolar patients in childbearing age and pregnancy.

	Prescription of Valproate		
	Late adolescence/ Young adulthood (18–24 years)	Childbearing-age, older adults (25–49 years)	Pregnant women
Years of clinical experience	**.13***	−.01	.01
Reproductive-related medical interview			
Abnormal menstruation	−.02	−.03	−.04
Having desire to bear children	−.03	.03	−.04
Method of contraception	.02	.01	.08
Internal medicine avoiding during pregnancy and breast feeding	.09	.06	−.05

*Partial Correlation coefficients were controlled for sex. *p < .05.*
Bold numbers are statistically significant.

April 2018, stated that valproate use would be rigidly regulated and that valproate treatment must not be used for women, including prepubertal young girls, unless alternative medications are not suitable or when the women are part of a pregnancy prevention program (29). Considering that fetal exposure to valproate in the first trimester must be avoided and that approximately 40% of pregnancies are unplanned or unintended (30), psychiatrists and physicians should not, in principle, prescribe valproate to girls and childbearing-aged women with bipolar disorder. Furthermore, since changes in valproate prescription patterns among these countries may be slow, societies, associations, and related guidelines that directly influence psychiatrists or physicians are expected to clearly share warnings about the dangers of valproate prescriptions to girls and childbearing-aged women with bipolar disorder in Japan and other countries. Additionally, the Japanese authorized societies or licensing agencies should issue warnings about teratogenic risks of valproate prescription not only for pregnant women but also childbearing-aged women.

In this study, psychiatrists working at general hospitals answered that they refrained from prescribing valproate to childbearing-aged women compared to those affiliated with other medical facilities, such as psychiatric hospitals and private clinics. There are two main possible interpretations of this result. Freudenreich and Kontos report that consultation-liaison psychiatrists have better opportunities and situations for learning other medical specialties through their interdisciplinary collaborative work (31). This may make sense because psychiatrists working at general hospitals, compared to other institutions, have better chances and experience in consulting for pregnant women with psychiatric diseases at their hospitals, which either have a birth center or obstetricians working in them. There are other reasons why psychiatric diseases and symptomatic and social severities of patients are different across general hospitals and other institutes. For instance, in/outpatients being treated by psychiatrists in psychiatric hospitals may have more severe symptomatology, impaired social ability due to long-term hospitalization, and compromised cognitive performance, including intellectual disability, than those in general hospitals. Therefore, it is difficult for such patients to become pregnant; hence, psychiatrists prescribe valproate to them. However, in the real-world, women with severe mental illness such as schizophrenia and autism are fertile, do get pregnant, and have newborns (32). Therefore, the societies and associations that largely influence psychiatrists, regardless of the type of medical institute, should provide warnings about valproate prescription for girls and women of childbearing age.

In addition, the frequencies of reproduction-related medical interviews were not correlated with the tendency to prescribe valproate to women of childbearing age, although years of psychiatric experience was positively correlated with this. These results were unexpected because our hypothesis was that psychiatrists who usually paid attention to future conceptions in their consultations of childbearing-age women would often not have prescribed valproate to these women. The interpretation of this result was that there may be two groups of psychiatrists regarding pregnancy; (1) those who refrained from prescribing valproate to childbearing-aged women, and (2) the other ones who prescribed it with caution. It is difficult to interpret the positive correlation between years of psychiatric experience and the tendency to prescribe valproate to childbearing-age women. This result is limited because of the lack of surveillance about real-world childbearing-aged women prescription of valproate, and the lack of assessment of each psychiatrist's valproate prescription dosage. Therefore, senior psychiatrists with enough clinical experience may have the opportunity to examine childbearing-aged women with more refractory bipolar disorder than junior ones. Further studies are needed to clarify this.

Regarding other psychotropics, especially lithium and carbamazepine prescriptions, the NICE 192 guideline cautions against use on girls and childbearing-aged women (20); however, the frequencies of lithium prescriptions were similar to those of valproate. Approximately 77% of responding psychiatrists answered that they frequently or sometimes prescribed lithium to bipolar women of childbearing age in Japan, and carbamazepine was not as frequently prescribed. These findings are consistent with our previous study (23). Fetal exposure to lithium in the first trimester is associated with increased risk of cardiac malformations (24). According to the NICE guideline, unless lithium is recommended to women planning pregnancies who do not clinically respond to other antipsychotics or mood stabilizers, but do respond to lithium, it should be avoided in the first trimester (20). Consequently, although the adverse effects of lithium use on the fetus are known to be dose-dependent, the present finding demonstrates that many psychiatrists tend to easily prescribe lithium to childbearing-aged women with bipolar disorder in Japan. Therefore, psychiatrists should be more careful when continuously prescribing lithium to girls and women of childbearing age.

Additionally, the present study shows that most psychiatrists are rather reluctant to prescribe medications including lamotrigine and some atypical antipsychotics with efficacy and/or relative safety in the treatment and prevention of mood episodes in pregnant women with bipolar disorder in Japan. Among major mental disorders, bipolar disorder is the highest risk group with regard to relapse and readmission during the postpartum period (33). Wesseloo et al.'s meta-analysis demonstrates that the postpartum relapse rates of bipolar women who were medication free during pregnancy (medication free during pregnancy: 66%, 95% CI, 57 to 75) were significantly higher than that of those who used prophylactic medication (using prophylactic medication: 23%, 95% CI, 14 to 37) (34). Considering that the psychiatrists who sometimes or frequently prescribe medications for bipolar female patients during the pregnancy were a minority, the present findings show the existence of evidence-practice gap in pharmacological treatment of pregnant women with bipolar disorder. Psychiatrists should provide more information on the potential risks and benefits of medication treatments of bipolar disorder, and implement a shared decision-making process with bipolar women of childbearing age before pregnancy.

We acknowledge that there are several limitations to this study. First, we were unable to measure the real-world valproate prescriptions (including the dosage) of the responding psychiatrists. Given that some female patients with bipolar disorder who consulted their responding psychiatrist were expected to have various comorbidities, intellectual disabilities, and complications (including epilepsy, early menopause, and bilateral ovarian ablation), valproate prescription may be adequate for them if prescribed with caution. Second, the response rate of 11.8% was low, although 571 psychiatrists responded to this questionnaire in Japan. The biggest possible reason for the low response rate in this survey was the large amount of questions in the questionnaire (326 items in total) since it was developed to investigate overall psychiatric practices in major depression and bipolar disorder throughout the stages of the women's lives. Hence, it was likely that lots of questions caused difficulties for almost 90% candidates to complete the questionnaire sheet. Third, the items about reproduction-related medical interviews were relatively scarce in the questionnaire; hence, this may have influenced the correlations between the answers and frequencies of valproate prescriptions.

CONCLUSION

This study demonstrates that most psychiatrists frequently or occasionally prescribed valproate for women of childbearing age in Japan, although almost all answered they did not prescribe valproate to pregnant women. Specifically, 70% of psychiatrists answered that they frequently or sometimes prescribed valproate for women aged 18 to 24 years. Considering that fetal exposure to valproate in the first trimester must be avoided, and that many pregnancies are unplanned or unintended, psychiatrists should not prescribe valproate to girls and women of childbearing age with bipolar disorder.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article will be made available by the authors, and to any qualified researcher without undue reservation. Requests to access the datasets should be directed to TH, t.hashimoto1109@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committees of the Graduate School of Medicine and School of Medicine, Chiba University. The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TH, MamiT, YaS, TakaT, TakeT, HW, MN, and MI contributed substantially to the conception and design of this study. MasuT, TH, and MamiT contributed to organizing the data, formal analysis, writing an original draft. AK, TakeT, KH, and MI contributed to the management of this study as supervisors. SK, AK, SE, YuS, TN, JH, and KH contributed substantially to facilitating data curation and study procedure as investigators. All authors contributed to the interpretation of data, revision of the manuscript, and approved of the submitted manuscript.

FUNDING

This work was supported by the Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research C Grant Number 17K10265. The members of this grant were TH, HW, MN, MI, YS, TakaT, and TakeT.

ACKNOWLEDGMENTS

We would like to thank all responding psychiatrists participating in the present questionnaire survey, despite their busy schedule. We also want to express our appreciation to the Japanese Association of Neuro-Psychiatric Clinics: Tokyo branch and Chiba branch, the Japan Psychiatric Hospitals Association: Ibaraki branch, Chiba branch and Tokyo branch, and the Japanese Society of General Hospital Psychiatry. We also would like to thank Editage (www.editage.jp) for English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00250/full#supplementary-material

REFERENCES

1. Coryell W, Fiedorowicz J, Leon AC, Endicott J, Keller MB. Age of onset and the prospectively observed course of illness in bipolar disorder. *J Affect Disord* (2013) 146:34–8. doi: 10.1016/j.jad.2012.08.031
2. Bauer M, Glenn T, Alda M, Andreassen OA, Angelopoulos E, Ardau R, et al. Influence of birth cohort on age of onset cluster analysis in bipolar I disorder. *Eur Psychiatry* (2015) 30:99–105. doi: 10.1016/j.eurpsy.2014.10.005
3. Dell'Osso B, Grancini B, Vismara M, De Cagna F, Maggi M, Molle M, et al. Age at onset in patients with bipolar I and II disorder: a comparison of large sample studies. *J Affect Disord* (2016) 201:57–63. doi: 10.1016/j.jad.2016.04.009
4. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* (1994) 51:8–19. doi: 10.1001/archpsyc.1994.03950010008002
5. Angst J. Course and prognosis of mood disorders. In: Gelder MG, Andreasen NC, Lopez-Ibor JJ, Geddes JR, editors. *New Oxford Textbook of Psychiatry*. Oxford: Oxford University Press (2009). p. 665–9.
6. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* (2007) 64:543–52. doi: 10.1001/archpsyc.64.5.543
7. Gutierrez-Rojas L, Gurpegui M, Ayuso-Mateos JL, Gutierrez-Ariza JA, Ruiz-Veguilla M, Jurado D. Quality of life in bipolar disorder patients: a comparison with a general population sample. *Bipolar Disord* (2008) 10:625–34. doi: 10.1111/j.1399-5618.2008.00604.x
8. Michalak EE, Murray GCollaborative RESearch Team to Study Psychosocial Issues in Bipolar Disorder (CREST.BD). Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. *Bipolar Disord* (2010) 12:727–40. doi: 10.1111/j.1399-5618.2010.00865.x
9. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry* (2011) 68:1058–64. doi: 10.1001/archgenpsychiatry.2011.113
10. Webb RT, Lichtenstein P, Larsson H, Geddes JR, Fazel S. Suicide, hospital-presenting suicide attempts, and criminality in bipolar disorder: examination of risk for multiple adverse outcomes. *J Clin Psychiatry* (2014) 75:e809–16. doi: 10.4088/JCP.13m08899
11. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. *J Affect Disord* (2015) 180:142–7. doi: 10.1016/j.jad.2015.03.027
12. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 3: The clinical guidelines. *Int J Neuropsychopharmacol* (2017) 20:180–95. doi: 10.1093/ijnp/pyw109
13. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin JM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry* (2018) 19:2–58. doi: 10.1080/15622975.2017.1384850
14. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* (2018) 20:97–170. doi: 10.1111/bdi.12609
15. The National Institute for Health and Care Excellence. . *Bipolar disorder assessment and management [CG185].* , Published date: September 2014, Last updated: (April 2018). Available from https://www.nice.org.uk/guidance/cg185.
16. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* (2016) 11: CD010224. doi: 10.1002/14651858.CD010224.pub2
17. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* (2010) 362:2185–93. doi: 10.1056/NEJMoa0907328
18. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* (2009) 360:1597–605. doi: 10.1056/NEJMoa0803531
19. Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open* (2017) 7:e017248. doi: 10.1136/bmjopen-2017-017248
20. The National Institute for Health and Care Excellence. . *Antenatal and postnatal mental health: clinical management and service guidance [CG192].* Published date: December 2014, Last updated: (April 2018). Available from https://www.nice.org.uk/guidance/cg192.

21. European Medicines Agency. (2014). *Press release: CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls*. EUROPEAN MEDICINES AGENCY, An official website of the European Union. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/11/news_detail_002220.jsp&mid=WC0b01ac058004d5c1.
22. Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia* (2015) 56:1006–19. doi: 10.1111/epi.13021
23. Yoshimura K, Hashimoto T, Sato Y, Sato A, Takeuchi T, Watanabe H, et al. Survey of Anticonvulsant Drugs and Lithium Prescription in Women of Childbearing age in Japan Using a Public National Insurance Claims Database. *Clin Neuropsychopharmacol Ther* (2018) 9:20–8. doi: 10.5234/cnpt.9.20
24. Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. *N Engl J Med* (2017) 376:2245–54. doi: 10.1056/NEJMoa1612222
25. Haberman SJ. The analysis of residuals in cross-classified tables. *Biometrics* (1973) 29:205–20. doi: 10.2307/2529686
26. Virta LJ, Kalviainen R, Villikka K, Keranen T. Declining trend in valproate use in Finland among females of childbearing age in 2012-2016 - a nationwide registry-based outpatient study. *Eur J Neurol* (2018) 25:869–74. doi: 10.1111/ene.13610
27. Murphy S, Bennett K, Doherty CP. Prescribing trends for sodium valproate in Ireland. *Seizure* (2016) 36:44–8. doi: 10.1016/j.seizure.2016.01.019
28. Wentzell N, Haug U, Schink T, Engel S, Liebentraut J, Linder R, et al. [Prescribing valproate to girls and women of childbearing age in Germany: Analysis of trends based on claims data]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* (2018) 61:1022–9. doi: 10.1007/s00103-018-2768-1
29. Iacobucci G. MHRA bans valproate prescribing for women not in pregnancy prevention programme. *BMJ* (2018) 361:k1823. doi: 10.1136/bmj.k1823
30. Singh S, Sedgh G, Hussain R. Unintended pregnancy: worldwide levels, trends, and outcomes. *Stud Fam Plann* (2010) 41:241–50. doi: 10.1111/j.1728-4465.2010.00250.x
31. Freudenreich O, Kontos N. "Professionalism, Physicianhood, and Psychiatric Practice": Conceptualizing and Implementing a Senior Psychiatry Resident Seminar in Reflective and Inspired Doctoring. *Psychosomatics* (2019) 60:246–54. doi: 10.1016/j.psym.2018.12.005
32. Power RA, Kyaga S, Uher R, MacCabe JH, Langstrom N, Landen M, et al. Fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse vs their unaffected siblings. *JAMA Psychiatry* (2013) 70:22–30. doi: 10.1001/jamapsychiatry.2013.268
33. Munk-Olsen T, Laursen TM, Mendelson T, Pedersen CB, Mors O, Mortensen PB. Risks and predictors of readmission for a mental disorder during the postpartum period. *Arch Gen Psychiatry* (2009) 66:189–95. doi: 10.1001/archgenpsychiatry.2008.528
34. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. *Am J Psychiatry* (2016) 173:117–27. doi: 10.1176/appi.ajp.2015.15010124

Conflict of Interest: TH reported personal fees from research support of a clinical trial that the signant health (former, blacket global) company manages. TakaT has received personal fees from Otsuka, GlaxoSmithKline, MSD, Dainippon-Sumitomo, Janssen, Eisai, Eli Lilly, Daiichi-Sankyo, Shionogi, and Tanabe-Mitsubishi. KH has received lecture honoraria for Dainippon-Sumitomo, Janssen, Meiji Seika, MSD, Otsuka, Takeda, and Tanabe-Mitsubishi, and has served as a consultant for Dainippon-Sumitomo, MSD, and Meiji Seika. HW has received speaker's honoraria for MSD and Eli Lilly. TakeT has received honoraria from Otsuka Pharmaceutical Co., Ltd. and Mochida Pharmaceutical Co., Ltd as potentially influencing but not directly related to this work. MI received consultant fees from Janssen, Elilly, Otsuka, and Meiji Seika Pharma and reports honoraria from Janssen, Eli Lilly, Otsuka, Meiji Seika Pharma, Astellas, Dainippon Sumitomo, Ono, Mochida, MSD, Eisai, Daiichi-Sankyo, Novartis, Teijin, Shionogi, Hisamitsu, and Asahi Kasei.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 22 April 2020
doi: 10.3389/fpsyt.2020.00314

Prevalence of Prediabetes and Diabetes Mellitus Type II in Bipolar Disorder

*Sarah Kittel-Schneider[1,2], Daniel Bury[2,3], Karolina Leopold[4,5], Sara Haack[4], Michael Bauer[4], Steffi Pfeiffer[4], Cathrin Sauer[4], Andrea Pfennig[4], Henry Völzke[6], Hans-Jörgen Grabe[7] and Andreas Reif[1]**

[1] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University, Frankfurt, Germany, [2] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Julius-Maximilians-University of Würzburg, Würzburg, Germany, [3] Department of Psychiatry and Psychotherapy Munich East, kbo-Isar-Amper-Klinikum, Haar, Germany, [4] Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Medical Faculty, Technische Universität Dresden, Dresden, Germany, [5] Department of Psychiatry, Psychotherapy and Psychosomatics, Vivantes Hospital am Urban and Vivantes Hospital im Friedrichshain, Charite Universitätsmedizin, Berlin, Germany, [6] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany, [7] Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany

OPEN ACCESS

Edited by:
Andrea Fagiolini,
University of Siena, Italy

Reviewed by:
Mirko Manchia,
University of Cagliari, Italy
Chiara Fabbri,
King's College London,
United Kingdom

***Correspondence:**
Andreas Reif
Andreas.reif@kgu.de

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 28 January 2020
Accepted: 30 March 2020
Published: 22 April 2020

Citation:
Kittel-Schneider S, Bury D, Leopold K, Haack S, Bauer M, Pfeiffer S, Sauer C, Pfennig A, Völzke H, Grabe H-J and Reif A (2020) Prevalence of Prediabetes and Diabetes Mellitus Type II in Bipolar Disorder. Front. Psychiatry 11:314. doi: 10.3389/fpsyt.2020.00314

Introduction: Bipolar disorder (BD) is characterized by recurrent episodes of depression and mania and affects up to 2% of the population worldwide. Patients suffering from bipolar disorder have a reduced life expectancy of up to 10 years. The increased mortality might be due to a higher rate of somatic diseases, especially cardiovascular diseases. There is however also evidence for an increased rate of diabetes mellitus in BD, but the reported prevalence rates vary by large.

Material and Methods: 85 bipolar disorder patients were recruited in the framework of the BiDi study (Prevalence and clinical features of patients with Bipolar Disorder at High Risk for Type 2 Diabetes (T2D), at prediabetic state and with manifest T2D) in Dresden and Würzburg. T2D and prediabetes were diagnosed measuring HBA1c and an oral glucose tolerance test (oGTT), which at present is the gold standard in diagnosing T2D. The BD sample was compared to an age-, sex- and BMI-matched control population (n = 850) from the Study of Health in Pomerania cohort (SHIP Trend Cohort).

Results: Patients suffering from BD had a T2D prevalence of 7%, which was not significantly different from the control group (6%). Fasting glucose and impaired glucose tolerance were, contrary to our hypothesis, more often pathological in controls than in BD patients. Nondiabetic and diabetic bipolar patients significantly differed in age, BMI, number of depressive episodes, and disease duration.

Discussion: When controlled for BMI, in our study there was no significantly increased rate of T2D in BD. We thus suggest that overweight and obesity might be mediating the association between BD and diabetes. Underlying causes could be shared risk genes, medication effects, and lifestyle factors associated with depressive episodes. As the latter

two can be modified, attention should be paid to weight changes in BD by monitoring and taking adequate measures to prevent the alarming loss of life years in BD patients.

Keywords: bipolar disorder, diabetes mellitus, prediabetes, affective disorders, metabolic syndrome, glucose metabolism, obesity, body mass index

INTRODUCTION

Bipolar disorder (BD) is characterized by recurrent episodes of depression and mania and affects up to 2% of the population worldwide. Patients suffering from BD have a reduced life expectancy of 10 years. The increased mortality, besides mortality caused by suicides, might be due to a higher rate of somatic diseases, especially cardiovascular diseases (1–7). There is also evidence that bipolar patients might have a higher risk for developing diabetes mellitus type II (T2D) (8). However, it remains unclear if the higher rates of somatic diseases and especially diabetes mellitus are caused by psychotropic medication, an unhealthier lifestyle, genetic risk factors, inflammatory mechanisms or shared pathophysiological mechanisms, or a combination of those factors. Additionally, the reported prevalence rates of T2D in BD vary from 6.7 to 26% in different populations (9–12).

Results from epidemiological studies estimate that the risk for T2D in bipolar patients is about threefold increased in comparison to nonpsychiatric populations (13). Conversely, in cohorts of diabetic patients higher comorbidity with psychiatric and especially affective disorders can be found (14). One factor conveying the risk of T2D in BD might be psychotropic medication, especially second generation antipsychotics (15–17). But also lithium and valproic acid are known to induce weight gain and by this could lead to dysregulation in glucose metabolism (18, 19).

However, dysregulation in glucose metabolism in BD patients has been described before the use of second generation antipsychotic medication as well as in drug-naïve patients (20). Therefore, other factors might also play a role, such as shared heritability due to shared risk gene variants. However, in a Japanese sample no association of risk genes of T2D with BD could be detected (21, 22) which was later confirmed in the largest GWAS to date. Notably however, there was a nominally significant correlation of bipolar disorder with body mass index, and in pathway analyses, genes involved in insulin secretion were enriched (23). A recent cohort study investigating 10,863 Danish men reported also an increased rate of T2D in patients with severe mental illness, which however was more pronounced in schizophrenia patients (HR = 1.92; 95%CI, 1.61–2.30). A Swedish study found a much stronger risk increase of cardiovascular disease in patients with schizophrenia and BD as compared to T2D risk (24). In an Amish family study, a positive genetic correlation of BD and T2D was found; however, this was a very distinct population so it is not clear whether this holds true to broader population samples (25).

Regarding environmental risk contributing to T2D in BD, several studies report an unhealthy life style in patients including physical inactivity especially in depressive phases (26, 27), higher alcohol and illegal substance consumption, nicotine dependence and greater intake of unhealthy food (28–31), and increased rates of psychological trauma/maltreatment in childhood (32, 33). Additionally, several endocrine and metabolic pathways could be playing a role in conveying a greater risk of T2D in BD, such as dysregulation of different neuropeptides (for example leptin, ghrelin, and adiponectin) and disturbances in the hypothalamus–pituitary–adrenal gland axis (34, 35). Furthermore, inflammatory and immune processes have been suggested to play a pathophysiological role in T2D as well as BD (34). In an own previous study, we could find hints for an increased prevalence of T2D in bipolar patients; however, we did not include a BMI-, sex- and age-matched control population (36). As there are inconsistent results regarding the prevalence of T2D and BD and the causal mechanisms are still unclear, we here investigated the prevalence of T2D and prediabetes in BD patients in comparison to an age-, sex- and BMI-matched control sample from the general population (37).

MATERIAL AND METHODS

Participants

Patients

Bipolar disorder patients were recruited in the framework of the BiDi study (Prevalence and clinical features of patients with Bipolar Disorder at High Risk for Type 2 Diabetes (T2D), at prediabetic state and with manifest T2D). This study was a cross-sectional study which was conducted as a collaborative study of the Department of Psychiatry and Psychosomatic Medicine of the University Hospital of Dresden and the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy of the University Hospital of Würzburg. Patients were recruited from the specialized bipolar clinics in Dresden and Würzburg between November 2009 and February 2012 and were mainly outpatients. All participants were diagnosed with a bipolar disorder using ICD-10 criteria from two independent specialists (SKS/AR and SH/KL). Inclusion criteria were age >= 18 years, being euthymic for 2 months [measured by Montgomery–Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), and Clinical Global Impression Scale Bipolar Disorder (CGI-BP S)]. Only euthymic patients were included, which was operationalized as a score ≤ 12 in the MADRS, ≤5 in the YMRS, and ≤2 in the CGI-BP Score. Medication had to be stable for at least 2 months. Exclusion criteria were organic affective disorder, acute or severe medical conditions (like acute and chronic infections, digestive diseases, carcinomas), pregnant and lactating women.

Diabetes mellitus type II (T2D) was diagnosed using the criteria of the *American Diabetes Association* (ADA) (38) for T2D which are:

- HbA1c ≥ 6.5%
- or fasting glucose ≥ 126 mg/dl (7.0 mmol/L)
- or 2 h plasma glucose ≥ 200 mg/dl (11.1 mmol/L) in the oral glucose tolerance test (oGTT)
- or glucose level at a random time point ≥ 200 mg/dl (11.1 mmol/l) and other symptoms of a diabetes mellitus

Prediabetes was also diagnosed following the criteria of the *American Diabetes Association* (ADA) (38) which are:

- Impaired fasting glucose (IFG): 100–125 mg/dl (5.6–6.9 mmol/L)
- Impaired 2 h plasma glucose (IGT) in the oGTT: 140–199 mg/dl (7.8–11.0 mmol/L)
- HbA1c values between 5.7 and 6. 4%

Only study participants who gave written informed consent were enrolled in the study, which complied with the latest Declaration of Helsinki and was approved by the Ethics Committees of the Universities of Würzburg and Dresden.

Healthy Comparison Group: Study of Health in Pomerania

As a mentally healthy comparison group, data from the Study of Health in Pomerania (SHIP study) were used (37, 39, 40). SHIP is a general population cohort study in Northeastern Germany that includes two independent cohorts. The baseline assessment of the first cohort (SHIP-0) was conducted between 1997 and 2001; 4,308 adults were included. Follow-up assessments were conducted between 2002 and 2006 (SHIP-1) and from 2007 to 2012 (SHIP-2). In parallel to the SHIP-2 recruitments, a second, independent cohort was selected in 2008 with 8,016 adults (SHIP-Trend). From this cohort, 4,420 adults were recruited for the basic assessment between 2008 and 2012. Inclusion criteria were age between 20 and 79, German nationality, and living in the Northeastern region. SHIP is an epidemiological study and had the primary aim to investigate the prevalence and incidence of population relevant diseases and risk factors for those diseases. By the comparison of two cross-sectional studies, (SHIP-0 and SHIP-Trend), prevalence trends of risk factors and diseases in Northeastern Germany were evaluated. To diagnose a diabetes mellitus, in the SHIP Trend cohort the oGTT was conducted [182]. From the SHIP Trend cohort, an age-, sex-, and BMI-matched sample consisting of 850 patients was selected.

Demographic and Phenotypic Data

Ethnical information, marriage status, psychosocial situation, age, and number of children were assessed in the bipolar group. Additionally, age of onset, polarity of first episode, number of episodes, rapid cycling, suicide attempts, and number of hospitalizations were recorded. Furthermore, current medication was assessed as well as information about alcohol and illegal drug use. Weight and height BMI and waist–hip ratio as well as blood pressure were measured. The demographic and phenotypic data are displayed in **Tables 1**–**6**. 27% (n = 23) of the bipolar patients fulfilled the NCEP ATP III criteria of a metabolic syndrome (MetS) (**Table 5**).

Oral Glucose Tolerance Test

The oral glucose tolerance test (oGTT) is a standardized test and validated diagnostic instrument in the clinical routine to verify the diagnosis of a diabetes mellitus and an impaired glucose tolerance (IGT) (38). The test was conducted following the WHO guidelines (38). Three days before the test, the patients refrained from their usual diet. 10 h before the test patients fasted (including food, alcohol, coffee, and increased activity). The oGTT was conducted between 8 and 11 am, and the patients did not take their medication directly before the test. The oGTT was not conducted three days before, during or 3 days after the menstrual bleeding. Venous blood was taken, and plasma glucose, insulin, and lipid levels were measured at fasting baseline. After that the patients ingested 75 g glucose dissolved in 300 ml water (*Roche Dextro OGT, Basel, Switzerland*). They were instructed to drink it in 5 min. After 120 min venous blood was drawn for the second time. Glucose was measured from the venous plasma collected in a fluoride tube which inhibits glycolysis. HBA1c was measured from blood collected in an EDTA tube, and lipids were measured from blood in serum tubes (total cholesterol, high-density cholesterol, low-density cholesterol, triglycerides). The analyses were conducted in the central clinical routine laboratories of the University Hospitals of Dresden and Würzburg.

Questionnaires

SF-12

The patients were evaluated regarding their health-related quality of life by using the SF-12 questionnaire. This is a short form of the SF-36-health questionnaire and includes eight dimensions (body functioning, bodily role function, pain, general assessment of health, vitality, social functioning, emotional role function, mental well-being) to measure the cross-disorder health-related quality of life during the past 4 weeks (41).

WHO-5

WHO-5 is a questionnaire for evaluating well-being. There are five questions that cover the dimensions mood, vitality and general interest during the past 2 weeks. A Likert scale is used

TABLE 1 | Demographic data.

	Bipolar sample		SHIP Trend control sample	
	n	%	n	%
	85		850	
Caucasian ethnicity	79	93	N/A	
Sex female:male	37:48	44 *vs*. 66	370:480	44 vs. 66
Age (years)	44.72 +/−12.63 SD		46.50 ± 11.87 SD	

Patients were matched 1:10 to controls regarding age, sex, and BMI. N, number; SD, standard deviation; N/A, not available.

TABLE 2 | Clinical phenotype bipolar patients.

Clinical Phenotype	Mean (SD)
Age at onset (years)	28.16 (±11.00)
Duration of disease (years)	16.60 (±10.71)
Number of hospital stays	4.12 (±4.48)
Number of episodes	14.61 (±13.48)
Number of depressed episodes	8.02 (±7.77)
Number of manic episoded	3.51 (±4.67)
Number of hypomanic episodes	4.06 (±5.88)
Rapid cycling (yes)	N23
Suicidal attempt (yes)	25
Medication	
Lithium	54
Carbamazepine	6
Oxcarbazepine	1
Lamotrigine	7
Valproate	20
Escitalopram	3
Paroxetine	1
Sertraline	2
Duloxetine	2
Venlafaxine	16
Reboxetine	1
Clomipramine	1
Doxepine	3
Trimipramine	1
Mirtazapine	2
Tranylcypromine	3
Agomelatine	3
Bupropion	2
Melperone	1
Amisulpride	1
Aripiprazole	7
Clozapine	3
Olanzapine	5
Quetiapine	30
Risperidone	3
Ziprasidone	1
Lorazepam	1
Bipolar Subtype (I *vs.* II)	68:17
Comorbid disorders	
Alcohol use disorder	5
Obsessive-compulsive disorder	2
ADHD	2
Nicotine use	28
Illegal drug use	2
Bulimia nervosa	1
Dissociative disorder	1
Dependent Personality Disorder	1
Marital status	
Married	51
Single	24
Divorced	10
Education	
9 years of schooling	2
13 years of schooling	3
Specialized job	53
College	9
University	17
Current work status	
Freelancer	4
Employed	30
Unemployed	9
Retired	31
Other	11

SD, standard deviation; N, number; ADHD, attention-deficit-/hyperactivity disorder.

TABLE 3 | Anthropometric data.

Anthropometric data	Bipolar sample	SHIP Trend control sample
	Mean (SD)	Mean (SD)
Weight (kg)	85.03 (±16.78)	N/A
Height (cm)	170.85 (±8.67)	
BMI, kg/m²	29.15 (±5.60)	28.61 (±3.94)
Waist circumference (cm)	100.66 (±16.00)	N/A
Hip circumference (cm)	109.76 (±19.15)	
WHR	0.91 (±0.11)	
Systolic blood pressure, mmHg	125.22 (±14.96)	
Diastolic Blood pressure, mmHg	78.24 (±11.26)	

N, number; SD, standard deviation; BMI, body mass index; WHR, waist–hip-ratio; N/A, not available.

from 0 (= never) to 5 (= always) and a sum score can be calculated with values between 0 and 25 (42). The WHO-5-questionnaire is recommended as a screening instrument for depression for example in patients with T1D and T2D (43).

Finnish Diabetes Risk Score Questionnaire

The *Finnish Diabetes Risk Score Questionnaire* (FINDRISC) was developed as a risk assessment to effectively prevent T2D in Finland (44). To use this instrument in Germany, a modified version (due to different life styles and eating habits) was developed (FINDRISK). Age, family history of diabetes mellitus, waist circumference, activity level, eating habits, arterial hypertension, increased blood glucose levels in the past, and body mass index are assessed. The sum score is 0 to 26 (45).

Montgomery–Åsberg Depression Rating Scale (MADRS)

The MADRS is a structured interview for the quantitative assessment of depressive symptoms severity. The maximum sum score is 60. It can be conducted evaluating the last 24 h or the last week (46).

Young Mania Rating Scale

The YMRS is a structured interview for the quantitative assessment of manic symptom severity during the last 48 h (47).

Clinical Global Impressions Scale for Bipolar Disorder

The CGI-BP is a scale to assess the clinical severity in bipolar affective disorder. The scale combines separate items for mania, depression and global impression of the bipolar patient. The severity of the disorder can be scored from 1 (not ill) to 7 (severely ill) (48).

Statistical Analysis

Prevalence of T2D and prediabetes in the SHIP-Trend- and BiDi-samples as well as the results of the questionnaires and

TABLE 4 | T2D and pre-diabetes in bipolar patients and controls.

	Bipolar sample	SHIP Trendcontrol sample	p-value
	Total sample n = 85	Total sample n = 850	
	n (%)	n (%)	
T2D	6 (7%)	54 (6%)	0.8
Prediabetes (all forms)	28 (33%)	377 (44%)	**0.043**
- IGT	5 (18%)	111 (29%)	**0.03**
- IFG	8 (29%)	301 (80%)	**0.001**
- HbA1c: 5.7–6. 4%	18 (64%)	105 (28%)	**0.001**

N, number; T2D, diabetes mellitus type II; IGT, impaired glucose tolerance; IFT, impaired fasting glucose; differences between bipolar and control patients were analyzed by t-test. Level of significance was set at p-value p < 0.05; significant p-values are displayed in bold.

TABLE 5 | Glucose and lipid metabolism data.

Blood results	Bipolar sample	SHIP Trend control sample	p-value
	Mean (SD) number of patients	Mean (SD) number of patients	
Fasting plasma glucose (mmol/l)	4.96 (±0.80), n = 85	5.52 (±0.8), n = 850	**<0.001**
Plasma glucose after 120 min (mmol/l)	5.37 (±2.01), n = 83	6.39 (±2.2), n = 850	**<0.001**
HbA1c, %	5.42 (±0.44), n = 85	5.20 (±0.6), n = 850	**<0.001**
Fasting Insulin (pmol/l)	87.6 (±98.3), n = 83	N/A	
Insulin after 120 min (pmol/l)	290.0 (±362.0), n = 80		
Triglycerides (mmol/l)	1.6 (±1.0), n = 79		
Cholesterol, mmol/l	5.3 (±1.3), n = 79		
HDL (mmol/l)	1.4 (±0.4), n = 79		
LDL (mmol/l)	3.2 (±1.0), n = 79		

N, number; SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; differences between bipolar and control patients were analyzed by t-test; level of significance was set at p < 0.05; significant p-values are shown in bold.

anthropometric measurements were assessed by descriptive statistics using SPSS (IBM® SPSS® Statistics 20). Data were tested for normal distribution and differences between groups were tested by χ^2-test and t-test. Furthermore, we investigated the correlation of metabolic parameters with the number of disease episode in the bipolar patients by Pearson's correlation test. Additionally, as a secondary analysis, a multivariate analysis was calculated to investigate differences in the multiple variates between the nondiabetic and (pre-)diabetic bipolar groups (MANOVA). The level of significance was set at p =< 0.05.

TABLE 6 | Comparison (pre-)diabetic and diabetic bipolar patients.

Parameter	Bipolar patients with T2D/pre-diabetes (SD), n = 34	Bipolar patients w/o diabetes/pre-diabetes (SD), n = 51	p-value
Ages (years)	48.82 (±11.99)	41.98 (±12.41)	**0.013**
Sex f:m	13:21	24:27	0.422
BMI, kg/m²	31.08 (±6.27)	27.87 (±4.75)	**0.014**
Waist circumference	104.85 (±15.33)	97.86 (±15.96)	**0.046**
Wait–hip-ratio	0.92 (±0.09)	0.907 (±0.10)	0.45
Metabolic syndrome	13 (38%)	10 (20%)	0.058
Marital status			
Single	11(32%)	13 (25%)	0.491
Married	21(62%)	30 (59%)	0.786
Divorced	2 (6%)	8 (16%)	0.169
Current work status			
Employed/ freelancer	11 (32%)	24 (47%)	0.14
Pensioned	17 (50%)	14 (27%)	
Unemployed	3 (9%)	6 (12%)	
Other	3 (9%)	7 (14%)	
Age of onset	28.91 (±10.49)	27.67 (±11.40)	0.61
Disease duration	20.0 (±11.14)	14.33 (±9.89)	**0.019**
Number of depressive episodes	10.91 (±9.10)	6.10 (±6.11)	**0.01**
Number of manic episodes	3.18 (±4.32)	3.31 (±4.90)	0.83
Number of hypomanic episodes	3.18 (±4.95)	2.22 (±5.20)	0.40
Number of mixed episodes	0.65 (±0.88)	0.67(±1.66)	0.95
Total number of episodes	17.91 (±14.33)	12.24 (±12.26)	0.054
Episodes per disorder year	0.9	0.85	0.485
Rapid Cycling	12 (35%)	11 (22%)	0.163
Sucidal attempts	9 (26%)	16 (31%)	0.627
Number of hospitalizations	4.03 (±3.49)	4.18 (±5.06)	0.883
FINDRISK-Score	10.91 (±4.98)	7.69 (±4.02)	**0.003**
WHO-5 Score	13.53 (±5.97)	14.65 (±5.00)	0.353
SF-12 Score	30.09 (±3.97)	31.33 (±2.21)	0.067

N, number; SD, standard deviation; differences between diabetic and nondiabetic bipolar patients were calculated by t-test or χ^2 test, respectively. Level of significance was set at p < 0.05. Significant p-values are marked in bold.

RESULTS

Prevalence of Diabetes Mellitus Type II and Prediabetes in Patients Suffering From BD *vs*. General Population

We diagnosed T2D and prediabetes by using the oGTT results and the HbA1c-value (according to ADA-criteria) (38). In the patient sample, 7% of the patients fulfilled the diagnostic criteria of T2D. In two of those cases, T2D had already been diagnosed before. In the

SHIP Trend control cohort, 6% of the control participants fulfilled the diagnostic criteria of T2D. The difference in T2D prevalence between BiDi and SHIP-Trend control group was not statistically significant ($\chi^2 = 0.064$, p = 0.8) (**Table 4**, **Figures 1A, B**).

Prediabetes could be diagnosed in 33% of the bipolar patients *vs.* 44% of the controls. In 18% of the prediabetic bipolar patients, impaired glucose tolerance (IGT) could be determined *vs.* 29% of the controls. 29% of the bipolar prediabetic patients had an impaired fasting glucose (IFG) *vs.* 80% of the prediabetic controls. 64% of the prediabetic bipolar patients showed an HbA1c value in the prediabetic range *vs.* 28% of the prediabetic controls. In 14% of the control individuals, IFG and IGT occurred simultaneously. 10% of the control participants had an increased HbA1c and IFG, whereas 2% had an increased HbA1c value and IGT. In 5% of the control population, all parameters were in the prediabetic range. Furthermore, IGT and an increased HbA1c value were found in7% of the control participants. 4% had IFG and an increased HbA1c value (**Table 4**, **Figures 1A, B**). None of the participants showed both IGT and IFG. Prediabetes was significantly more common in the control group in comparison to the bipolar sample ($\chi^2 = 4.106$, p = 0.043).

Comparison of the fasting glucose levels of both groups showed that BD patients had significantly lower glucose levels than control participants [t(933) = 6.395, p = <0.001, see **Table 5**]. Additionally, blood glucose levels after 120 min in the oGTT were significantly lower in BD patients than in control participants [t(931) = 4.056, p = <0.001, see **Table 5**]. However, HbA1c values of the bipolar sample were significantly higher in comparison to the SHIP Trend control population [t(933) = −3.234, p = <0.001).

Here, the rates of diabetes mellitus type II (T2D) and prediabetic conditions (IGT, impaired glucose tolerance; IFG, impaired fasting glucose) as well as HbA1c values are displayed in a Venn diagram for the bipolar sample (BiDi) and the age-, sex- and BMI-matched sample from the general population (SHIP).

Comparison of the Prediabetic/Diabetic BD Patients *vs.* Nondiabetic Bipolar Patients

To investigate the risk factors for diabetes in the sample of bipolar patients, we compared the prediabetic and diabetic bipolar patients with the nondiabetic bipolar patients. The prediabetic/diabetic bipolar patients were significantly older and had a significantly longer disease duration, had a significantly higher BMI and waist circumference in comparison to the nondiabetic bipolar patients (**Table 5**). Furthermore, they have had suffered from a higher number of depressive episodes and had significantly higher scores in the FINDRISK. The other variables were not significantly different between the groups (**Table 6**). Additionally, there was no significant difference in the medication between the diabetic and nondiabetic bipolar groups (lithium carbonate: $\chi^2 = 1{,}430$, p = 0.232; valproate: $\chi^2 = 2.452$, p = 0.117; quetiapine: $\chi^2 = 0.859$, p = 0.354). There was also no difference in the distribution between patients taking olanzapine and clozapine as drugs with a potential high metabolic risk and patients taking aripiprazole as a drug with a potential protective effect against diabetes between the nondiabetic and the (pre-)diabetic group ($\chi^2 = 1{,}122$, p = 0.571). Furthermore, there was a significant positive correlation between the blood glucose levels, HbA1c and BMI, and the number of depressive episodes, but not manic or mixed episodes (see **Table 7**). We additionally conducted a multivariate analysis (MANOVA) to investigate group differences between the nondiabetic and the (pre-)diabetic group. We were taking age, BMI, disease duration, and number of depressive episodes into

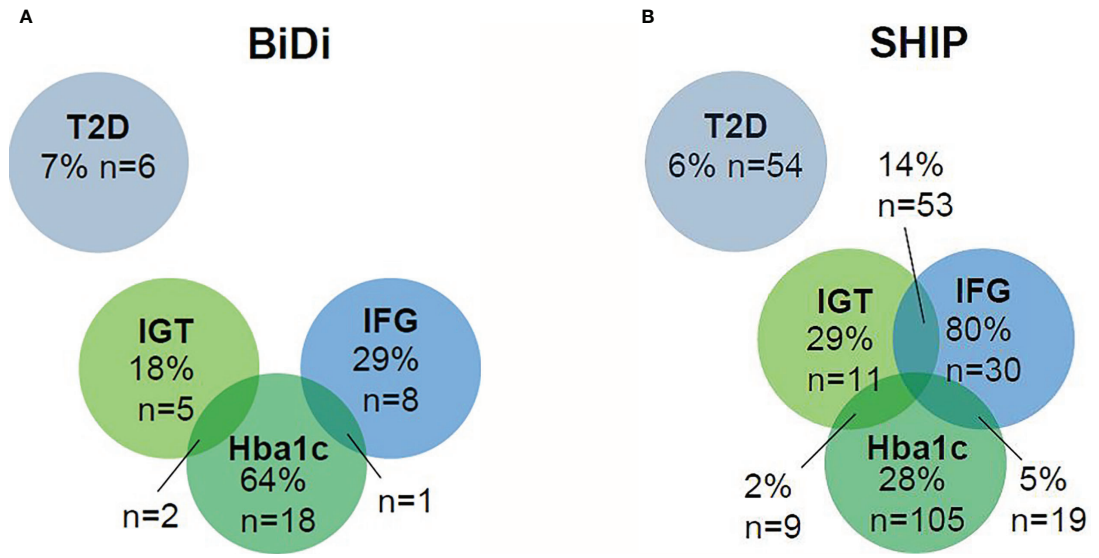


FIGURE 1 | (A, B) T2D and prediabetes rates in bipolar patients and controls.

TABLE 7 | Correlation of metabolic parameters with disorder severity.

		Fasting plasma glucose (mmol/l)	Plasma glucose after 120 min (mmol/l)	HbA1c, %	BMI, kg/m^2
Number of depressed episodes	Pearson Correlation	,245*	0.212	,428**	,306**
	Sig. (2-tailed)	**0.024**	**0.051**	**0.0001**	**0.004**
Number of manic episodes	Pearson Correlation	0.052	0.078	0.147	0.163
	Sig. (2-tailed)	0.634	0.476	0.180	0.137
Number of hypomanic episodes	Pearson Correlation	0.059	0.014	0.177	0.059
	Sig. (2-tailed)	0.593	0.896	0.107	0.595
Number of mixed episodes	Pearson Correlation	0.022	0.095	–0.015	,240*
	Sig. (2-tailed)	0.842	0.387	0.894	**0.027**
Number of all episodes	Pearson Correlation	0.185	0.167	,368**	,284**
	Sig. (2-tailed)	0.090	0.128	**0.001**	**0.008**
Disease duration	Pearson Correlation	,323**	0.170	,433**	,243*
	Sig. (2-tailed)	**0.003**	0.119	**0.0001**	**0.025**

*Pearson's correlation test was conducted. **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed). Level of significance was set at p = 0.05, significant p-values are shown in bold. Number of bipolar patients included in the analysis was 85.*

account as covariates. All those variates (age, BMI, number of episodes, disease duration) remained significantly different between the bipolar groups in the multivariate analysis (p = 0.006 and between subject effects were for age p = 0.013, for BMI p = 0.009, for depressive episodes p = 0.004 and for disease duration p = 0.016, respectively).

DISCUSSION

In our study, we could not find an increased rate of T2D in bipolar patients in comparison to age-, sex- and BMI-matched controls. These findings are in contrast to previous studies reporting increased prevalence of T2D in bipolar patients (9–12). When we restricted the analysis of our data to nonmatched controls and used the older (2006) instead of the newer ADA-criteria (49), our previously published report also suggested an increased rate of diabetes and prediabetes in BD in line with previous studies (36). However, when comparing the parameters directly to an age-, sex- and BMI-matched matched control population, we could no longer find any difference in T2D rates and even lower rates of prediabetes and lower levels of fasting glucose as well as oGTT values in BD. Only the HbA1c values were significantly higher in our bipolar sample compared to the SHIP-Trend general population sample although the effect size was rather small (Cohen's d = 0.037).

Our main finding, *i.e.* that the rate of T2D in BD is not increased, in comparison to a general population sample might well be due to the fact that we used age-, sex- and BMI-matched controls. Obesity is a major risk factor for T2D (50) and is also positively associated with BD (OR = 1.77, 95% CI: 1.40–2.23; Q = 44.62, P < 0.001) (51, 52). Therefore, we speculate that the increased risk for T2D in other studies might be a consequence of significantly increased rates of obesity in the BD compared to the general population. In comparison with another German general population study [*Studie zur Gesundheit Erwachsener in Deutschland* (DEGS1, 2008–2011)] our BiDi group with a mean BMI of 29.15 had a significantly higher BMI as the age-stratified controls (53). In the DEGS1 cohort, 67% of the men and 53% of the females in the same age range as our BiDi sample had a BMI >= 25. In our BiDi sample, 78% of the participants had a BMI > 25. Taken together, we propose that overweight and obesity might be the mediating factors between BD and T2D, and that the risk for T2D in BD in comparison to the general population may not be increased in BD as such but rather the risk towards obesity. A previous Italian study and a follow-up study could also show that abdominal obesity as a major factor of the metabolic syndrome was associated with a higher rate of T2D in bipolar patients (54, 55). The higher rate of obesity can be due to either lifestyle factors (food pattern, sedentary lifestyle), medication influence (especially second-generation antipsychotics such as olanzapine and quetiapine) (56) as well as shared risk genes for BD and BMI (57). However, as a limiting factor in our study, we did not include other factors that, especially in men, have shown to increase the risk of T2D like smoking and arterial hypertension (58, 59). In our sample, there was however no significant difference between the types of mood stabilizing medication in the diabetic *vs*. the nondiabetic group. But then, also valproate and lithium can lead to weight gain and not only atypical antipsychotics (19, 60). Also, our sample size in the medication subgroups was too small to make definite conclusions hereon. Interestingly, in a multivariate analysis comparing the nondiabetic and (pre-)diabetic bipolar groups, disease duration and number of depressive episodes, as well as BMI and age, remained statistically significant between the groups. Furthermore, metabolic parameters were significantly correlated with the number of depressed episodes. There are previous studies that suggest that comorbid insulin resistance, diabetes mellitus type **II,** and an increased BMI might lead to a more severe course in bipolar patients (61–63). From our data, we might conclude that increased BMI is the major contributor to an increased risk for T2D in BD in comparison to the general population; however, disease duration and depressive polarity might add to the risk of developing T2D in BD patients. However, as our study was a cross-sectional and not a longitudinal study, we cannot confirm the direction of the association of impaired metabolic parameters and a more severe course. Diagnosing and monitoring of overweight and prediabetes and T2DM in BD are furthermore of importance as there is growing evidence that impaired glucose metabolism and

T2D might lead to worse response to treatment with mood stabilizers (64).

As being overweight is a modifiable risk state, special emphasis should be paid to lifestyle modification in BD patients to avoid detrimental general health outcomes including T2D. Unhealthy lifestyle that increases the risk of obesity seems more to be an issue of depressive episodes than manic episodes supposedly due to lack of activity and unhealthy eating patterns. However, as we did not assess information about activity and diet in association with mood episodes, we only can speculate about this. In a pilot study investigating the effectiveness of lifestyle interventions to reduce glucometabolic risks in BD, there were positive preliminary results (65). Several associations and societies recommend metabolic monitoring in patients taking second-generation antipsychotic drugs; however this is not yet implemented fully in clinical routine (38, 66). We here strongly recommend routing monitoring of at least noninvasive anthropometric measures such as BMI and WHR to detect weight increase early on and to take appropriate measures.

Several previous studies have pointed towards an increased prevalence of T2D in BD. For example, Cassidy and colleagues reported a prevalence of T2D in bipolar patients of 9.9% which was significantly higher than the 3.4% diabetes mellitus rate in the control population in their study (12). Lilliker et al. described that 10% of BD patients suffer from diabetes as compared to 2% in their non-bipolar sample (9). Regenold et al. found the T2D prevalence as high as 26% in bipolar-I patients, compared to 13% in the control population (11). In a Belgium sample, diabetes was prevalent in 6.7% of the bipolar group which was twice as often as in the age-matched control group (10). The main reason for the wide range of prevalence rates in bipolar sample between 6.7%, which is similar to our sample, and 26% most likely lies in the different mean age of the various samples. Age is a validated risk factor of T2D, the higher the age, the higher the prevalence of T2D, especially from the age of 50 years on (67). The lowest prevalence rates were accordingly found in the samples with lower mean age, as it was the case in our sample with 7% T2D prevalence with a mean age of 44.7 years. The bipolar sample from Belgium with a 6.7% T2D included bipolar patients with a mean age of 42.1 years, and the sample of Cassidy et al., with a prevalence of 9.9%, had a mean age of 45.3 years (10, 12). In line with this, patients suffering from both BD and T2D in our sample also were significantly older than the nondiabetic bipolar patients. Another reason for differing T2D prevalence might be due to diagnostic and assessment procedures. The majority of studies used information based on the hospital medical records (9, 11, 12), only van Winkel and colleagues validated the diagnosis by using the oGTT, as done in our study (10). Due to the large number of undiagnosed T2D cases in the general population, prevalence rates that only rely on self-report or medical records might be too low. The *Kora F4 Survey* showed a prevalence of previously undiagnosed T2D of 2.0% in addition to the already known T2D of 2.2% in the general population aged between 35 and 59 years using the oGTT (68). Also other studies estimate about 50% existing but undiagnosed T2D cases in the general population worldwide (69).

Another notable difference between our and the other studies is that we enrolled only euthymic patients. In contrast to Regenold et al., van Winkel et al., and Lilliker et al., we only included patients who were euthymic and on stable medication for at least 2 months, as the metabolic status might be influenced in acute episodes.

A systematic review and meta-analysis investigating the prevalence of diabetes mellitus in BD, schizophrenia, and major depression reported a mean T2D prevalence of 9.4% in BD (70). In comparison to age- and sex-adjusted control population, this was a relative risk of 1.89 in patients with BD ($n = 54{,}688$; 95% confidence interval: 1.29–2.77, $p < 0.001$). The authors of this review came to the conclusion that there were also quite large geographical differences in T2D prevalence in the general population which need to be taken into account when comparing bipolar patients and the general population (70). In our sample, there were controls mainly from the northeastern part of Germany compared to a mainly southern sample of bipolar patients. However, the diabetes mellitus prevalence between north and south of Germany has shown to be very similar in the recent years (71).

In conclusion, we could not find an increased prevalence of prediabetes and T2D in BD when an age-, sex- and BMI-matched control sample is used in comparison. Comparing diabetic and nondiabetic bipolar patients, we could identify disease duration and more depressive episodes as potential risk factors for developing T2D or potentially strengthen previous findings of comorbid (pre-)diabetes mellitus as risk factor for a more severe course of the disorder. The direction of interaction we could not determine due to the cross-sectional character of our study. The FINDRISK score was significantly higher in the prediabetic and T2D bipolar patients which strengthens the validity for a screening tool also in patient populations. We hypothesize that obesity might be mediating the previously reported increased T2DM prevalence in BD in comparison to the general population, and medication side effects might contribute to this as well as a longer duration of the disorder and depressive polarity. However, due to the small number of patients in the subgroups, we could not determine differential effects of the different mood stabilizing drugs. Adequate weight and metabolic monitoring and intervention may lead to improved outcomes in this patient group, which is especially important given the reduced life expectancy of patients with BD due to somatic disorders (7).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of the Universities of

Würzburg, Dresden and Greifswald. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK-S, AR, and DB recruited the patients and collected the sample. DB collected the phenotypic data, drew the blood, and analyzed the data. SK-S wrote the paper draft. AR took part in writing and revising the final manuscript. SH and AP designed the study. SH and KL recruited the patients and collected the samples in the study center Dresden. SP built and managed the data base. SP and CS checked the data quality in the study center Dresden. AP and MB supervised the study management in the study center Dresden and critically reviewed the manuscript. H-JG and HV provided the data of the SHIP cohorts.

FUNDING

This study has been supported by a grant of the medical faculty of the Technische Universität Dresden to SH and AP. This publication was funded by the University of Frankfurt. SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania.

ACKNOWLEDGMENTS

We like to thank Theresia Töpner for excellent technical support in the preprocessing of the samples. We thank the patients and controls for participating in the study.

REFERENCES

1. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. *J Clin Psychiatry* (2006) 67(11):e16. doi: 10.4088/JCP.1106e16
2. Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. *Psychosom Med* (2006) 68 (5):684–91. doi: 10.1097/01.psy.0000237316.09601.88
3. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* (2015) 72(4):334–41. doi: 10.1001/jamapsychiatry.2014.2502
4. Khan A, Faucett J, Morrison S, Brown WA. Comparative mortality risk in adult patients with schizophrenia, depression, bipolar disorder, anxiety disorders, and attention-deficit/hyperactivity disorder participating in psychopharmacology clinical trials. *JAMA Psychiatry* (2013) 70(10):1091–9. doi: 10.1001/jamapsychiatry.2013.149
5. Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *Br J Psychiatry* (2017) 211(3):175–81. doi: 10.1192/bjp.bp.117.202606
6. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* (2017) 16(2):163–80. doi: 10.1002/wps.20420
7. Schneider F, Erhart M, Hewer W, Loeffler LA, Jacobi F. Mortality and Medical Comorbidity in the Severely Mentally Ill. *Dtsch Arztebl Int* (2019) 116(23-24):405–11. doi: 10.3238/arztebl.2019.0405
8. Charles EF, Lambert CG, Kerner B. Bipolar disorder and diabetes mellitus: evidence for disease-modifying effects and treatment implications. *Int J Bipolar Disord* (2016) 4(1):13. doi: 10.1186/s40345-016-0054-4
9. Lilliker SL. Prevalence of diabetes in a manic-depressive population. *Compr Psychiatry* (1980) 21(4):270–5. doi: 10.1016/0010-440X(80)90030-9
10. van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. *Bipolar Disord* (2008) 10(2):342–8. doi: 10.1111/j.1399-5618.2007.00520.x
11. Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. *J Affect Disord* (2002) 70(1):19–26. doi: 10.1016/S0165-0327(01)00456-6
12. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry* (1999) 156(9):1417–20. doi: 10.1176/ajp.156.9.1417
13. McIntyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. *Ann Clin Psychiatry* (2005) 17(2):83–93. doi: 10.1080/10401230590932380
14. Lustman PJ, Griffith LS, Clouse RE, Cryer PE. Psychiatric illness in diabetes mellitus. Relationship to symptoms and glucose control. *J Nerv Ment Dis* (1986) 174(12):736–42. doi: 10.1097/00005053-198612000-00005
15. Guo JJ, Keck PEJr., Corey-Lisle PK, Li H, Jiang D, Jang R, et al. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: A retrospective, population-based, case-control study. *J Clin Psychiatry* (2006) 67(7):1055–61. doi: 10.4088/JCP.v67n0707
16. Haupt DW, Newcomer JW. Abnormalities in glucose regulation associated with mental illness and treatment. *J Psychosom Res* (2002) 53(4):925–33. doi: 10.1016/S0022-3999(02)00471-3
17. Yood MU, DeLorenze G, Quesenberry CPJr., Oliveria SA, Tsai AL, Willey VJ, et al. The incidence of diabetes in atypical antipsychotic users differs according to agent–results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* (2009) 18(9):791–9. doi: 10.1002/pds.1781
18. Keck PE, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. *J Clin Psychiatry* (2003) 64(12):1426–35. doi: 10.4088/JCP.v64n1205
19. Torrent C, Amann B, Sanchez-Moreno J, Colom F, Reinares M, Comes M, et al. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. *Acta Psychiatr Scand* (2008) 118(1):4–18. doi: 10.1111/j.1600-0447.2008.01204.x
20. Taylor V, MacQueen G. Associations between bipolar disorder and metabolic syndrome: A review. *J Clin Psychiatry* (2006) 67(7):1034–41. doi: 10.4088/JCP.v67n0704
21. Kajio Y, Kondo K, Saito T, Iwayama Y, Aleksic B, Yamada K, et al. Genetic association study between the detected risk variants based upon type II diabetes GWAS and psychotic disorders in the Japanese population. *J Hum Genet* (2014) 59(1):54–6. doi: 10.1038/jhg.2013.116
22. Torkamani A, Topol EJ, Schork NJ. Pathway analysis of seven common diseases assessed by genome-wide association. *Genomics.* (2008) 92(5):265–72. doi: 10.1016/j.ygeno.2008.07.011
23. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* (2019) 51(5):793–803. doi: 10.1038/s41588-019-0397-8
24. Bent-Ennakhil N, Cecile Perier M, Sobocki P, Gothefors D, Johansson G, Milea D, et al. Incidence of cardiovascular diseases and type-2-diabetes mellitus in patients with psychiatric disorders. *Nord J Psychiatry* (2018) 72 (7):455–61. doi: 10.1080/08039488.2018.1463392
25. Kember RL, Hou L, Ji X, Andersen LH, Ghorai A, Estrella LN, et al. Genetic pleiotropy between mood disorders, metabolic, and endocrine traits in a multigenerational pedigree. *Transl Psychiatry* (2018) 8(1):218. doi: 10.1038/s41398-018-0226-3
26. Elmslie JL, Mann JI, Silverstone JT, Williams SM, Romans SE. Determinants of overweight and obesity in patients with bipolar disorder. *J Clin Psychiatry* (2001) 62(6):486–91; quiz 92-3. doi: 10.4088/JCP.v62n0614

27. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. *Bipolar Disord* (2007) 9(5):443–52. doi: 10.1111/j.1399-5618.2007.00386.x
28. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. *JAMA*. (2000) 284(20):2606–10. doi: 10.1001/jama.284.20.2606
29. Garcia-Portilla MP, Saiz PA, Benabarre A, Florez G, Bascaran MT, Diaz EM, et al. Impact of substance use on the physical health of patients with bipolar disorder. *Acta Psychiatr Scand* (2010) 121(6):437–45. doi: 10.1111/j.1600-0447.2009.01498.x
30. Chengappa KN, Levine J, Gershon S, Kupfer DJ. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disord* (2000) 2(3 Pt 1):191–5. doi: 10.1034/j.1399-5618.2000.020306.x
31. Waxmonsky JA, Thomas MR, Miklowitz DJ, Allen MH, Wisniewski SR, Zhang H, et al. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. *Gen Hosp Psychiatry* (2005) 27(5):321–8. doi: 10.1016/j.genhosppsych.2005.05.003
32. Aas M, Bellivier F, Bettella F, Henry C, Gard S, Kahn JP, et al. Childhood maltreatment and polygenic risk in bipolar disorders. *Bipolar Disord* (2019). 22(2):174–81. doi: 10.1111/bdi.12851
33. Huffhines L, Noser A, Patton SR. The Link Between Adverse Childhood Experiences and Diabetes. *Curr Diabetes Rep* (2016) 16(6):54. doi: 10.1007/s11892-016-0740-8
34. Soczynska JK, Kennedy SH, Woldeyohannes HO, Liauw SS, Alsuwaidan M, Yim CY, et al. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. *Neuromol Med* (2011) 13(2):93–116. doi: 10.1007/s12017-010-8140-8
35. McIntyre RS, Danilewitz M, Liauw SS, Kemp DE, Nguyen HT, Kahn LS, et al. Bipolar disorder and metabolic syndrome: an international perspective. *J Affect Disord* (2010) 126(3):366–87. doi: 10.1016/j.jad.2010.04.012
36. Leopold K, Reif A, Haack S, Bauer M, Bury D, Loffler A, et al. Type 2 diabetes and pre-diabetic abnormalities in patients with bipolar disorders. *J Affect Disord* (2016) 189:240–5. doi: 10.1016/j.jad.2015.09.041
37. Sievers C, Auer MK, Klotsche J, Athanasoulia AP, Schneider HJ, Nauck M, et al. IGF-I levels and depressive disorders: results from the Study of Health in Pomerania (SHIP). *Eur Neuropsychopharmacol* (2014) 24(6):890–6. doi: 10.1016/j.euroneuro.2014.01.008
38. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care* (2010) 33 Suppl 1:S62–9. doi: 10.2337/dc10-S062
39. Block A, Schipf S, Van der Auwera S, Hannemann A, Nauck M, John U, et al. Sex- and age-specific associations between major depressive disorder and metabolic syndrome in two general population samples in Germany. *Nord J Psychiatry* (2016) 70(8):611–20. doi: 10.1080/08039488.2016.1191535
40. Volzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol* (2011) 40(2):294–307. doi: 10.1093/ije/dyp394
41. Ware JJr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* (1996) 34(3):220–33. doi: 10.1097/00005650-199603000-00003
42. Topp CW, Ostergaard SD, Sondergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom* (2015) 84(3):167–76. doi: 10.1159/000376585
43. Hajos TR, Pouwer F, Skovlund SE, Den Oudsten BL, Geelhoed-Duijvestijn PH, Tack CJ, et al. Psychometric and screening properties of the WHO-5 well-being index in adult outpatients with Type 1 or Type 2 diabetes mellitus. *Diabetes Med* (2013) 30(2):e63–9. doi: 10.1111/dme.12040
44. Salinero-Fort MA, Carrillo-de Santa Pau E, Abanades-Herranz JC, Dujovne-Kohan I, Cardenas-Valladolid Jen nombre del Grupo M. [Baseline risk of Diabetes Mellitus in Primary Health Care Services by FINDRISC test, associated factors and clinical outcome after 18 months of follow-up]. *Rev Clin Esp* (2010) 210(9):448–53. doi: 10.1016/j.rce.2010.03.008
45. Schwarz PE, Schuppenies A, Gruhl U, Hoffmann R, Bornstein SR, Schulze J, et al. [Prevention of type 2 diabetes in Germany. Ideas, evidence, implementation]. *Med Klin (Munich)* (2006) 101(9):730–6. doi: 10.1007/s00063-006-1100-2
46. Schmidtke A, Fleckenstein P, Moises W, Beckmann H. [Studies of the reliability and validity of the German version of the Montgomery-Asberg Depression Rating Scale (MADRS)]. *Schweiz Arch Neurol Psychiatr* (1988) 139(2):51–65.
47. Muhlbacher M, Egger C, Kaplan P, Simhandl C, Grunze H, Geretsegger C, et al. [Reliability and concordance validity of a German version of the Young Mania Rating Scale (YMRS-D)]. *Neuropsychiatr* (2011) 25(1):16–25.
48. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* (1997) 73(3):159–71. doi: 10.1016/S0165-1781(97)00123-6
49. American Diabetes A. Standards of medical care in diabetes–2013. *Diabetes Care* (2013) 36 Suppl 1:S11–66. doi: 10.2337/dc13-S011
50. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature.* (2006) 444(7121):840–6. doi: 10.1038/nature05482
51. Zhao Z, Okusaga OO, Quevedo J, Soares JC, Teixeira AL. The potential association between obesity and bipolar disorder: A meta-analysis. *J Affect Disord* (2016) 202:120–3. doi: 10.1016/j.jad.2016.05.059
52. Barton BB, Zagler A, Engl K, Rihs L, Musil R. Prevalence of obesity, metabolic syndrome, diabetes and risk of cardiovascular disease in a psychiatric inpatient sample: results of the Metabolism in Psychiatry (MiP) Study. *Eur Arch Psychiatry Clin Neurosci* (2019). doi: 10.1007/s00406-019-01043-8
53. Mensink GB, Schienkiewitz A, Haftenberger M, Lampert T, Ziese T, Scheidt-Nave C. [Overweight and obesity in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* (2013), 56 (5–6)786–94. doi: 10.1007/s00103-012-1656-3
54. Salvi V, D'Ambrosio V, Rosso G, Bogetto F, Maina G. Age-specific prevalence of metabolic syndrome in Italian patients with bipolar disorder. *Psychiatry Clin Neurosci* (2011) 65(1):47–54. doi: 10.1111/j.1440-1819.2010.02160.x
55. Salvi V, D'Ambrosio V, Bogetto F, Maina G. Metabolic syndrome in Italian patients with bipolar disorder: a 2-year follow-up study. *J Affect Disord* (2012) 136(3):599–603. doi: 10.1016/j.jad.2011.10.025
56. Schneider-Thoma J, Efthimiou O, Bighelli I, Dorries C, Huhn M, Krause M, et al. Second-generation antipsychotic drugs and short-term somatic serious adverse events: a systematic review and meta-analysis. *Lancet Psychiatry* (2019) 6(9):753–65. doi: 10.1016/S2215-0366(19)30223-8
57. Bahrami S, Steen NE, Shadrin A, O'Connell K, Frei O, Bettella F, et al. Shared Genetic Loci Between Body Mass Index and Major Psychiatric Disorders: A Genome-wide Association Study. *JAMA Psychiatry* (2020). doi: 10.1001/jamapsychiatry.2019.4188
58. Yuan S, Larsson SC. A causal relationship between cigarette smoking and type 2 diabetes mellitus: A Mendelian randomization study. *Sci Rep* (2019) 9(1):19342. doi: 10.1038/s41598-019-56014-9
59. Yang F, Ma Q, Liu J, Ma B, Guo M, Liu F, et al. Prevalence and major risk factors of type 2 diabetes mellitus among adult psychiatric inpatients from 2005 to 2018 in Beijing, China: a longitudinal observational study. *BMJ Open Diabetes Res Care* (2020) 8(1):e000996. doi: 10.1136/bmjdrc-2019-000996
60. Bowden CL. Valproate. *Bipolar Disord* (2003) 5(3):189–202. doi: 10.1034/j.1399-5618.2003.00031.x
61. Cairns K, McCarvill T, Ruzickova M, Calkin CV. Course of bipolar illness worsens after onset of insulin resistance. *J Psychiatr Res* (2018) 102:34–7. doi: 10.1016/j.jpsychires.2018.03.006
62. Calkin CV, Ruzickova M, Uher R, Hajek T, Slaney CM, Garnham JS, et al. Insulin resistance and outcome in bipolar disorder. *Br J Psychiatry* (2015) 206(1):52–7. doi: 10.1192/bjp.bp.114.152850
63. Calkin C, van de Velde C, Ruzickova M, Slaney C, Garnham J, Hajek T, et al. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disord* (2009) 11(6):650–6. doi: 10.1111/j.1399-5618.2009.00730.x
64. Steardo L Jr., Fabrazzo M, Sampogna G, Monteleone AM, D'Agostino G, Monteleone P, et al. Impaired glucose metabolism in bipolar patients and response to mood stabilizer treatments. *J Affect Disord* (2019) 245:174–9. doi: 10.1016/j.jad.2018.10.360
65. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, Exercise, and Wellness Treatment in bipolar disorder: proof of

concept for a consolidated intervention. *Int J Bipolar Disord* (2013) 1(1):24. doi: 10.1186/2194-7511-1-24
66. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care* (2009) 32(6):1037–42. doi: 10.2337/dc08-1720
67. Rathmann W, Scheidt-Nave C, Roden M, Herder C. Type 2 diabetes: prevalence and relevance of genetic and acquired factors for its prediction. *Dtsch Arztebl Int* (2013) 110(19):331–7. doi: 10.3238/arztebl.2013.0331
68. Meisinger C, Strassburger K, Heier M, Thorand B, Baumeister SE, Giani G, et al. Prevalence of undiagnosed diabetes and impaired glucose regulation in 35-59-year-old individuals in Southern Germany: the KORA F4 Study. *Diabetes Med* (2010) 27(3):360–2. doi: 10.1111/j.1464-5491.2009.02905.x
69. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin Pract* (2014) 103(2):150–60. doi: 10.1016/j.diabres.2013.11.001
70. Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* (2016) 15(2):166–74. doi: 10.1002/wps.20309
71. Volzke H, Ittermann T, Schmidt CO, Baumeister SE, Schipf S, Alte D, et al. Prevalence trends in lifestyle-related risk factors. *Dtsch Arztebl Int* (2015) 112 (11):185–92. doi: 10.3238/arztebl.2015.0185

Conflict of Interest: SK-S has received speaker's and author's honoraria from Medice and Takeda. AR has received speaker fees and honoraria (publications, advisory boards) from Medice, Shire/Takeda, Servier, neuraxpharm, Janssen, and SAGE. KL has been an advisor to and received speaker's honoraria and travel support from Janssen, Lundbeck, Otsuka and Recordati. She received grant support from Janssen and Otsuka. AP has received speaker's honoraria and travel support from Janssen and Lundbeck. MB has been an advisor to Janssen-Cilag, neuraxpharm und Sunovion, and received speaker's honoraria from Hexal AG, Janssen-Cilag und Sunovion. H-JG has received travel grants and speaker's honoraria from Fresenius Medical Care, Neuraxpharm, and Janssen Cilag as well as research funding from Fresenius Medical Care.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 27 April 2020
doi: 10.3389/fpsyt.2020.00247

Stabilization Beyond Mood: Stabilizing Patients With Bipolar Disorder in the Various Phases of Life

Alessio Simonetti[1,2,3†], *Alexia E. Koukopoulos*[3,4†], *Georgios D. Kotzalidis*[3,5], *Delfina Janiri*[2,3], *Lavinia De Chiara*[3,5], *Luigi Janiri*[6,7] *and Gabriele Sani*[6,7*]

[1] Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, United States, [2] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy, [3] Centro Lucio Bini, Rome, Italy, [4] Azienda Ospedaliera Universitaria Policlinico Umberto I, Sapienza School of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy, [5] NESMOS Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Sant'Andrea University Hospital, Rome, Italy, [6] Institute of Psychiatry, Università Cattolica del Sacro Cuore, Rome, Italy, [7] Department of Psychiatry, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy

OPEN ACCESS

Edited by:
Andreas Reif,
University Hospital Frankfurt, Germany

Reviewed by:
Sarah Kittel-Schneider,
University Hospital Würzburg, Germany
Giuseppe Tavormina,
Independent Researcher, Provaglio d'Iseo, Italy

***Correspondence:**
Gabriele Sani
gabriele.sani@unicatt.it

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *27 January 2020*
Accepted: *13 March 2020*
Published: *27 April 2020*

Citation:
Simonetti A, Koukopoulos AE, Kotzalidis GD, Janiri D, De Chiara L, Janiri L and Sani G (2020) Stabilization Beyond Mood: Stabilizing Patients With Bipolar Disorder in the Various Phases of Life. Front. Psychiatry 11:247. doi: 10.3389/fpsyt.2020.00247

Background: There are different ways to define stabilization and currently, the main standpoint regards it as no-depression/no-mania. Furthermore, each person is physiologically different from childhood to adulthood, and in old age, thus the meaning of stabilization should take into account both growth and maturity. We aimed to review systematically studies focusing on mood stabilization in all phases of bipolar disorder (BD) and across all life phases, including pregnancy and the perinatal period, which is still a different phase in women's life cycles.

Methods: We carried out a PubMed search focusing on studies of bipolar disorder treated with drugs and aimed at stabilization with the following search strategy stabiliz*[ti] OR stabilis*[ti] OR stable[ti] OR stability[ti]) AND mood[ti] AND bipolar. In conducting our review, we followed the *PRISMA* statement. Agreement on inclusion was reached by consensus of all authors through a Delphi rounds procedure.

Results: The above search strategy produced 509 records on January 25, 2020. Of them, 58 fitted our inclusion criteria and were discussed. The eligible studies spanned from September 1983 to July 6, 2019.

Conclusions: No clear-cut indications could be drawn due to a number of limitations involving sample inconsistency and different methods of assessing mood stabilization. The evidence collected so far does not allow recommended treatments for Adolescents, pregnant or perinatal women, and aged patients. However, adults, not within these groups, better focused upon. For their manic/mixed phases, second generation antipsychotic drugs may be useful in the short-to-medium run, alone or combined with mood stabilizers (MSs). However, MSs, and especially lithium, continue to be pivotal in chronic treatment. Bipolar depression should rely on MSs, but an antidepressant may be

added on and can prove to be helpful. However, there are concerns with the tendency of antidepressants to induce the opposite polarity or mood instability, rendering the need for concurrent MS prescription mandatory.

Keywords: mood, stabilization, antidepressant drugs, antipsychotic drugs, lithium, mood stabilizers

INTRODUCTION

The treatment of bipolar disorder (BD) is currently unsatisfactory. Despite the good results obtained in the treatment of its acute manic phase, this may also be the result of the natural course of the disorder. The challenge would be to obtain a clinical response that maintains patients euthymic, without mood swings, and for a sustained time-period. The latter is unfortunately an unmet need, because few patients manage to stay in treatment for a sufficient time to be declared as remitted. In fact, 40% (1) to 60% (2) of patients discontinue lithium after 5-7 years, and despite good adherence, some 13% of patients who were responders for five years, become resistant to lithium treatment after 10 years (3). BD has its onset usually in late adolescence and early adulthood, less often in later adulthood or advanced age, and seldom during childhood (4), with each range of age at onset displaying a normal-like distribution (5). Since it runs a cyclic course, with manic and depressive episodes and with relatively asymptomatic intervals, and is a biologically heterogeneous entity with precise neural (6–9) and peripheral correlates (10), BD needs to be treated according to subtype and for the entire life span (11). Drug treatment of BD is further complicated not only by the side effects that keep patients away from treatment, but also by long-term drug-induced alterations that prompt doctors to stop or switch to other drugs. For example, there is much concern about the long-term nephrotoxicity of lithium (12–14), but other mood stabilizers (MSs) are not devoid of dangerous side effects (15). Hence, drug treatment of BD has to be tailor-cut to patient's individual needs (16).

Different concepts are included in what we mean by mood stabilization. Mood is normally swaying between what is not mania and not depression, something we call euthymia, but is not a flat line. Consequently, an optimal MS should keep the patient within this range. However, hypomania, which is subsyndromal with respect to mania, is not an acceptable state, since it is often linked to BD-II type and is likely to be followed by bipolar depression, which is a clinical state most unpleasant to the patients and their doctors. It is generally accepted that to be called a MS, a drug must relieve at least one phase of BD and not to cause the opposite. However, this simplistic definition would include antidepressant (ADs) and antipsychotic drugs (APs) as well, not causing respectively (hypo)mania or depression, adding much to the confusion. There is much debate about how much ADs trigger manic switches and how some second-generation APs are endowed with antidepressant action and currently indicated by the US Food and Drug Administration (FDA) for depression (for example, lurasidone and brexpiprazole). This prompted Nassir Ghaemi (17) to develop an elaborate concept of MS, proposing that a MS should be conservatively defined as "an agent with efficacy in two of the three phases of bipolar illness (acute depression, acute mania, prophylaxis)". In this definition, prophylaxis is meant as a protection from the occurrence of either manic or depressive episodes. This definition excludes all APs and leaves lithium, carbamazepine, valproate, and lamotrigine. Terence Ketter's proposal many years later (18), retained much of the essence of Ghaemi's proposed definition, by stating "any treatment that is effective in any phase of bipolar disorder (an America-centric approach would be to say FDA-approved for any phase of bipolar disorder) but not active at dopamine receptors (thus excluding antipsychotics)". He should have added directly at *dopamine* receptors, since lithium and other MSs indirectly affect dopaminergic transmission (19–21). Both these definitions are acceptable and the drugs they envisage as MSs are the ones we will here consider. The identification of a neurochemical signature of mood stabilization, like a decreased glutamate-to-gamma aminobutyric acid ratio or genetic markers such as the GAD1 rs1978340 allele A (22), would greatly aid and steer the future pharmacological treatment strategies. However, their adoption in treatment models of BD should await confirmation by future studies (and the identification of other markers as well is to be expected.

The onset of BD during infancy is an extremely rare event. However, in many instances, it develops during adolescence. The

Abbreviations: AAQ, Anger Attacks Questionnaire; AD(s), antidepressant drug(s); AE(s), anticonvulsant(s), antiepileptic(s); AP(s), antipsychotic(s); APT, adjunctive personalized treatment; ARP, aripiprazole; BD, bipolar disorder; -I, type I; -II, type II; BL, baseline; BPRS, Brief Psychiatric Rating Scale; BRMaS, Bech-Rafaelsen Mania Scale; CARS-M, Clinician-Administered Rating Scale for Mania; CBZ, carbamazepine; CGI, Clinical Global Impressions; -S, severity; -I, improvement; CGI-BP, Clinical Global Impressions Overall Scale for Bipolar Disorder; CLZ, clozapine; DB, double-blind; EQ-5D, the quality of life questionnaire in relation to health status "Euroqol"; FAST, Functioning Assessment Short Test; FGA(s), first-generation antipsychotic drug(s); GAF, Global Assessment of Functioning; GAS, Global Assessment Scale; GPT, gabapentin; HAL, haloperidol; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale (-N, item number specifying version); HCs, healthy controls; HDRS, Hamilton Depression Rating Scale; HR, hazard ratio; IDS, Inventory of Depressive Symptomatology; LAM, lamotrigine; LSEQ, Leeds Sleep Evaluation Questionnaire; Li^+, lithium; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MS, mood stabilizer; NOS, not otherwise specified; n.s., not significant; OLZ, olanzapine; OPT, optimized personalized treatment; PANSS, Positive And Negative Syndrome Scale; pts., patients; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, QTP, quetiapine (-XR, extended-release), RISP, risperidone; SABT, schizoaffective-bipolar type; SCZ, schizophrenia spectrum disorders; SGA(s), second-generation antipsychotic drug(s); SUD, substance use disorder; TCAs, tricyclic antidepressants; TOOL, the TOlerability and quality Of Life; TPX, topiramate; TRD, treatment-resistant depression; VPA, valproate; YMRS, Young Mania Rating Scale; yrs, years; ZIPR: ziprasidone; $\bar{x}$, mean; ♂, male; ♀, female; ±, standard deviation; , titrated up to or went from to; ↑, increase(d); ↓, decrease (d), drop.

latter is a period of rapid physiological changes and adaptation, with the brain in continuous maturation. It is accepted that the brain does not conclude its developmental trajectory before the 24th year of life (23). Any action of a drug at this stage might affect further development, hence particular caution is mandatory in facing cases of adolescent BD. Furthermore, the brain in the two genders matures differently, both in normal (24) and BD adolescents (25), thus forcing treating clinicians to personalize their interventions by taking into account multiple factors, including gender, and substance use that could arrest a normal maturational process in the neurobiological interplay between the "inbuilt" underlying disorder and the "acquired" substance use disorder (26). The gender concern comes to the fore when women become pregnant. During this particular phase of life, the hormonal turmoil that occurs during gestation and the post-partum makes the woman vulnerable to psychiatric events, including later first occurrences or recurrences of BD (27, 28). The old age comes with a decay of functioning bodily systems, including the brain, so the clinical expression of BD and the organism's response to drugs are consequently affected. Generally, dose adjustments of the same types of medications are sufficient to deal with BD in the elderly.

Aim of the Review

To identify drug treatment patterns for BD stabilization across different phases of life, we conducted a systematic review with keywords focusing on mood stabilization and bipolar disorder. The studies emerging from database search were subsequently subdivided according to the age range involved or the special condition (pregnancy or postpartum).

METHODS

We conducted our review according to the *P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses (*PRISMA*) statement (29). We search the PubMed database using the following strategy: stabiliz*[ti] OR stabilis*[ti] OR stable[ti] OR stability[ti]) AND mood[ti] AND bipolar. Papers were individually searched for adherence to our inclusion criteria. Retrieved relevant papers, comprising reviews and meta-analyses, were searched in their reference lists for providing additional papers with adequate research data and meeting our inclusion criteria. These were: double blind, placebo or comparator-controlled trials, open-label trials and naturalistic studies investigating the efficacy/effectiveness of drugs given either as monotherapy or add-on medication and belonging to drug classes like MSs, ADs, first generation APs (FGAs), second-generation APs (SGAs), anticonvulsant benzodiazepines (BDZs), or nonconventional mood-stabilizing medications (e.g., allopurinol) in reducing manic, hypomanic, mixed, or depressive symptoms and/or preventing the occurrence of new mood episodes in patients with BD.

Exclusion criteria were: reviews and meta-analyses, animal and *in vitro* studies, unfocused studies, i.e., studies with nonclinical outcomes not reporting efficacy data, editorials and opinion papers, like letters to the editor with no data or comments on other literature, case reports and case series with no reliable statistics, studies not focusing on BD or including disorders other than BD without separately reporting on BD, congress/conference abstracts, studies lacking clinical data, studies focusing on pharmacokinetics, surveys, studies of registries, papers reporting on data originally published by others. When a study was extended and used the same sample on which results were previously reported, we eliminated the first report and kept the paper with the larger sample, provided that quality of reporting was maintained. We accurately avoided to include studies referring to the same patient sample.

Inclusion and exclusion were based on consensus among all authors; unanimity was required for both and was achieved through Delphi rounds. Two rounds were sufficient to reach complete agreement among authors.

RESULTS

Our search produced 509 records on January 25, 2020. Authors identified 3 duplicates, which were excluded; hence, the pooled records amounted to 506. Excluded were: 158 reviews, 72 animal studies, 62 unfocused studies, 60 opinion/editorial papers, 28 case reports/case series, 28 studies with inadequate design, 22 *in vitro* (nonanimal) studies, 5 studies on mixed samples which did not provide data for subgroups affected by BD (identified as lumping), 4 congress/conference abstracts without complete data, 3 studies not focusing on BD samples, identified as no BD, 2 studies lacking clinical data, 1 study on pharmacokinetics, 1 survey, 1 registry study, 1 study which reported data originally published by others (sample overlap). Therefore, the final number of studies included in this review was 58. The results of our search is shown as a *PRISMA* flowchart in **Figure 1** with the reasons of exclusion. Detailed, study per study information about inclusion/exclusion is provided in the supplement. The search of reference lists of reviews yielded no further articles.

Included studies are summarized in **Table 1**. They spanned from September 1983 to July 6, 2019, while the complete output spanned from April 1970 to December 19, 2019. We split our included records as childhood and adolescence (*N*=3), adulthood (*N*=52), old age (*N*=2), and pregnancy/perinatal period (*N*=1). One study was conducted on both elderly and adult patients. Since all nonadult trials were few, we applied a further distinction on studies of adults, subdivided into acute phase (*N*=31), single drug (*N*=3), add-on (*N*=25) or mixed (*N*=3), and long-term with survival curves (Kaplan-Meier) (*N*=10). All articles were in English, in spite of the fact that non-English language was not an exclusionary criterion.

DISCUSSION

Our aim in writing this review was to clarify which drug treatments achieve stabilization in the various phases of BD and across which age ranges or physiological conditions, like

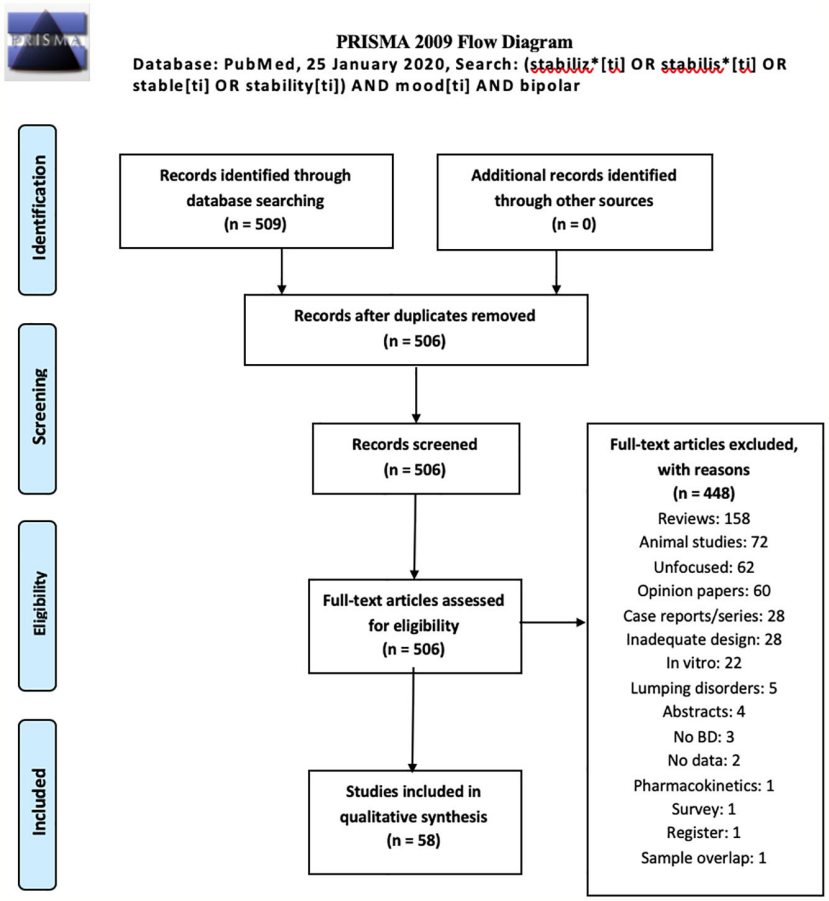


FIGURE 1 | *PRISMA* flowchart of our review's results (30).

pregnancy and motherhood. Ideally, drug treatment strategies should have been tested phase-specifically in each age; however, studies were not sufficiently numerous for the childhood, older age and pregnancy, so the major focus will be on adulthood. Furthermore, rather than stabilization, the focus of most studies was on symptom improvement, so a reduction in depressive symptoms during the depressive phase and the reduction of excitement symptoms during manic/hypomanic phases are taken *per se* as stabilization, which *sensu strictu* are not.

Adulthood

In this review, most results regarded adult patients in various phases of their disorder, so we will expose our findings according to the phase and the type of pharmacological treatment employed.

Manic/Hypomanic/Mixed

In a multicenter naturalistic study, Perugi et al. (84) investigated rates of remission and improvement in mood symptoms and functioning in manic patients treated with MSs and/or APs: Remission rates were 82% in 4 weeks, with Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Bipolar (CGI-BP) mania scores rapidly decreasing. However, the authors did not identify any factors that were associated with remission. Although the extent of the occurrence of mixed states in BD is debated, it is estimated to be around 30% (89). In these cases, treatment should comprise judicious polytherapy (90).

Add-on SGAs

Risperidone. Acute treatment with add-on risperidone to MS (lithium [Li^+], valproate and carbamazepine) has been investigated in five studies, which include one naturalistic (39), two placebo-controlled (42, 47), and two-open label studies (36, 51). Add-on risperidone (4 mg/day) has proven to be superior to placebo in decreasing manic/mixed symptoms as shown by greater reduction of YMRS and Clinical Global Impressions (CGI) scores. In two separate open-label studies, add-on risperidone (3-4 mg/day) showed similar rates of response after 4 and 6 weeks (74% and 70% respectively), while euthymia after 6 months was present in 73% of patients. Add-on risperidone (2-6 mg/day) to MS failed to show superior antimanic effects than add-on haloperidol (range: 4-12 mg/day) in one study (42), whereas in another study of inpatients, it showed to be superior to add-on SGAs in reducing mania at discharge (39). In the same

TABLE 1 | Summary of included studies.

Study	Population	Design	Results	Conclusions
31	17 euthymic BD-I on Li+ × 35±37 months (7 ♂; 10 ♀) $\bar{x}$=37±10 *vs*. 21 HCs (7 ♂; 14 ♀) $\bar{x}$ =30±8 (the latter were significantly younger, p<0.05)	Self-rated mood stability of pts. with BD and HCs with VAMS × 11 days	Patients on Li^+ did not differ from HCs on VAMS ratings, but rated themselves as less swinging than HCs (6.9±4 *vs*. 12.5±6; p<0.01); two patients withdrawn from Li + developed a manic episode; another did not, but developed mood instability	Li^+ confers mood stabilization independently from age or gender
32	120 BDI, aged >60 ($\bar{x}$=40.3±15.3; 52 ♂ and 68 ♀). Two groups: manic (N=50); mixed (N=70), further divided in those who have received Li^+, AEs, or both	Naturalistic, retrospective (length of hospital stay). Outcome measures: between-group differences; Remission criteria: CGI-I score ≥2	Serum VPA levels were higher in mixed (84.7 ± 13.9) than manic (64.6 ± 12.8) group. In mixed, pts. receiving AE+Li^+ have a slower remission than those receiving Li^+ alone or AE alone. Many pts. on Li^++AE had the AE added after Li^+ proved ineffective. After adding AE to Li^+, they achieved remission in 2-3 weeks. In the whole pt. group, weeks needed to achieve adequate MS serum level was a predictor of remission	Effectiveness of Li^+ and AEs in acute treatment of mixed or pure mania are similar. Time course to remission seems to be influenced by the speed with which patients achieve a therapeutic serum MS levels
33	72 BD inpts. aged >60 (mean age 67.19 ± 5.34); 27 ♂ and 45 ♀	Retrospective chart review; Pts. were maintained on MS monotherapy with Li^+ (41), CBZ (11), or VPA (20) during hospitalization; Outcome measures: length of treatment and change in GAF scores	Length of hospital stay was 27.5±15.4 days for pts. on CBZ, 22.1±11.2 days for pts. on Li+, and 24.8±13.5 days for pts. on VPA. ↑GAF 28.8±11.8 for pts. on CBZ, 29.9±15.8 for pts. on Li^+, and 35.2±10.9 for pts. on VPA	No significant differences in outcome measures of acutely ill geriatric pts. with BD who were treated with Li^+, VPA, or CBZ alone
34	10 BD-I, mixed, aged 37-72 ($\bar{x}$ =50.4±2.8; 9 ♂; 1 ♀)	Open, ad- on gabapentin 900 2700 mg/day × 4 weeks; outcome measures: reduction of HDRS and BRMaS	Add on gabapentin ↓ HDRS (15 8) and BRMaS scores (8 1) at week 1. BRMaS scores stabilized through week 4; HDRS scores continued to ↓ (8 4)	Gabapentin potentiates the effect of the other mood stabilizers in subjects with BD and a mixed state
35	27 BD, depressed, aged 37-72 ($\bar{x}$=41 ±12; 9 ♂; 18 ♀, 11 BD-I, 16 BD-II). Two consecutive HDRS>16	DB, add-on paroxetine (36 mg/ day) or additional MS (Li^+, 1300 mg/day; VPA 1200 mg/day) Li^+, in pts. already treated with an MS (Li^+ or VPA, same dosages as above) × 6 weeks. Outcome measures: HDRS; YMRS; GAF scores	After 6 weeks, significant ↓ in HDRS scores in both groups, with no differences between groups. YMRS unchanged in both groups	Both adding another MS and adding an AD are effective in treating BD depression
36	31 adults with DSM-IV BD, last episode mixed	Open add-on risperidone $\bar{x}$=4.2 mg/day on ongoing mood stabilizer × 6 months, weekly assessed with YMRS, CGI, PANSS, and HDRS. Response criteria: YMRS ≥50%↓from BL AND CGI ≥2↓from BL	26 completers (84%); 74% responders at week 4; significant improvement on all scales, from week 1 onward on YMRS and HDRS, and from week 4 on CGI and PANSS; 73% asymptomatic at 6 months	Risperidone effective as add-on, but results need replication
37	158 depressed BD-I inpts. ($\bar{x}$ age=52.6±15; 50♂; 108♀)	Retrospective, naturalistic, evaluation of the impact of AD treatment on switch incidence from depression to mania/ hypomania	25% switches; TCAs associated with higher risk of switching, reduced risk if ADs +MS	Better add AD only when MS is established
38	11 BD, aged 19 – 46 ($\bar{x}$=29.4±10.7;	Open, add-on vitamin and mineral capsules (36 supplements) ×≥6 weeks (range:	As compared with the first assessment, at last assessment, HDRS decrement was 55% and YMRS decrement was 66%. Rates of response were 87.5%. Number of standard medications/pt ↓ from 2.7±2.0 to 1.0±1.1	Vitamin and mineral capsules have beneficial

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
	10♂; 1♀; 6 BD-I, 4 BD-II)	6-21 weeks). Outcome measures: reduction in HDRS, YMRS, and BPRS scores; Response criteria (≥20% improvement on all scales)		psychotropic effects
39	155, BDI, manic; 4 groups: MS + atypical AP (RISP or OLZ, N=69, $\bar{x}$ =39.72 ± 14.50 11 BD, aged 19 – 46 ($\bar{x}$=29.4±10.7; 32♂; 37♀); MS + typical AP (N=69, $\bar{x}$=40.86 ± 16.11, 37♂; 32♀); MS + combination of typical and atypical (first typical than switch with atypical, N= 17, 41.06 ± 18.08, 8♂; 9♀)	Naturalistic, retrospective; outcome measures: length of stay, CGI improvement	No differences in length of stay were found. At discharge, subjects with MS + atypical AP and subjects with MS + combination between typical and atypical AP showed smaller CGI improvement scores (1.59±.58; 1.56±.63 respectively) than those with MS + typical AP (2.04±.73). Same results when subgroups showing psychotic features were selected. Subgroup of subjects treated with MS + RISP showed greater CGI score improvement than those treated with MS + typical AP	SGAs, in particular RISP, might be more effective than typical APs combined with MS, to treat manic episodes. If pts. require initial treatment with MS+FGA, they might have a better outcome if they switch to an SGA after the 1st week of treatment
40	64 depressive pts. (IDS≥16) while on mood stabilizers, aged 22.5-75,3 yrs ($\bar{x}$= 44.8±11.8; 38 ♂; 26 ♀; 43 BD-I, 19 BD-II; 1 BD NOS, 1 SABT)	5-site DB; randomization to add-on bupropion 100 450 mg/day, sertraline 50 200 mg/day, or venlafaxine 75 375 mg/day, on ongoii8yhoy po60nk0long mood stabilizers × 10 weeks; nonresponders, rerandomized to other AD × 10 weeks, if still nonresponders, to the third; 1-year continuation on what works; Assessment with CGI-BP, response criterion, score 1 or 2	21 nonresponders rerandomized, 10 of them further rerandomized; a total of 95 acute-phase treatments were available for outcome assessment. 35 pts. exposed to acute phase treatment were responding (37%). During the 95 acute AD-exposure phases, there were 13 (14%) switches to mania/hypomania	Some depressions subsided and some switched to mania, but conclusive considerations could not be made due to the peculiarities of the design. Furthermore, final results were not available and 1 site could not administer bupropion
41	19 depressed outpts. BD-II ($\bar{x}$ age=29; 13 ♂; 6 ♀)	12-weeks open, divalproex sodium single dose 250 mg increased by 250 mg every 4 days until symptom relief in medication naïve *vs*. MS naïve; response criterion, ≥50% ↓ in HDRS scores	63% responders; higher response in medication naïve group	Results support divalproex sodium monotherapy in BD-II depression
42	156 BD-I, manic/mixed, aged 18-65 yrs. Three groups: RISP+MS (N=52; median=41 yrs; 26 ♂; 26 ♀); HAL+MS (N=53; median=44 yrs; 30 ♂; 23 ♀); placebo + MS (N=51; median=43 yrs; 24 ♂; 27 ♀)	3-week DB, placebo-controlled trial of RISP (range 2-6 mg)+MS (VPA: 65.4±27.1 μg/ml; Li^+: 0.7 ±0.3 meq/l) and HAL (4-12 mg) +MS (VPA: 76.2±25.6; Li^+: 0.7 ±0.2 meq/l). Outcome measures: changes in YMRS scores, % of pts. scoring 1 on the CGI-I ("very much improved")	RISP+MS and HAL+MS lowered YMRS scores more than placebo+MS (-14.3 *vs*. -13.4 *vs*. -8.2, respectively). RISP+MS and HAL+MS obtained higher rates of "very much improved" on the CGI-I than placebo+MS (50% *vs*. 53% *vs*. 30%, respectively). No between-group differences in psychotic *vs*. nonpsychotic and manic *vs*. mixed subpopulations. The HAL+MS group worsened more than placebo +MS scores on the Extrapyramidal Symptom Rating Scale from BL to endpoint (2 *vs*. -0.1, respectively, and maximum score 1.9 *vs*. 5.4)	Both HAL and RISP are effective adjunctive treatments for manic and mixed states. RISP has a safer profile
43	115 BD-I, manic or mixed, aged 18-70 yrs ($\bar{x}$=39yrs; 60♂; 58♀)	DB, placebo-controlled trial of OLZ (5-20 mg/day)+MS (Li^+, VPA). Each group further divided in MS nonresponders *vs*. other (responders or those who were	YMRS ↓ more in the OLZ+MS than in the OLZ+placebo group. Previous response to VPA or Li^+ does not affect results (YMRS ↓ in OLZ+VPA responders *vs*. OLZ +VPA-others: -14.7 *vs*. -14.8; YMRS ↓ in placebo+VPA responders *vs*. placebo +VPA-others: -8.8 *vs*. -8.0; YMRS ↓ in OLZ+Li^+ responders *vs*. OLZ+Li^+-others: -15.9 *vs*. -13.9; YMRS ↓ in placebo+ Li^+-responders *vs*. placebo+Li^+-others: -6.5	OLZ was superior to placebo in treating mania. This secondary

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
		not exposed to MSs before randomization (MS-naïve). Outcome measures: YMRS score ↓, percentage of remission	*vs*. -8.9; proportion of pts. who remitted in OLZ+VPA responders *vs*. OLZ+VPA-others: 61.9% *vs*. 60.6%; proportion of pts. who remitted in placebo+VPA responders *vs*. placebo+VPA-others: 40.0% *vs*. 34.8%; proportion of pts. who remitted in OLZ+Li^+ responders *vs*. OLZ+Li^+-others: 66.7% *vs*. 56.7%; YMRS score ↓ in placebo+Li^+-responders *vs*. placebo+Li^+-others: 33.3% *vs*. 36.8%	analysis suggests that OLZ monotherapy is similarly effective for pts. whether or not they have previously failed to respond to another MS for mania
44	36 BD depressive, aged 18-70. Two groups: TPX+MS +SGAs (*N*=18; $\bar{x}$ =39 yrs; 11 ♂; 7 ♀;10 BD-I, 8 BD-II); and bupropion+MS +SGAs (*N*=18; $\bar{x}$ =43 yrs; 10 ♂; 8 ♀; 9 BD-I, 9 BD-II)	8-week, single blind add-on therapy with TPX (50-100 mg/day), or bupropion (100-400 mg/day) to MS (Li^+: 980.0 ±388.3 mg; VPA: 1106.25 ±400.36 mg) and SGAs. Outcome measures: response rates, changes in YMRS, HDRS, and CGI-I	After 8 weeks, TPX+MS+SGA and bupropion+MS+SGA showed similar response rates (56% *vs*. 59%, respectively). Time to response ranged from 2 to 4 weeks. Both groups showed similar rates of ↓ from BL on the HDRS (20.5 to 10; 20 to 9.5 respectively), CGI-I, and YMRS (7 to 2; 8 to 2 respectively)	Both adjunctive TPX and bupropion were associated with reductions in depressive symptoms
45	60 BD, depressive; two groups: Paroxetine+MS (N=30; $\bar{x}$=47.1 ±15.2 yrs; 11 ♂; 19 ♀;23 BD-I, 7 BD-II); Venlafaxine+MS (N=30; $\bar{x}$=45.5 ±13.7 yrs; 9 ♂; 21 ♀;21 BD-I, 9 BD-II); HDRS>17	6-week RCT of add-on paroxetine ($\bar{x}$=32.3mg ± 11.2 or venlafaxine ($\bar{x}$=32.3mg ± 11.2) to MS (Li, 0.7 mg/L; VPA, 50 µg/ml; CBZ, 4µg/ml). Outcome measures: response, remission, switch rates.	After 6 weeks: Groups did not differ in HDRS ↓ (paroxetine+MS: -6.9; venlafaxine+MS: -9.0); similar proportions of responders (paroxetine+MS: 50%; venlafaxine+MS: 59%); similar remission rates (paroxetine+MS: 37%; venlafaxine+MS: 41%); similar switch rates (paroxetine+MS: 3%; venlafaxine+MS: 13%)	Both venlafaxine and paroxetine are effective add-on treatments to MSs for bipolar depression. Switch rates, especially during treatment with venlafaxine, raise some concerns
46	318 BD aged 24-89 ($\bar{x}$=53.3±15.1; 41% ♂; 59% ♀)	Retrospective, naturalistic; Evaluation of anxiety comorbidity and response to MS (Li^+ or AEs); remission criterion, no mood episodes for 2 years	24% with anxiety comorbidity; anxiety comorbidity associated with poorer response to AEs. No differences in response to Li^+	Anxiety comorbidity ↓response to AEs
47	150 BDI, manic or mixed, aged 19 – 65; two groups (MS + RISP, N=75, median=37y, 32♂; 43♀); MS + Placebo, N=75, median 42y, 31♂; 44♀)); median:37y for MS + RISP group, 42y for MS + placebo group; 32♂; 43♀ for MS + RISP group, 31♂; 44♀ for MS + placebo group	Randomized, double blind, placebo controlled. MS + RISP (4mg/day) or MS + placebo x 3 weeks. Outcome measures: changes in YMRS at day 8 and endpoint (last available observation), % subjects showing 50% YMRS improvement, time to response (30% YMRS score reduction), CGI 1/2	Compared to BL, ↓ YMRS was significantly greater in the MS + RISP group (-10.2 ±1.1) than MS + Placebo group (-6.7±1.0) at week 1. At endpoint, 59% of pts. in the MS+ RISP group showed ≥50% ↓YMRS scores, compared with 41% in the MS + placebo group. 48% at week 1 and 61% at endpoint of the MS + RISP group scored 1 or 2 on the CGI, compared with 31% at week 1 and 43% at endpoint in the placebo group. Compared to BL, at week 1 and endpoint, BPRS ↓ was significantly greater in the MS+RISP group (-7.5±.09 and -10.1±1.1, respectively) than in the MS+placebo group (-3.8± 0.8 and -4.8± 1.1 respectively). At endpoint, the MS+RISP group had significantly greater improvement in the hostility and thought disturbance subscales of the BPRS than did the MS+placebo group	RISP, in association with MS, is more efficacious than placebo in the improvement in manic symptoms. Improvement in manic symptom is also rapid
48	BD aged 18-65 with at least one manic episode requiring hospitalization; DB study: 156 BD (80 ♂; 76 ♀); Open: 85 BD (39 ♂; 46 ♀)	3-week DB: MS+RISP, MS +placebo or MS+haloperidol; then 10-week open-label, add-on RISP; remission criterion, YMRS≤12	Greater remission in RISP or haloperidol group compared to placebo; 79% of pts. in remission after 10-week open-label treatment with RISP	RISP+MS combination is efficacious in manic episodes requiring hospitalization

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
49	22 BD with TRD. Two groups: pramipexole+MS (N=12; $\bar{x}$=40.9; ±8.2%; 4♂; 8♀; 9 BD-I, 3BD-II; placebo+MS (N=10; $\bar{x}$=43.3±6.2; 7♂; 3♀; 6BD-I, 4BD-II); YMRS<12; HDRS >18	6-week, double-blind, placebo-controlled, single center trial of add-on pramipexole (1.0-2.5 mg/day) to MS (Li^+ 1137.5 ±381.5 mg/day; VPA 916.7 ±129.1 mg/day; CBZ 400.0 ± 282.8 mg/day; LAM 283.3 ± 144.3 mg/day; GPT 450±212.1 mg/day). Outcome measures: ≥↓ 50% in HDRS scores; changes in CGI-S.	After 6 weeks, 67% of pts. on pramipexole+MS showed ≥↓ 50% on HDRS compared to 20% in the placebo+MS group. Mean change from baseline in HDRS was greater in pts. taking pramipexole+MS (48.0%±33.1) than for those taking placebo+MS (21.4%±36.3). Pramipexole+MS showed lower CGI-S (2.7±1.4) than placebo+MS (4.4±1.3). After 6 weeks, pramipexole+MS showed greater CGI-S score ↓ (-2.4±1.8) than placebo (-0.30±1.3)	Pramipexole is effective for TRD in BD.
50	45 BD, depressed, aged 18-75 yrs ($\bar{x}$ =42.2±11.5; 30♂; 15♀; 30 BD-II; 15 BD-II); HDRS ≥10; YMRS≤12; GAF≤70	Open-label, add-on citalopram to MS (Li^+, VPA, or CBZ). 8-week acute phase and for those who responded, 16 weeks continuation phase. Outcome measures: changes in YMRS and HDRS, occurrence of anger attacks (using modified AAQ) at 8 weeks; survival analyses at 8 and 16 weeks	At BL 38.6% have anger attacks, which dropped to 14.6% after 8 weeks. 73.3% of those having anger attacks at baseline did not have them after 8 weeks, whereas 8.7% of those who did not have anger attacks at baseline reported anger attacks after 8 weeks. Treatment response and rates of response to depression were unrelated. Survival analyses were similar between groups. Trait anger predicts anger attacks at BL and at week 8	Anger attacks in BD respond favorably to add-on citalopram and are better predicted by trait anger than hypomanic or depressive symptoms
51	99 BD-I aged 18-70, in remission from a manic/ mixed episode; two groups: OLZ+MS (N=51; $\bar{x}$=43.5; 52.9%♂; 46.1%♀); Placebo+MS (N=48; $\bar{x}$=39.0; 43.8% ♂; 55.2% ♀); DSM-IV A and B criteria severity for current manic episode ≤3, no more than two B criteria, DSM-IV A criteria severity for current depression ≤3, no more than three A criteria	Double-masked placebo-controlled trial of add-on OLZ (5-20 mg) to MS (Li^+, 954.6-1174.7 mg/day or VPA, 1060.4-1512 mg/day). Outcome measures: a) syndromic relapse: occurrence of DSM-IV manic, depressive, or mixed episode; b) symptomatic relapse: HDRS or YMRS≥15	Time to symptomatic relapse into either mania or depression was significantly longer for the combination group compared with the monotherapy group (163 days for OLZ+MS; 42 days for Placebo+MS). Women and white patients with OLZ+MS showed longer times to symptomatic relapse than pts with Placebo+MS (84 *vs*. 67 days, respectively)	OLZ+MS reduced relapse in BD episodes
52	909 BDI, manic or hypomanic, aged 16-60 ($\bar{x}$=35.1 ±13.7; 8♂; 10♀). YMRS>20 (for manics), YMRS>7 (for hypomanics)	Open label, add-on RISP to MS (Li^+, VPA, CBZ, TPX), × 6 weeks; Outcome measures: reduction in YMRS, SARS, and CGI; response criterion (>50% reduction YMRS)	After 6 weeks, reduction of scores on the YMRS (from 32.9 ± 10.8 to 9.5 ±8.4) and CGI-severity (from 4.8 ± 1.1 to 2.1 ±.8) was significant. Response rates at week 6 were 70.7%. A higher reduction in the YMRS and CGI scores was found in the subgroup with psychotic features (24.2 ± 11.9; 2.9 ± 1.4 respectively) compared to the subgroup without psychotic features (22.6 ± 11.6; 2.5 ± 1.5 respectively)	RISP is effective for BD manic/ hypomanic episode treatment
53	18 BDI, manic or hypomanic ($\bar{x}$=35.1 ± 13.7; 8♂; 10♀)	Open label, add-on QTP (mean 267.9±105.4 mg/day) × 4 weeks. Outcome measures: ↓ in YMRS, HDRS, BPRS and CGI; response criterion (>50% ↓ on the YMRS)	After 4 weeks, YMRS ↓ from 28.2 ± 7.6 to 9.3 ± 5.7; HDRS ↓ from 2.7 ± 2.4 to .9 ± 1; BPRS ↓ from 32.8 ± 11.2 to 15.8 ± 11.6; CGI ↓ from 5±0.8 to 2.3 ± .7. Response rates at week 4 were 72.2%	Add-on QTP is an effective treatment for manic/ hypomanic episode of BD
54	59 UP-MDD, but scoring high on Angst's hypomania; good responder group: $\bar{x}$ age=47; 17% ♂; 83% ♀; poor responder group: $\bar{x}$ age=52; 19% ♂; 81% ♀	Retrospective, naturalistic, comparison between good and poor responders to MS augmentation on ADs; remission criterion, clinical judgment of treating psychiatrists	30% good responders, 70% poor responders; greater delay in prescribing MS augmentation and lower rate of MS in poor responders. No differences in hypomania and temperaments. Higher suicidal risk and agitation in poor responders	MS augmentation should be instituted without delay in patients with MDD meeting Angst's criteria for hypomania

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
55	479 BD aged 18-65 (215 ♂; 264 ♀)	Retrospective, naturalistic; BD discharged on MS, MS+FGA, MS+SGA; relapse criterion, rate and time to rehospitalization	No differences between groups in rehospitalization time and rate (23% BD discharged on MS, 27% MS+FGA, 25% MS+SGA)	Augmentation with antipsychotics does not improve mood stability
56	287 BD-I manic or mixed; aged 18-70 yrs; two groups: TPX+MS ($\bar{x}$=41.0 ±12.2; 58♂; 85♀); Placebo+MS ($\bar{x}$ =39.0±11.9; 67♂; 77♀). YMRS ≥18	12-week, DB, placebo controlled, add-on TPX (50-400 mg/day) to MS (Li^+, $\bar{x}$ serum level 0.7 mEq/l, or VPA, $\bar{x}$ serum level 70 µg/ml) and AP. Outcome measures: score change on YMRS, MADRS, CGI-S, BPRS, GAS	↓ YMRS scores in both TPX (-10.1±8.7) and placebo (-9.6±8.2) groups, with no between-group differences. CGI, BPRS, MADRS and GAS improved, without between-group differences	Add-on treatment with TPX is not superior to placebo in ↓ manic/mixed episodes
57	159 BD, depressive ($\bar{x}$=41.6±12.2; 83♂; 76♀; 115 BD-I, 42 BD-II). 228 acute AD trials, 111 AD continuation phase trials	Randomized, add-on bupropion ($\bar{x}$=286±132 mg/day), venlafaxine ($\bar{x}$=195±112 mg/day), and sertraline (286±132 mg/day) to MS (Li^+, AE, AP). Acute phase: 10 weeks, those improved entered continuation phase (1 yr). If patients did not respond acutely to initial AD trial, they were randomly assigned to another AD. Outcome measures: response (CGI-BP=1 or 2; occurrence of 1) brief hypomania; 2) recurrent brief hypomania; 3) switch to full hypomania; 4) switch to mania	Acute phase: 48.7% of the trials reached response, that dropped to 32.5% after excluding those who had a switch. Switch rate to full (hypo)mania was 19.3%. 111 subjects reached sufficient response to enter the continuation phase. Continuation phase:67.8% trials showed AD response, but response rate in absence of a switch was 42.5%. 36.8% of trials switched to (hypo)mania. AD switch rates were not significantly different among the three ADs. In both acute and continuation phases, the threshold/subthreshold switch ratio was lowest with bupropion (acute: 0.85; continuation: 1.2), intermediate with sertraline (1.6 and 1.65, respectively) and higher with venlafaxine (3.6 and 3.75, respectively)	AD augmentation is not likely to yield a high rate of sustained AD response without a switch throughout both the acute and continuation treatment phases. Venlafaxine was associated with the highest relative risk of switch and bupropion with the lowest
58	10 drug-naïve BD-II aged 18-65 with monthly mood episodes	Randomized, DB, escitalopram 10 mg vs placebo for 9 months	Reduction in depression severity, percentage of impaired days in the escitalopram group	Results support usefulness of SSRIs in BD-II treatment
59	1127 BD-I after a recent manic or depressive episode (456 ♂; 671 ♀)	Open, LAM 100-200 mg/day +sedative/hypnotics vs LAM 100-200 mg/day+other psychotropics; stabilisation criterion, CGI≤3 for ≥4 weeks	Higher stabilization rates for LAM 100-200 mg/day+sedative/hypnotics vs other psychotropics	Adjunctive therapy with sedative/hypnotics may be useful in BD acute symptom control
60	55 BD-I ($\bar{x}$ age=35 ±12.8, 34 ♂; 21 ♀)	Retrospective, naturalistic, SGA monotherapy *vs*. SGAs+MS for 6 months; relapse criterion, recurrence of mood episode	Clinical improvement in both groups, no differences in relapse	SGAs can be useful in the long-term management of BD-I
61	10 BD-I outpts. (11–17 years) using a single MS and/or SGA, who had shown weight gain >5% of BL weight	Open. 11-week; medication switched to TPX during the first 4 weeks until 150 mg/day; YMRS main outcome to measure treatment response	Significant ↓in both YMRS score (F=10.21; p<0.01) and weight (F=8.04; p<0.01). $\bar{x}$ weight loss=2.62 kg at endpoint. 6/7 completers (85%) did not show symptom worsening on the YMRS after 11 weeks. Significant BMI ↓ from BL to endpoint (p=0.017). No increase in adverse events	TPX seems to have antimanic effects during the treatment maintenance phase associated with weight reductions
62	89 pregnant women ($\bar{x}$ age 32.7 years±5.4) BD-I (N=61) or BD-II (N=28)	Prospective observational study; Two groups based on MS status: 1) use of at least one MS at conception and continued ≥12 weeks of pregnancy; 2) MS	During pregnancy, a total of 70.8% (63/89) of women experienced ≥1 episode of illness. Recurrence risk was 2.3 times greater after discontinuation of MS (53/62, 85.5%) than with continued treatment (10/27, 37.0%). Discontinuers spent >40% of pregnancy in an illness episode, *vs*. 8.8% of pregnancy of women continuing on MS. Median time to first recurrence was 9.0 (95% CI=8.0–13.0) weeks for	Discontinuation during pregnancy of MS, particularly if abruptly,

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
		discontinuation during 6 months before conception to 12 weeks of gestation. Follow up each trimester and at 6, 12, 24, and 52 weeks postpartum to ascertain recurrence of mania, hypomania (lasting ≥1 week), major depression, or a mixed state, and current treatments	discontinuers and >40 weeks (95% CI indeterminate) for continuers. Abrupt or rapid discontinuers (1–14 days; N=35) had 50% risk of recurrence within 2.0 (95% CI=1.0–6.0) weeks, gradual discontinuers (≥15 days, N=27) required 22.0 (95% CI=16.0–38.0) weeks to reach 50% recurrence risk (χ^2= 25.9, df=1, p<0.0001). Excess of depressive-dysphoric polarity *vs*. manic-hypomanic episodes after discontinuation of MS (55/62 recurrences, 88.7%, versus 12/62, 19.3%, or 4.6-fold) compared to continued treatment (5/27, 18.5%, *vs.* 9/27, 33.3%, or 1.8-fold). Treatment-related risk factors, besides MS discontinuation, included: 1) polytherapy with two or more psychotropics (RR=2.3, p<0.001); 2) use of AD (RR=2.0, p<0.001); 3) primary MS other than Li^+ (RR=1.6, p<0.001); 4) previous switch from depression to mania/hypomania during past AD treatment (RR=1.5, p<0.009); 5) abrupt MS discontinuation (RR=1.4, p=0.008). AD use and treatment discontinuation each operated independently as risk factors, even after adjusting for other indices of illness severity	carries a high risk for new morbidity in women with BD, especially for early depressive and dysphoric states. However, this risk is reduced markedly by continued MS treatment
63	232, BD, euthymic, aged 22-79 ($\bar{x}$ =52.2 ± 9.7; 81 ♂; 158 ♀, BD-I N=91; BD-II N=141). 6 groups: QTP monotherapy (N=41); Li^+ monotherapy (N=39); VPA monotherapy (N=73); LAM monotherapy (N=31); QTP + Li^+ (N=25); QTP + VPA (N=23)	Naturalistic, 4-yr follow-up. Mean QTP doses: monotherapy, 214 mg/day; QTP+Li^+, 223.5 mg/day; QTP+VPA, 237.4 mg/day; LAM 72.2 mg/day. Mean plasma levels for Li^+ or VPA, 0.7 mEq/l ± 0.2 for Li^+ monotherapy, 0.7 mEq/l ± 0.1 for Li^++QTP, 52.1±17.2 ng/ml for VPA monotherapy, and 60.5 ng/ml ± 17.9 SD for VPA+QTP. Outcome measures: duration of euthymia/proportion of pts with no mood recurrences	After 4 years, pts. with Li^++QTP and Li^++VPA showed higher proportion of no mood episode (80% and 78.3%, respectively) than those with QTP alone (29.3%), Li^+ alone (46.2%) and LAM alone (41.9%). Pts. with Li^++QTP and Li^++VPA did not relapse for longer times (41.4 and 39.2 months, respectively) than pts. on QTP (33.1 months) and VPA (30.1 months). Only pts. with Li^++QTP did not relapse for longer times than Li^+ alone (33.1 months). Pts. with Li^+ were superior to those with QTP in proportion of subjects without relapses and time spent without relapse	QTP as either monotherapy or combination therapy (with Li^+ or VPA) has been found to be effective in preventing both major and sub-threshold depressive episodes
64	108 BD, euthymic, drug-free, ($\bar{x}$=52.2 ± 9.7; 43♂; 65 ♀, BD-I N=39; BD-II N=69). 3 groups: BD with early onset (<30y), middle onset (>30 and <45y), and late onset (>45y)	Naturalistic, 24-month follow-up. Drug free pts. received SGAs, Li^+ or VPA. Outcome measure: relapse rates	After 24 months, $\bar{x}$ depressive relapses were less in the early-onset group ($\bar{x}$=0.66) than middle- ($\bar{x}$=1.37) and late-onset ($\bar{x}$=1.26)	MS treatment seemed to be more effective in preventing depressive episodes in early-onset BD pts. compared to middle- and late-onset pts. Middle- and late-onset BD pts. were similar
65	966 BD-I (open-label phase), with a recent depressive episode, aged ≥18 yrs.; 463 BD-I (randomization phase), aged ≥18 yrs.	First phase: open-label trial on LAM monotherapy (200-400 mg/day) for 16 weeks. Second phase: double-blind placebo-controlled trial on LAM monotherapy (200-400 mg/day). Outcome measures: occurrence of an intervention for manic/hypomanic/mixed symptoms, YMRS score ≥ 4, YMRS score ≥ 8, and YMRS score ≥ 14, survival analyses	Open-label phase: Compared to BL, YMRS ↑ by ≥14 points in 10% of pts., ↑ by ≥8 points in 20% of pts., by ≥4 points in 35% of pts. YMRS ↑ predicted by number of manic/hypomanic/mixed episodes in the preceding year. Randomized phase: no differences in % or HR of event occurrence between groups, LAM had consistently higher estimates of survival than placebo across all 4 thresholds of mania MRS scores at screening, and presence of ≥3 manic/hypomanic/mixed episodes in the preceding year significantly increased HR of reaching an event	LAM showed similar rates of manic relapse to placebo. During maintenance treatment, the likelihood of emergent manic or hypomanic features appears driven more by the pre-existing or historical burden of mania features, rather than the use of LAM
66	109 BD-II, depressive, aged 18-65 yrs ($\bar{x}$ =40.3	Naturalistic, follow up (52 weeks) of add-on LAM (145.5±113.2 mg/day) to MS (Li^+ or VPA) and	CGI-BP-S depression score ↓after 4 weeks of LAM add-on. Scores on the CGI-BP-S ↓ by about 1.8 points in the first 12 weeks and then remained stable. 49% completers. Completers and drop-outs differed for number of psychiatric	LAM is an effective add-on treatment for

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
	±11.5; 27♂; 82♀). CGI-BP-S depression score≥3 for >12 weeks on maintenance with Li^+ or VPA+other medications (ADs and APs allowed)	APs (QTP, OLZ, ZIPR). Outcome measures: change in CGI-BP-S depression score	hospitalizations (0.7±0.9 vs. 1.4±2.2) and history of suicide attempts (11.4% *vs*. 30.8%, respectively)	bipolar depression. Number of prior hospitalizations for depression and history of attempted suicide may be associated with poor response to adjunctive LAM treatment
67	23 adult BD inpts. (12 ♂; 11 ♀; 17 BD-I, 6 BD-II), HDRS ≥20	Randomized, DB, MS +citalopram 40 mg/day +ARP 10-30mg/day *vs*. MS +citalopram 40 mg/day+placebo for 6 weeks; remission criterion, HDRS ≤9	No differences between the two groups	Augmentation with ARP does not improve mood stability
68	50 BD, depressive pts., aged 18-70 ($\bar{x}$ =439.7±10.3; 23 ♂; 31 ♀; 20 BD-I, 34 BD-II); MADRS>20 and YMRS<12	6 week – double-blind, placebo-controlled trial of VPA monotherapy (mean 1606±44 mg/day, range 1000–2000 mg/day). Outcome measure: improvement on MADRS, YMRS, CGI-BP, HARS. % pts. achieving response (≥50% ↓ in MADRS from BL)	VPA group improved more on the MADRS compared with placebo group at weeks 3, 4, 5, and 6 (mean change of MADRS total score for VPA over placebo=4.32). This is mainly driven by differences in the BDI subgroup. VPA group responded for 38.1% and remitted for 23.1%, placebo group improved and remitted by 10.7%	VPA is effective in treating bipolar depression in the BD-I subset
69	139 BD-I with manic or mixed episode after 6-week olanzapine *vs*. haloperidol *vs*. placebo DB trial. Monotherapy group (N=100): ($\bar{x}$=41.8; 41% ♂; 59% ♀); Combination group (N=39): ($\bar{x}$=43.2; 46% ♂; 54% ♀)	Open, 56-site (Japan) study; olanzapine 5-20 mg/day monotherapy switch from previous trial × 18 weeks, if lack of efficacy: olanzapine + MS (Li^+, CBZ or VPA); safety assed by treatment-emergent adverse events; Remission criterion, YMRS≤12	Monotherapy group: 59% treatment-emergent adverse events, remission 93%; Combination group: treatment-emergent adverse events 79.5%, remission 61.5%	Results support efficacy of combination therapy of olanzapine + MS if olanzapine monotherapy lacks of efficacy
70	40 BD aged 24-84 yrs ($\bar{x}$=49±16; 10 ♂; 30 ♀; 21 BD-I, 19 BD-II) CGI-BP≥5	Open, add-on memantine 10-30 mg/day × 12 months; response/remission criterion, CGI-BP 1 or 2	After 6 months, 47.5% scored 1 and 25% 2; after 12 months, 52.5% 1 and 20% 2	Memantine helps overcoming resistance if added on ongoing treatment
71	13 BD, depressive, aged ≥18 yrs (6 ♂; 7 ♀; 12 BD-I, 1 BD-II). HDRS>15, YMRS>12.	8-week, open-label, add-on nefazodone 300-600 mg/day +MS or AP (Li^+ 450- 600 mg/day; LAM 400 mg/day; VPA, 750-1250 mg/day; CBZ 400-600 mg/day, CLZ, 325 mg/day). Outcome measures: changes in HDRS and CGI-BP, remission, response	69% responded after 8 weeks, 31% remitted. HRDS ↓ from 26.1 ± 5.1 at BL to 18.5 ± 10.1 at week 8; CGI-BP ↓ from 24.2± 0.6 at BL to 3.4 ± 1.3 at week 8, both significant	The effectiveness of add-on nefazodone therapy is moderate
72	83 BD-I aged 18-65 (31 ♂; 52 ♀) with sleep disturbances, ≥5 Pittsburgh Sleep Quality Index	Randomized, DB, add-on ramelteon 8 mg × 24 weeks *vs*. placebo; relapse criterion, MADRS score ≥16 and/or YMRS≥15 or need of drug treatment	48.2% relapse. Ramelteon group less likely to relapse	Ramelteon has a potential utility in maintain mood stability
73	7423 PBD (N 3131 aged 6–12; N 4292 aged 13–18). Age $\bar{x}$	Retrospective cohort study. The outcome measures were psychiatric hospital admission,	Pts. who initiated on MS and SGA had comparable risk of psychiatric hospital admission (HR = 1.172, 95%CI: 0.827–1.660). Compared with those who initiated on MS, pts. who initiated on SGA were less likely to discontinue treatment	SGAs might be more effective and better

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
	12.73±3.38 on either MS (2479) or SGA (4944)	all cause medication discontinuation and treatment augmentation	(HR=0.634, 95% CI: 0.419–0.961) and less likely to receive treatment augmentation (HR=0.223, 95%CI: 0.103–0.484)	tolerated than traditional MSs in BD maintenance treatment
74	23 euthymic BD (Age $\bar{x}$=48.13 yrs.±14.73; 16 ♂; 7 ♀)	Naturalistic, follow up. Outcome measures: mean time to recurrence after MS discontinuation	Median time of recurrence (all manic relapses) is 10 months. Total number of episodes and number of manic episodes negatively correlate with time to recurrence	Rates of relapse in the Indian population are similar to those present in western countries
75	3240 BD (1270 ♂; 1970 ♀) with no AD treatment during the previous year	Retrospective, naturalistic; AD monotherapy *vs*. AD+MS; switch to mania criterion, rate of mania 0-3 months, 3-9 months	↑ risk of switch was confined to pts. on AD monotherapy	AD monotherapy is associated with ↑ risk of mania
76	180 BD-I aged 18-65 (59♂; 121 ♀) in acute manic episode	Randomized, DB, add-on allopurinol 300 mg/die vs placebo × 6 weeks; response criterion, ≥50% ↓ in YMRS	No differences between groups in response	Results do not support add-on allopurinol as a treatment for acute mania
77	59 BD-II > 18 years old ($\bar{x}$ =4±12.5; 27 ♂; 32 ♀;) responded to treatment, HDRS ≤ 16	Randomized, DB, venlafaxine or Li^+ monotherapy × 12 weeks, 6 additional months to evaluate relapse; response criterion, ≥50% ↓ in HDRS; relapse criterion, HDRS≥14+CGI≥4 for ≥14 days	67.7% venlafaxine versus 34.4% lithium subjects responded; no difference in relapse between treatment conditions during continuation monotherapy	Continuation venlafaxine and Li^+ monotherapies provide similar prophylactic effectiveness
78	201 adult BD-I hospitalized for a manic episode (113 ♂; 88 ♀)	Retrospective, naturalistic; MS monotherapy, MS+SGA, MS +FGA; response criterion, 1-year rehospitalization	1-year rehospitalization rates lower in MS+SGA group (6.3%) compared to MS monotherapy group (24.3%) and to MS+FGA group (20.6%)	Results support efficacy of atypical antipsychotic adjunctive therapy to MS
79	Drug naïve BD aged 18-65 ($\bar{x}$ age= 38.8 yrs.; 56 ♂; 12 ♀) with mixed depression	Open, CBZ, Li^+ or VPA monotherapy × 8 weeks; response criterion, ↓ ≥50% in HDRS+one mania scale (YMRS, CARS-M, BRMaS)	High agreement between the three mania rating scales; response on HDRS +YMRS=22.1%, on HDRS+BRMaS=20.6%, and on HDRS+CARS-M=23.5%	Results support the use of any scale to assess the efficacy of MSs in mixed depression; overall response is about 20%
80	344 BDI, depressive, aged 17-70 ($\bar{x}$=45.2 ±12.6; 78 ♂; 122 ♀). HDRS >18 and YMRS>8	8 week-DB, 67-cent3r (15 countries) RCT of add-on agomelatine (25-50 mg) on VPA or Li^+. Additional 10-month continuation phase. Outcome measures: MADRS improvement; response criteria (MADRS improvement ≥50%); changes in HDRS, HARS, CGI, LSEQ, QLESQ	No differences. Results became significant (greater improvement in the agomelatine group *vs*. placebo) after excluding sites with pts. showing high placebo response	Agomelatine added on Li^+ or VPA MS is ineffective for bipolar depression. Concerns for patient recruitment in some centers
81	159 BD-I aged ≥17 yrs. ($\bar{x}$=37.9±13.49; 79 ♂; 79 ♀). Patients remitted from recent manic episode on Li^+ or VPA and RISP or OLZ add-on	Patients randomized to placebo substitution of RISP or OLZ at week 0 (*N*=52), after 25 weeks (*N*=54), and no substitution for 52 weeks (*N*=53) (endpoint). Outcome measures: Event rates (occurrence of any mood episode), time of any mood episode	After 52 weeks, event rate was higher in the 0-week group than in the 24- and 52-week groups. Time to any mood episode was longer in the 24- and 52-week groups compared to the 0-week group. No differences were found between 24- and 52-week groups. Time to mood episode was unchanged after considering subgroups taking OLZ. Instead, in those taking RISP, time to any mood episode in the 52-week group was similar to that in the 0-week group and shorter than in the 24-week group	Use of adjunctive SGAs to MS is beneficial for 24 weeks. However, these benefits are not apparent over 24 weeks. Relapse prevention by

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
				OLZ lasts longer than the one provided by RISP
82	80 BD aged 18-55 (23 ♂; 57♀; 65 BD-I, 15 BD-II)	Retrospective, naturalistic, treatment with Li^+ and/or VPA for more than 2 years; response criterion, total Alda Scale score>5	34% good responders; no differences between Li^+ and VPA groups. In the Li^++VPA group, psychotic, mixed, and atypical features associated with poorer response	Li^+ and VPA show similar efficacy. Polypharmacy is associated with poor response
83	32 BD with subthreshold symptoms, aged 18-65 ($\bar{x}$=43.75 ±10.1; 12 ♂; 20 ♀; 21 BD-I, 11 BD-II). YMRS< 14 and/or MADRS>8 and <14	12-week, double blind-placebo controlled trial of QTP-XR, 300-600 mg, in addition to MS (Li^+, VPA, LAM). Outcome measures: MADRS, HDRS-5, YMRS, CGI-BD score changes. Rates of remission, and early response: % of patients with HDRS<8 and YMRS<8, level of functioning (as assessed by FAST, GAF, EQ-5D, TOOL) and functional remission	The mean changes in MADRS total score from BL to week 6 were -2.44 in the QTP-XR and +2.50 in the placebo group. Changes in HDRS-5 at week 6 were -1.44 in the QTP-XR and +0.28 in the placebo group. At week 12, the QTP-XR group scored higher on the FAST-autonomy subdomain	QTP-XR is effective in treating subthreshold depressive symptoms
84	243 BDI, manic, aged 18-83 ($\bar{x}$ =49.1±13.7; 107 ♂; 137 ♀)	Naturalistic, 34-center (Italy) 12-week follow-up study. Pts. starting/switching to AP and/or MS. Outcome measures: predictive factors of remission (YMRS ↓ ≥50%) and changes from baseline on YMRS, MADRS, FAST, CGI-BP	After 12 weeks, remission rate was 82.3%. No variables found to associate with remission. After 12 weeks, YMRS change was -22.0 ± 10.7. BL CGI-BP depression weakly predicted YMRS change. MADRS change was -6.1±8.2. BL YMRS weakly predicted MADRS change. CGI-mania and CGI-total score change was -6.1±8.2 and -2.7±1.6, respectively. BL YMRS scores weakly predicted CGI-mania and CGI-total score change. Mean FAST change was -17.4±17.3. BL YMRS scores predicted FAST score change	The initiated/changed pharmacological treatment for mania was associated with rapid improvement in manic symptoms and functioning. In contrast, the study has not clearly shown the association of any of the examined intrinsic and extrinsic factors with remission and clinical improvement
85	273 BD aged >18 ($\bar{x}$=40.8±11.07; 81 ♂; 192 ♀; 173 BD-I, 100 BD-II). Two trajectory-based groups: adherent (N=210) and nonadherent (N=63)	Naturalistic, 12-week follow-up. Outcome measures: factors differentiating adherent vs nonadherent group	The nonadherent group spent less time in euthymia (47%) than the adherent group (67.8%). Women more represented in the nonadherent (82.5%) than in the adherent group (66.7%)	Characteristics associated with belonging to the less adherent class were more time with symptoms (i.e., not euthymic), and female gender
86	413 youth BD aged 7-17.11; *N*=886 Li^+, *N*= 1.752 MS	Naturalistic, longitudinal study. Data from the Course and Outcome of Bipolar Youth (COBY) study. Follow-up every 6 months over a mean follow-up of 10 years. "Lithium blocks": Li^+ for more than 75% of the follow-up weeks, regardless of other medications. "MS blocks": MS	During Li^+ (*vs*. MS) follow-up periods, pts. were older, less likely to have lifetime anxiety, and less likely to be on AD (p<0.005). After covariate adjustment, the Li^+ group (*vs*. MS) had half as many suicide attempts (p=0.03), fewer depressive symptoms (p=0.004), less psychosocial impairment (p=0.003), and less aggression (p=0.0004)	Li^+ is associated with decreased suicidality, less depression, and better psychosocial functioning than MSs in a

(Continued)

TABLE 1 | Continued

Study	Population	Design	Results	Conclusions
		but not Li^+, for more than 75% of the time, i.e., antimanic AEs, FGAs and SGAs, and/or LAM. Clinical outcomes: suicide attempts and suicidal ideation; threshold and subthreshold depression; threshold and subthreshold (hypo)mania; psychosocial functioning; hospitalization; aggression; and SUD		population of youths with BD
87	91 BD aged 18-70 ($\bar{x}$ age=41.6±14.2; 47 ♂; 44♀; 63 BD-I, 28 BD-II)	Retrospective, naturalistic, 2-site Campanian study; impaired glucose metabolism (*N*=49) *vs*. normal glucose metabolism (*N*=42); response to MS criterion, Alda scale score ≥7	Impaired glucose metabolism predicted low treatment response to MSs; in the impaired glucose metabolism sample, good response 4.4%, moderate response 23.1%, and poor response 22%; in the normal glucose metabolism sample, good response 17.6% (p=0.012), moderate response 23.1% (n.s.), and poor response 9.9% (p=0.001)	BD with impaired glucose metabolism are at risk for a poor response to MSs; poor metabolism predicts significantly less good response
88	16224 BD aged <65. Three treatment strategies: 6775 pts. (41.8%) MS (Li^+, VPA, valpromide, CBZ, LAM) without SGA. 7268 pts. (44,8%) SGA (ARP, OLZ, RISP, QTP) without MS; 2181 pts. (13,4%) combination of MS +SGA	Historic cohort study using French national healthcare databases. Outcomes: treatment discontinuation, switch or addition, psychiatric hospitalization, suicide attempt, and death	The 1-year adjusted cumulative incidence of treatment failure was 75.7% (95%CI 74.9;76.3) in pts. using MS, 75.3% (74.6;76.0) in pts. using SGA, and 60.5% (58.3;62.6) in pts. with the combination. The adjusted difference in incidence of treatment failure for SGA compared with MS was -0.40% (-1.4;0.6 p=0.4) in the whole population, -2.2% (-3.3; -1.2 p<0.002) in pts. <65 years. Early discontinuation was the most often first occurring event over follow-up for all three treatment strategies. Treatment addition and discontinuation were slightly less frequent with SGA than with MS, while psychiatric hospitalization occurred more often in the SGA group. The 1-year adjusted cumulative incidence of partial discontinuation was 59.6% (95%CI 57.3;61.7) in pts. with combined treatment. The incidence of mortality was quite high as first event, particularly in the group receiving combinations. Treatment failure occurred in 64.8% (95%CI 64.0–65.6) of pts. with MS, 67.4% (95%CI 66.7;68.2) of pts. with SGAs, and 50.8% (95%CI 48.6;53.0) of pts. with a combination. The adjusted cumulative incidence of early treatment discontinuation was 37.0% (95%CI 36.1;37.8) with MS, 38% (95%CI 37.3;38) with SGAs, and 28.4% (95%CI 26.4;30.2) with a combination. Discontinuation was significantly more frequent with SGAs than with MSs with an adjusted difference in cumulative incidence=2.6% (95%CI 1.5;3.7; p<0.002)	The rate of treatment failure is very high in all age groups and for all treatment strategies. SGAs did not perform better than MSs in the whole study population and were even worse in the sensitivity analyses. SGAs are slightly more effective than MSs in younger pts., but less effective in older ones
88	3862 BD aged 65 and over. Three treatment strategies: MS: N 1450 (37.5%) SGA: N 2074 (53.7%) MS+SGA: N 338 (8.8%)	Historic cohort using French national healthcare databases. Outcomes: treatment discontinuation, switch or addition, psychiatric hospitalization, suicide attempt, and death	The adjusted difference in incidence of treatment failure for SGA compared with MS was +6.7% (4.1;9.1 p<0.002). Treatment addition was less frequent with SGA than with MS, while early discontinuation, psychiatric hospitalizations, and death were more frequent with SGA. When considering each type of outcome separately without stopping the follow-up when another type of outcome occurred, pts. with SGA (with or without MS) were at higher risk of death	SGAs are less effective in older pts. and fail more often than MSs in older pts. Mortality was particularly high in older pts. treated with SGA or a combination

study, no differences in effectiveness/efficacy were found as compared with add-on olanzapine (5-20 mg/day).

Olanzapine. Acute effectiveness/efficacy of olanzapine was investigated in one double-blind, placebo-controlled trial (43). Add-on olanzapine treatment (5-20 mg/day) to patients previously treated with MSs (Li^+ or valproate) was superior to placebo in reducing YMRS scores and was associated with higher rates of remission. Furthermore, olanzapine monotherapy was similarly effective independently from whether the patients had failed or succeeded in the past to respond to another MS for mania.

Quetiapine. Effectiveness of add-on quetiapine (mean 267.9 ± 105.4 mg/day) to a MS in reducing manic/mixed symptoms was investigated by one open-label trial (53). After four weeks, add-on quetiapine reduced both manic and depressive symptoms, as demonstrated by the reduction of both YMRS and Hamilton Depression Rating Scale (HDRS) scores.

Mood-stabilizers

Add-on MS (Li^+, carbamazepine, and valproate) to olanzapine (5-20 mg) in manic/mixed patients was associated with greater remission rates (61% *vs*. 95%) than olanzapine monotherapy (69). On the other hand, Goldberg et al. (32) showed that patients with Li^+ or AE monotherapy had similar response rates and duration of remission, whereas time to remission in cases of combined therapy is somehow longer. This outcome may be related to the fact that people receiving combined treatment added the antiepileptic after an ineffective Li^+ trial. After starting the combined therapy, time to remission was similar to the monotherapy group, i.e., 2-3 weeks.

Gabapentin (900-1200 mg/day) add-on treatment to antimanic drugs (Li^+, valproate, and risperidone) was effective in rapidly reducing HDRS and Bech-Rafaelsen Mania Scale (BRMaS) scores after 1 week. In the following month, BRMaS scores stabilized, whereas HDRS scores continued to decrease (34). On the other hand, topiramate (50-400 mg/day) added on a MS (Li^+, valproate) or an AP failed to show superior efficacy than placebo add on after 12-weeks (56).

Other

Add-on memantine in not stabilized BD is related to 47.5% and 52.5% rates of remission after 6 and 12 months (70), whereas sedatives (mainly BDZs) added on lamotrigine monotherapy (100-200 mg/day) in patients with either manic or depressive episode, were associated with higher rates of stabilization than adding other psychotropic drugs (mainly SGAs, ADs, and MSs) (59). Add-on nutritional supplements, like vitamins and minerals, proved able to reduce in some patients both manic and depressive symptoms (38), whereas allopurinol was not superior to placebo in reducing manic symptoms (76). However, allopurinol also improved YMRS scores in its double-blind study and with a greater effect size than what vitamins and chelated minerals were able to achieve in the open study.

Summarizing the evidence of studies treating acute episodes of mania or mixed, adding one SGA to a MS seems the best strategy to stabilize mood. The evidence of the antimanic effect of SGAs are most prominent for risperidone, a bit less for olanzapine and quetiapine. There are no differences between olanzapine and risperidone or valproate and Li^+ as regards their antimanic effect. The evidence of differences between SGAs and FGAs as for their antimanic effect is at least poor and conflicting.

Depression

Add-on SGAs

Two double-blind placebo-controlled trials evaluated the effectiveness of aripiprazole (67) and quetiapine (83) as add-on treatments for bipolar depression. Quante et al. (67) failed to demonstrate superiority of augmentation therapy with aripiprazole (10-30 mg/day) as compared to placebo in patients treated with citalopram (40 mg/day) and a MS. Conversely, Garriga et al., showed that add-on quetiapine-extended release (300-600 mg/day) to a MS (Li^+, valproate, or carbamazepine) was superior to placebo in improving subthreshold depressive symptoms after 6 weeks, and also in improving functioning after 12 weeks.

MSs

Hantouche et al. (54) assessed the characteristics of poor *vs*. good responders to add-on MSs (Li^+, carbamazepine, and valproate) treatment to ADs in major depressive disorder patients with depression who met Angst's criteria for lifetime presence of subtle hypomanic and cyclothymic features, i.e., patients that the authors consider as belonging to the bipolar spectrum. Poor responders were prescribed a MS later than good responders, suggesting that MS augmentation should be undertaken without delay.

Valproate Monotherapy. Two studies investigated the effectiveness of valproate monotherapy in relieving depressive symptoms (41, 68). Valproate was associated with a 63% response after one year in patients with BD-II. Valproate monotherapy was also superior to placebo in improving HDRS scores after 3, 4, 5, and 6 weeks. However, differently from Winsberg et al. (41), such difference in Muzina et al. (68) was mainly driven by data regarding the subgroup affected by BD-I.

Lamotrigine. Two studies investigated the effectiveness/efficacy of lamotrigine in BD depression, either as monotherapy (65), or as add-on treatment (66). After 16 weeks, lamotrigine monotherapy (200-400 mg/day) increased YMRS scores by more than 4 points in 35% of patients, and such increase was predicted by the number of manic/hypomanic/mixed episodes in the preceding year. lamotrigine add-on treatment (145.5 ± 113.2 mg/day) to a MS (Li^+ or valproate) or APs (quetiapine, olanzapine, or ziprasidone) reduced CGI-BP-S scores after 4 and 12 weeks. Such scores remained significantly lower during the following year, indicating successful stabilization.

Topiramate. Effectiveness of add-on topiramate (50-100 mg/day) in reducing both manic and depressive symptoms and in inducing response was compared with add-on bupropion (100-400 mg/day) to a MS (Li^+ or valproate) and SGAs. Add-on treatments with either topiramate or bupropion were able to induce similar response rates (56% *vs*. 59%, respectively), within a similar time lag (2-4 weeks). Reductions in YMRS, HDRS, and CGI-I scores were also similar.

ADs

Bottlender et al. (37) evaluated the impact of AD treatment on the incidence of switches from depression to mania/hypomania in 158 BD-I patients with depression. Rates of switches were 25%, with higher risks for patients taking tricyclic antidepressants (TCAs) and lower for those on combined AD +MS treatment.

Add-on paroxetine. Three studies evaluated the effectiveness/efficacy of paroxetine in reducing depressive symptoms and rates of switch. Young et al. (35) compared the effectiveness/switch rates of either add-on paroxetine (36 mg/day) or additional MS (Li^+, 1300 mg/day or valproate 1200 mg/day) to stable MS treatment. Both add-on treatments were associated with signif-

icant reductions in HDRS scores after 6 weeks, with no significant YMRS score increases.

Vieta et al. (45) compared add-on treatment with paroxetine (32.3 mg ± 11.2) or venlafaxine (179.2mg ± 91.0) to a MS (Li^+, valproate, or carbamazepine) and investigated response, remission, and switch rates. After 6 weeks, similar proportions of responders (paroxetine+MS: 50%; venlafaxine+MS: 59%) and similar remission rates (paroxetine+MS: 37%; venlafaxine+MS: 41%) were found. Venlafaxine showed higher, even though not significantly so, rates of remission (48% *vs*. 43% with paroxetine). Nevertheless, the authors concluded that acute add-on treatment with venlafaxine raises concerns due to the higher rates of switch, although rates did not differ significantly, but only numerically (13% with venlafaxine, 3% with paroxetine). Authors stressed the need to replicate their preliminary findings, but no follow-up ensued.

Venlafaxine, Sertraline, and Bupropion. Amsterdam et al. (77) showed superiority of venlafaxine monotherapy over placebo in BD-II patients as concerns response rates at the 12-week endpoint (67.7% *vs*. 34.4%, respectively). Two randomized trials investigated the effectiveness/switch rates of add-on venlafaxine, sertraline or bupropion to MSs (Li^+, valproate, or carbamazepine). Post et al. (40) reported a 37% response rate after 10 weeks, with 14% of switches into mania/hypomania, On the other hand, Leverich et al. (57) showed that after 10 weeks, response rates were 48.7%. However, response rates dropped to 32.5% after excluding patients who had a switch. Switch rate to full (hypo)mania was 19.3%, with higher rates for venlafaxine and lowest for bupropion. Both studies showed that AD augmentation is not likely to yield a high rate of sustained AD response without a switch.

Escitalopram. The study of Parker et al. (58) showed superiority of 10 mg of escitalopram monotherapy over placebo in a double-blind crossover study lasting 9 months, in reducing symptom severity and percent days impaired in a small sample of 10 drug-naïve patients with BD-II and monthly mood episodes.

Other. Goldberg et al. (49) evaluated the effectiveness of add-on pramipexole (1.0-2.5 mg/day) to MSs (Li^+, valproate, or carbamazepine) in improving HDRS and CGI-S scores. After 6 weeks, pramipexole was superior to placebo in reducing depressive symptoms (pramipexole+MS was followed by more than 50% drop in HDRS scores compared to 20% in the placebo +MS; furthermore, it was associated with lower CGI-S scores (2.7 ± 1.4) than placebo+MS (4.4 ± 1.3). On the other hand, add-on therapy with agomelatine (25-50 mg) to a MS (Li^+ and valproate) was not superior to add-on treatment with placebo in reducing depression after8 weeks (80). Goldberg et al. (71) found moderate antidepressant effect of nefazodone (300-600 mg/day) added on a MS (Li^+, lamotrigine, valproate or carbamazepine) or an AP (clozapine).

Concluding, in the acute treatment of depression, adding ADs on ongoing MS treatment is effective in improving mood symptoms but it is also related to an increase in switch rates, specifically in BD-I or mixed samples. The evidence points to higher switch rates during add-on treatment with venlafaxine, a drug that inhibits the reuptake of both norepinephrine and serotonin, or TCAs, a group of drugs that are effective in blocking both transporters similarly to venlafaxine, than with selective serotonin reuptake inhibitors (SSRIs) or bupropion, which blocks the reuptake of norepinephrine and dopamine, and leaves the serotonin transporter almost unaffected. Risk of switch seems intermediate for SSRIs and lower with bupropion. ADs are effective in the short-term treatment of BD-II, even in monotherapy, but switch rates are not clearly evaluated across studies. Monotherapy with valproate and lamotrigine showed also short-term effectiveness, like topiramate and quetiapine-extended release add.

Long-Term Studies

APs

Two retrospective naturalistic studies investigated rates of relapse over a 1-year period in patients with BD (59, 78) treated with MS monotherapy, MS+SGAs and MS+FGAs, and reported conflicting results. Rehospitalization rates have been reported not to differ after a 1-year follow-up (Patel et al., 2006) or to be lower in patients receiving MS+SGAs, compared to MS monotherapy and MS+FGAs (78). Differences in sample characteristics [BD-I in Patel et al. [2006] and BD-I/BD-II mixed sample in Hochman et al. (78)] or type of SGA used might have played a role in such discrepancy. In partial agreement with Patel et al. (55), Tournier et al. (88), found similar treatment discontinuation rates, i.e., > 60% across the aforementioned three groups during a 1-year period, with slightly, but not significantly lower rates in the MS+SGAs combined group than the other two. Bernardo Dell'Osso et al. (64) investigated relapse rates after over 2 years in patients with early, middle, and late onset of BD, and found that MS treatment (Li^+ or valproate+SGAs) are more effective in preventing depressive episodes in those patients with an early BD onset.

Olanzapine, Risperidone, and Quietiapine. Two placebo-controlled trials (51, 80) and one naturalistic study (63) investigated the effectiveness in relapse prevention of olanzapine, risperidone and quetiapine. Tohen et al. (41) found that patients on combined olanzapine (5-20 mg)/MS (Li^+, 954.6-1174.7 mg/day or valproate, 1060.4-1512 mg/day) treatment had a longer mean time to symptomatic relapse into mania or depression then patients receiving MS+placebo (163 and 42 days, respectively). The effectiveness of add-on olanzapine was superior than add-on placebo or add-on risperidone in increasing the time of syndromic relapse during the short- (24 weeks), but not in the long-term (81). Altamura et al. (63) investigated rates of relapse over 4 years in patients treated with Li^+ or valproate or lamotrigine or quetiapine as monotherapy or a combination of quetiapine to either Li^+ or valproate. Patients with a combined treatment (quetiapine+Li^+ and quetiapine+valproate) showed higher rates of euthymia (80% and 78.3%, respectively) than those with quetiapine alone (29.3%), Li^+ alone (46.2%) and lamotrigine alone (41.9%). Patients with Li^++quetiapine and Li^++valproate did not relapse for longer times (41.4 and 39.2 months, respectively) than patients on quetiapine (24.9 months) and valproate (26.3 months) alone. Only patients with Li^++quetiapine did not relapse for significantly longer times than Li^+ alone (33.1

months). Furthermore, patients with Li^+ monotherapy showed smaller relapse rates than those with quetiapine monotherapy.

MSs

DePaulo et al. (31) investigated self-reported mood stability in patients with BD on long-term lithium therapy and found greater ratings of absence of mood swings than HCs. Ahn et al. (82) found that treatment response rates did not differ among patients with add-on Li^+ to SGAs (quetiapine, olanzapine, risperidone, aripiprazole, paliperidone, clozapine, amisulpride), or other MSs (lamotrigine and carbamazepine) as compared to those receiving add-on treatment with valproate. On the other hand, Savas et al. (60) found that adjunctive therapy with MSs (Li^+, valproate, carbamazepine or lamotrigine) to SGAs (risperidone, olanzapine or quetiapine) was not superior in preventing relapses as compared with SGAs alone over a 6 month-period.

Mean time of relapse after MS discontinuation was investigated by Sharma et al. (74) in a sample of Indian patients. Mean time to relapse was 10 months, and all relapses were manic, thus replicating existing data in samples belonging to Western countries. Steardo et al. (87) showed that impaired glucose metabolism was associated to poor long-term response to MSs (Li, valproate, lamotrigine, and carbamazepine) and APs. On the other hand, Henry et al. (46) showed that anxiety was a predictor of poor long-term (2 years) response to AEs, but not to Li^+.

One open label, placebo-controlled trial (65) tested the effectiveness of lamotrigine monotherapy (100-200 mg/day) in reducing switch rates over 6 months. The authors found no differences between lamotrigine and placebo in percentage or hazard ratio for a medical intervention due to the onset of a mood episode. However, patients on lamotrigine monotherapy had consistently higher survival estimates than patients on placebo. Furthermore, YMRS scores at screening and presence of ≥3 manic/hypomanic/mixed episodes in the preceding year significantly increased the hazard ratio for a mood episode. The authors concluded that emergent manic or hypomanic features appear to be driven by the pre-existing or historical burden of mania features, rather than the use of lamotrigine.

ADs

Amsterdam et al. (77) found no difference in relapse rates over 6 months between patients with BD-II treated with venlafaxine or with lithium monotherapy. Two studies evaluated manic switch rates over one year of add-on bupropion, venlafaxine or sertraline to MS in patients who had responded in the past to AD augmentation (40, 57). In both studies, switch rates were higher than 30% (33% and 36%). AD switch rates were not significantly different among the three ADs; however, the threshold/subthreshold switch ratio was lowest with bupropion (1.2), intermediate with sertraline (1.65), and highest with venlafaxine (3.75). The long-term administration of 25-50 mg/day of the strong melatonin MT_1 and MT_2 receptor agonist and moderate serotonin 5-HT_{2C} and 5-HT_{2B} receptor antagonist, agomelatine, as an add-on to a MS, did not result in different switch rates compared to placebo added on a MS (80). However, also the response rates were similar in the two groups, raising questions about the antidepressant potency of agomelatine.

Other

Norris et al. (72) investigated the long-term effectiveness of add-on ramelteon (8 mg/day), a sleep inducer which shares with agomelatine the strong melatonin MT_1 and MT_2 receptor agonist activity, and is also endowed with weak MT_3 and 5-HT_{2B} activity, to standard medications (including APs, MSs, ADs, and stimulants) in stabilized patients with BD over a 6-month period. As compared with placebo, patients with add-on ramelteon showed lower rates of relapse into any mood episode than placebo.

Studies focusing on stabilization of adult patients make the greatest part of those included in this review. As far, results appear to be inconsistent if not conflicting, but there is weak evidence supporting either the addition of a SGA to MS or using a SGA alone, which both confer mood stabilization that is superior to that obtained using MSs alone, at least in the medium term. For timeframes extending over six months, results are more conflicting. However, evidence supporting the effectiveness of combined therapy in reducing relapse is stronger than the one supporting the superiority of the use of MS or SGA alone. Li^+ seems not to be superior to valproate in stabilizing mood as an add-on treatment. Add-on ADs to MSs are related with higher switch rates. If this holds true for BD-I or mixed samples, there is a week, preliminary evidence that this might not be true for BD-II.

Children/Adolescents

Tramontina et al. (61) showed that the switch to a monotherapy with topiramate (150 mg/day) in youth (11-17 years) with BD, previously treated with MSs (Li^+, valproate) or SGAs (risperidone), was associated to both reduction of YMRS scores and weight loss after 4 weeks.

Chen et al. (73) retrospectively investigated relapse rates after 12 months of treatment with either MSs (Li^+, valproate, or carbamazepine) or SGAs (risperidone, aripiprazole or quetiapine). Patients who initiated MSs and SGAs had a comparable risk of psychiatric hospital admission; however, patients who initiated on SGAs were less likely to discontinue treatment and less likely to receive treatment augmentation. Hence, the authors concluded that in youths with BD, SGAs might be more effective and better tolerated than traditional MSs as a maintenance treatment. Conversely, Hafeman et al. (86) investigated suicide attempts and suicidal ideation, rates of threshold and subthreshold depression, (hypo)mania, psychosocial functioning, hospitalization, aggression, and substance use disorders in patients receiving Li^+ or medications other than Li^+ (AEs, FGAs and SGAs), regardless of other psychotropic medications, for more than 75% of the 10-year follow up. They found that Li^+-treated youths were less likely to have lifetime anxiety, and less likely to be on ADs. Youth on Li^+ had half as many suicide attempts, fewer depressive symptoms, psychosocial impairment due to illness, and less aggression than those not treated with Li^+.

Elderly

Sanderson et al. (33) compared length of stay and symptom improvement in elderly inpatients receiving monotherapy with

Li^+, valproate, or carbamazepine and found no significant differences across the groups. Tournier et al. (88) investigated rates of treatment discontinuation, switch, adjunctive medication, hospitalization, suicide attempt, and death over a 1-year period in patients treated with either MS (Li^+, valproate, carbamazepine, and lamotrigine), SGAs (risperidone, aripiprazole, quetiapine, and olanzapine) or a combination of the two classes. Treatment failure was higher in those receiving SGAs than MSs. Addition of another drug was less frequent in those taking SGAs than in those taking MSs, while early discontinuation, psychiatric hospitalizations and death occurred more frequent in patients who were prescribed SGAs. The authors concluded that, in older patients, SGAs are less effective and fail more often than MSs. Mortality was particularly high in SGA-treated elderly patients, either as a monotherapy or in combination with MSs.

Pregnancy

Viguera et al. (62) studied 89 pregnant women with polytherapy (including MSs, ADs, APs) for BD who 1) used at least one MS (Li^+, valproate, carbamazepine, gabapentin, lamotrigine) or AP (olanzapine and quetiapine) at conception and continued treatment for more than 12 weeks; 2) discontinued MSs during the 6 months preceding the conception and for the following 12 weeks. Pregnant women were followed up each trimester and at 6, 12, 24, and 52 weeks postpartum to ascertain recurrence of mania, hypomania (lasting ≥1 week), major depression, or a mixed state, and current treatments. The authors found that 70.8% of women experienced ≥1 episode during pregnancy. Risk of recurrence was 2.3 times higher in those who discontinued treatment than in those who continued (85.5% *vs*. 37.0%, respectively). Discontinuers spent >40% of pregnancy in an illness episode, *vs*. 8.8% of pregnancy of women continuing on MS. Median time to first recurrence was 9.0 weeks for discontinuers and >40 weeks for continuers. Those who abruptly or rapidly discontinued MS treatment (< 14 days) had 50% risk of recurrence within 2 weeks, whereas gradual discontinuers (> 14 days) required 22 weeks to reach 50% risk of recurrence. Treatment-related risk factors, besides MS discontinuation, included polytherapy with two or more psychotropic drugs, use of ADs, primary MS other than Li^+, and previous switch from depression to mania/hypomania during past AD treatment.

Final considerations

Stabilizing treatments through the lifespan differ. In youth, SGAs are more tolerated and effective than MS in stabilizing mood (73). However, Li^+ remains the cornerstone of mood stabilization as seeb in pediatric populations with BD, as it protects from impulsive acts and suicidal behavior (86). Furthermore, Li^+ is also important for dimensions related to impulsive behavior and mood dysregulation, which are often encountered in such population (91). In adults, the use of add-on SGAs to MS in the treatment of manic/mixed state is still important, at least in the first half year of treatment. The combined treatment seems to confer greater mood stabilization. There is also preliminary evidence for greater effectiveness of some SGAs, like olanzapine, quetiapine, and risperidone, compared to MS monotherapy, but confirmatory studies are needed. In the elderly, the use of SGAs is contraindicated because of the impact on health and higher risk of death (all APs have a warning for increased risk of stroke in the elderly). Henceforth, the ratio of SGA/MS use varies across the lifespan, being highest during youth (frequent use for longer times of SGAs), intermediate in adult life (combined therapy), and low in the elderly (greater use of MSs).

Limitations

We based our conclusions on findings of sometimes underpowered studies, conducted with no double blinding, and often conducted on small samples. There is temporal discontinuity in the included studies, in that earlier years are less densely represented than recent years, and this might have affected the relative quality of the included studies. However, we found that most pre-millennial studies to be of high quality in both design and performance whereas not all recent trends in article standards resulted in improved data. The ways in which mood stabilization was considered and measured differed among studies. Only one study asked participants to rate their mood on a continuous visual scale, most others measured it as a reduction in HDRS or YMRS scores. This affected the evaluation of the stabilizing effect of the drug tested. Generally, we could not meta-analyze the eligible studies due to their extreme methodological differences in both design and assessment of outcomes; for example, about half were open-label and the other half double-blind. Furthermore, many were sponsored by the pharmaceutical industry, raising concerns that they could be biased in some sense. Risk of bias was high in most studies. Another limitation was that we did not assess the effects of physical therapies, like electroconvulsive therapy, deep and repetitive transcranial magnetic stimulation, and direct current transcranial stimulation, that may play a part in BD patients' treatment (92-94), but this would go beyond the scope of this review.

Summarizing, the indications for different treatments across the lifespan in BD are not supported by sufficient evidence, but appear nevertheless to differ. This is due to the dearth of studies carried out heretofore. The need for the future is for studies following the same methodology and adopting a consensus definition of stabilization.

CONCLUSIONS

Mood stabilization is currently achieved at suboptimal levels. The evidence gathered heretofore is quite insufficient to propose treatment recommendations for cAdolescents, pregnant women, and elderly people. Regarding adults, in manic/mixed phases AP drugs, especially SGAs, have shown usefulness in acute to medium term treatment, especially in combination with MSs. The latter, especially Li^+, is still the mainstay of chronic treatment, even though there is increasing evidence supporting the superiority of long-term combined therapy. Depressive phases of BD benefit from MS and quetiapine treatment, and there is some concern with the switch-inducing potential of some

ADs, but less with others. The use of ADs in bipolar depression is safer when the AD is prescribed along with a MS.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ supplementary material.

AUTHOR CONTRIBUTIONS

GS and AS designed the review. All authors were involved in selection of eligible material and in Delphi rounds to reach consensus. AS and GK wrote the introduction, methods and results, designed the search strategy, gathered eligible material, and supervised the writing of the paper along with LJ and GS. GS, AK, DJ, and LD wrote the discussion. GK and AS wrote the limitations and conclusions. All authors approved the final form of the document. AS and AK equally contributed to the writing of the manuscript.

ACKNOWLEDGEMENTS

We wish to thank the Librarians of the Library of the Faculty of Medicine and Psychology of the Sapienza University of Rome Ms. Mimma Ariano, Ms. Felicia Proietti, Ms. Ales Casciaro, Ms. Teresa Prioreschi, and Ms. Susanna Rospo for providing us precious bibliographic material.

REFERENCES

1. Nilsson A, Axelsson R. Factors associated with discontinuation of long-term lithium treatment. *Acta Psychiatr Scand* (1989) 80(3):221–30. doi: 10.1111/j.1600-0447.1989.tb01331.x
2. Schumann C, Lenz G, Berghöfer A, Müller-Oerlinghausen B. Non-adherence with long-term prophylaxis: a 6-year naturalistic follow-up study of affectively ill patients. *Psychiatry Res* (1999) 89(3):247–57. doi: 10.1016/s0165-1781(99)00108-0
3. Maj M, Pirozzi R, Magliano L. Late non-response to lithium prophylaxis in bipolar patients: prevalence and predictors. *J Affect Disord* (1996) 39(1):39–42. doi: 10.1016/0165-0327(96)00018-3
4. Larsson S, Lorentzen S, Mork E, Barrett EA, Steen NE, Lagerberg TV, et al. Age at onset of bipolar disorder in a Norwegian catchment area sample. *J Affect Disord* (2010) 124(1-2):174–7. doi: 10.1016/j.jad.2009.10.031
5. Nowrouzi B, McIntyre RS, MacQueen G, Kennedy SH, Kennedy JL, Ravindran A, et al. Admixture analysis of age at onset in first episode bipolar disorder. *J Affect Disord* (2016) 201:88–94. doi: 10.1016/j.jad.2016.04.006
6. Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, et al. The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry* (2007) 62(8):910–6. doi: 10.1016/j.biopsych.2007.02.001
7. Kupferschmidt DA, Zakzanis KK. Toward a functional neuroanatomical signature of bipolar disorder: quantitative evidence from the neuroimaging literature. *Psychiatry Res* (2011) 193(2):71–9. doi: 10.1016/j.pscychresns.2011.02.011
8. Kotzalidis GD, Rapinesi C, Savoja V, Cuomo I, Simonetti A, Ambrosi E, et al. Neurobiological Evidence for the Primacy of Mania Hypothesis. *Curr Neuropharmacol* (2017) 15(3):339–52. doi: 10.2174/1570159X14666160708231216
9. Janiri D, Sani G, De Rossi P, Piras F, Banaj N, Ciullo V, et al. Hippocampal subfield volumes and childhood trauma in bipolar disorders. *J Affect Disord* (2019) 253:35–43. doi: 10.1016/j.jad.2019.04.071
10. Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry* (2008) 65(4):395–407. doi: 10.1001/archpsyc.65.4.395
11. Sani G, Perugi G, Tondo L. Treatment of bipolar disorder in a lifetime perspective: is lithium still the best choice? *Clin Drug Investig* (2017) 37(8):713–27. doi: 10.1007/s40261-017-0531-2
12. Hetmar O, Brun C, Ladefoged J, Larsen S, Bolwig TG. Long-term effects of lithium on the kidney: functional-morphological correlations. *J Psychiatr Res* (1989) 23(3-4):285–97. doi: 10.1016/0022-3956(89)90034-4
13. Bendz H, Aurell M, Balldin J, Mathé AA, Sjödin I. Kidney damage in long-term lithium patients: a cross-sectional study of patients with 15 years or more on lithium. *Nephrol Dial Transplant* (1994) 9(9):1250–4. doi: 10.1093/ndt/9.9.1250
14. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, et al. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. *Int J Bipolar Disord* (2017) 5(1):27. doi: 10.1186/s40345-017-0096-2
15. Keränen T, Sivenius J. Side effects of carbamazepine, valproate and clonazepam during long-term treatment of epilepsy. *Acta Neurol Scand* (1983) 68(Suppl. 97):69–80. doi: 10.1111/j.1600-0404.1983.tb01536.x
16. Perugi G, De Rossi P, Fagiolini A, Girardi P, Maina G, Sani G, et al. Personalized and precision medicine as informants for treatment management of bipolar disorder. *Int Clin Psychopharmacol* (2019) 34(4):189–205. doi: 10.1097/YIC.0000000000000260
17. Ghaemi SN. On defining 'mood stabilizer'. *Bipolar Disord* (2001) 3(3):154–8. doi: 10.1034/j.1399-5618.2001.030304.x
18. Ketter TA. Definition of the term "mood stabilizer". *Bipolar Disord* (2018) 20(1):74–5. doi: 10.1111/bdi.12579
19. Scatton B, Fage D, Oblin A, Zivkovic B, Arbilla S, Langer SZ, et al. Influence of GABA mimetics and lithium on biochemical manifestations of striatal dopamine target cell hypersensitivity. *Psychopharmacology* (1985) 85-87 (Suppl. 2):39–45. doi: 10.1007/978-3-642-70140-5_5
20. Del' Guidice T, Beaulieu JM. Selective disruption of dopamine D2-receptors/beta-arrestin2 signaling by mood stabilizers. *J Recept Signal Transduct Res* (2015) 35(3):224–32. doi: 10.3109/10799893.2015.1072976
21. Fortin SM, Chartoff EH, Roitman MF. The aversive agent lithium chloride suppresses phasic dopamine release through central GLP-1 receptors. *Neuropsychopharmacology*. (2016) 41(3):906–15. doi: 10.1038/npp.2015.220
22. Scotti-Muzzi E, Chile T, Moreno R, Pastorello BF, da Costa Leite C, Henning A, et al. ACC Glu/GABA ratio is decreased in euthymic bipolar disorder I patients: possible in vivo neurometabolite explanation for mood stabilization. *Eur Arch Psychiatry Clin Neurosci* (2020). doi: 10.1007/s00406-020-01096-0
23. Hochberg Z, Konner M. Emerging adulthood, a pre-adult life-history stage. *Front Endocrinol* (2020) 10:918. doi: 10.3389/fendo.2019.00918
24. Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, et al. Sex differences in the structural connectome of the human brain. *Proc Natl Acad Sci U S A* (2014) 111(2):823–8. doi: 10.1073/pnas.1316909110
25. Mitchell RH, Metcalfe AW, Islam AH, Toma S, Patel R, Fiksenbaum L, et al. Sex differences in brain structure among adolescents with bipolar disorder. *Bipolar Disord* (2018) 448–58. doi: 10.1111/bdi.12663
26. Janiri D, Di Nicola M, Martinotti G, Janiri L. Who's the leader, mania or depression? Predominant polarity and alcohol/polysubstance use in bipolar disorders. *Curr Neuropharmacol* (2017) 15(3):409–16. doi: 10.2174/1570159X14666160607101400
27. Sharma V. Relationship of bipolar disorder with psychiatric comorbidity in the postpartum period-a scoping review. *Arch Womens Ment Health* (2018) 21(2):141–7. doi: 10.1007/s00737-017-0782-1
28. Tebeka S, Le Strat Y, Dubertret C. Is parity status associated with bipolar disorder clinical features, severity or evolution? *J Affect Disord* (2018) 225:201–6. doi: 10.1016/j.jad.2017.08.042

29. Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535
30. Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097
31. DePaulo JRJr, Correa EI, Folstein MF. Does lithium stabilize mood? *Biol Psychiatry* (1983) 18(9):1093–7. doi: 10.1016/0006-3223/83/0900-1093
32. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar patients. *J Clin Psychiatry* (1998) 59(4):151–8. doi: 10.4088/JCP.v59n0402
33. Sanderson DR. Use of mood stabilizers by hospitalized geriatric patients with bipolar disorder. *Psychiatr Serv* (1998) 49(9):1145–7. doi: 10.1176/ps.49.9.1145
34. Sokolski KN, Green C, Maris DE, DeMet EM. Gabapentin as an adjunct to standard mood stabilizers in out patients with mixed bipolar symptomatology. *Ann Clin Psychiatry* (1999) 11(4):217–22. doi: 10.1023/a:1022361412956
35. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. *Am J Psychiatry* (2000) 157(1):124–6. doi: 10.1176/ajp.157.1.124
36. Benabarre A, Vieta E, Colom F, Martínez A, Reinares M, Corbella B. Treatment of mixed mania with risperidone and mood stabilizers. *Can J Psychiatry* (2001) 46(9):866–7. doi: 10.1177/070674370104600925
37. Bottlender R, Rudolf D, Strauss A, Möller HJ. Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. *J Affect Disord* (2001) 63(1-3):79–83. doi: 10.1016/s0165-0327(00)00172-5
38. Kaplan BJ, Simpson JS, Ferre RC, Gorman CP, McMullen DM, Crawford SG. Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder. *J Clin Psychiatry* (2001) 62(12):936–44. doi: 10.4088/jcp.v62n1204
39. Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. *J Clin Psychiatry* (2001) 62(12):975–80. doi: 10.4088/jcp.v62n1210
40. Post RM, Altshuler LL, Frye MA, Suppes T, Rush AJ, Keck PEJr, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. *Bipolar Disord* (2001) 3(5):259–65. doi: 10.1034/j.1399-5618.2001.30505.x
41. Winsberg ME, DeGolia SG, Strong CM, Ketter TA. Divalproex therapy in medication-naïve and mood-stabilizer-naïve bipolar II depression. *J Affect Disord* (2001), 67(1–3207–12. doi: 10.1016/s0165-0327(01)00434-7
42. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* (2002) 159(7):1146–54. doi: 10.1176/appi.ajp.159.7.1146
43. Baker RW, Goldberg JF, Tohen M, Milton DR, Stauffer VL, Schuh LM. The impact of response to previous mood stabilizer therapy on response to olanzapine versus placebo for acute mania. *Bipolar Disord* (2002) 4(1):43–9. doi: 10.1034/j.1399-5618.2002.40103.x
44. McIntyre RS, Mancini DA, McCann S, Srinivasan J, Sagman D, Kennedy SH. Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disord* (2002) 4(3):207–13. doi: 10.1034/j.1399-5618.2002.01189.x
45. Vieta E, Martinez-Arán A, Goikolea JM, Torrent C, Colom F, Benabarre A, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J Clin Psychiatry* (2002) 63(6):508–12. doi: 10.4088/jcp.v63n0607
46. Henry C, Van den Bulke D, Bellivier F, Etain B, Rouillon F, Leboyer M. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J Clin Psychiatry* (2003) 64(3):331–5. doi: 10.4088/JCP.v64n0316
47. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *Br J Psychiatry* (2003) 182(2):141–7. doi: 10.1192/bjp.182.2.141
48. Bowden CL, Myers JE, Grossman F, Xie Y. Risperidone in combination with mood stabilizers: a 10-week continuation phase study in bipolar I disorder. *J Clin Psychiatry* (2004) 65(5):707–14. doi: 10.4088/jcp.v65n0518
49. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* (2004) 161(3):564–6. doi: 10.1176/appi.ajp.161.3.564
50. Mammen OK, Pilkonis PA, Chengappa KN, Kupfer DJ. Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. *J Clin Psychiatry* (2004) 65(5):627–33. doi: 10.4088/JCP.v65n0506
51. Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry* (2004) 184:337–45. doi: 10.1192/bjp.184.4.337
52. Bahk WM, Yoon JS, Kim YH, Lee YH, Lee C, Kim KS, et al. Risperidone in combination with mood stabilizers for acute mania: a multicentre, open study. *Int Clin Psychopharmacol* (2004a) 19(5):299–303. doi: 10.1097/01.yic.0000138821.85744.20
53. Bahk WM, Yoon BH, Lee KU, Chae JH. Combination of mood stabilizers with quetiapine for treatment of acute bipolar disorder: an open label study. *Hum Psychopharmacol* (2004b) 19(3):181–5. doi: 10.1002/hup.577
54. Hantouche EG, Akiskal HS, Lancrenon S, Chatenêt-Duchêne L. Mood stabilizer augmentation in apparently "unipolar" MDD: predictors of response in the naturalistic French national EPIDEP study. *J Affect Disord* (2005) 84(2-3):243–9. doi: 10.1016/j.jad.2004.01.006
55. Patel NC, Crismon ML, Pondrom M. Rehospitalization rates of patients with bipolar disorder discharged on a mood stabilizer versus a mood stabilizer plus an atypical or typical antipsychotic. *J Behav Health Serv Res* (2005) 32(4):438–45. doi: 10.1007/bf02384203
56. Chengappa RKN, Schwarzman LK, Hulihan JF, Xiang J, Rosenthal NR. Clinical Affairs Product Support Study-168 Investigators. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* (2006) 67(11):1698–706. doi: 10.4088/jcp.v67n1105
57. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PEJr, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* (2006) 163(2):232–9. doi: 10.1176/appi.ajp.163.2.232
58. Parker G, Tully L, Olley A, Hadzi-Pavlovic D. SSRIs as mood stabilizers for Bipolar II Disorder? A proof of concept study. *J Affect Disord* (2006) 92(2-3):205–14. doi: 10.1016/j.jad.2006.01.024
59. Spaulding T, Westlund R, Thomason C, White R, Dann R, Thompson T. Adjunctive treatment for mood stabilization of patients with bipolar I disorder treated with lamotrigine. *CNS Spectr* (2006) 11(9):711–6; quiz 719. doi: 10.1017/s1092852900014802
60. Savas HA, Yumru M, Kaya MC, Selek S. Atypical antipsychotics as "mood stabilizers": a retrospective chart review. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) 31(5):1064–7. doi: 10.1016/j.pnpbp.2007.03.007
61. Tramontina S, Zeni CP, Pheula G, Rohde LA. Topiramate in adolescents with juvenile bipolar disorder presenting weight gain due to atypical antipsychotics or mood stabilizers: an open clinical trial. *J Child Adolesc Psychopharmacol* (2007) 17(1):129–34. doi: 10.1089/cap.2006.0024
62. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* (2007) 164(12):1817–24; quiz 1923. doi: 10.1176/appi.ajp.2007.06101639
63. Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR. Quetiapine and classical mood stabilizers in the long-term treatment of Bipolar Disorder: a 4-year follow-up naturalistic study. *J Affect Disord* (2008) 110(1-2):135–41. doi: 10.1016/j.jad.2008.01.017
64. Dell'Osso B, Buoli M, Riundi R, D'Urso N, Pozzoli S, Bassetti R, et al. Clinical characteristics and long-term response to mood stabilizers in patients with bipolar disorder and different age at onset. *Neuropsychiatr Dis Treat* (2009) 5:399–404. doi: 10.2147/NDT.S5970
65. Goldberg JF, Calabrese JR, Saville BR, Frye MA, Ketter TA, Suppes T, et al. Mood stabilization and destabilization during acute and continuation phase

treatment for bipolar I disorder with lamotrigine or placebo. *J Clin Psychiatry* (2009) 70(9):1273–80. doi: 10.4088/JCP.08m04381
66. Chang JS, Moon E, Cha B, Ha K. Adjunctive lamotrigine therapy for patients with bipolar II depression partially responsive to mood stabilizers. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) 34(7):1322–6. doi: 10.1016/j.pnpbp.2010.07.020
67. Quante A, Zeugmann S, Luborzewski A, Schommer N, Langosch J, Born C, et al. Aripiprazole as adjunct to a mood stabilizer and citalopram in bipolar depression: a randomized placebo-controlled pilot study. *Hum Psychopharmacol* (2010) 25(2):126–32. doi: 10.1002/hup.1096
68. Muzina DJ, Gao K, Kemp DE, Khalife S, Ganocy SJ, Chan PK, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry* (2011) 72(6):813–9. doi: 10.4088/JCP.09m05570gre
69. Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. *Curr Med Res Opin* (2012) 28(5):701–13. doi: 10.1185/03007995.2012.666961
70. Koukopoulos A, Serra G, Koukopoulos AE, Reginaldi D, Serra G. The sustained mood-stabilizing effect of memantine in the management of treatment resistant bipolar disorders: findings from a 12-month naturalistic trial. *J Affect Disord* (2012) 136(1-2):163–6. doi: 10.1016/j.jad.2011.09.040
71. Goldberg JF. A preliminary open trial of nefazodone added to mood stabilizers for bipolar depression. *J Affect Disord* (2013) 144(1-2):176–8. doi: 10.1016/j.jad.2012.04.037
72. Norris ER, Burke K, Correll JR, Zemanek KJ, Lerman J, Primelo RA, et al. A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. *J Affect Disord* (2013) 144(1-2):141–7. doi: 10.1016/j.jad.2012.06.023
73. Chen H, Mehta S, Aparasu R, Patel A, Ochoa-Perez M. Comparative effectiveness of monotherapy with mood stabilizers versus second generation (atypical) antipsychotics for the treatment of bipolar disorder in children and adolescents. *Pharmacoepidemiol Drug Saf* (2014) 23(3):299–308. doi: 10.1002/pds.3568
74. Sharma PS, Kongasseri S, Praharaj SK. Outcome of mood stabilizer discontinuation in bipolar disorder after 5 years of euthymia. *J Clin Psychopharmacol* (2014) 34(4):504–7. doi: 10.1097/JCP.0000000000000160
75. Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PK, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. *Am J Psychiatry* (2014) 171(10):1067–73. doi: 10.1176/appi.ajp.2014.13111501
76. Weiser M, Burshtein S, Gershon AA, Marian G, Vlad N, Grecu IG, et al. Allopurinol for mania: a randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. *Bipolar Disord* (2014) 16(4):441–7. doi: 10.1111/bdi.12202
77. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. *J Affect Disord* (2015) 185:31–7. doi: 10.1016/j.jad.2015.05.070
78. Hochman E, Krivoy A, Schaffer A, Weizman A, Valevski A. Antipsychotic adjunctive therapy to mood stabilizers and 1-year rehospitalization rates in bipolar disorder: A cohort study. *Bipolar Disord* (2016) 18(8):684–91. doi: 10.1111/bdi.12459
79. Shansis FM, Reche M, Capp E. Evaluating response to mood stabilizers in patients with mixed depression: A study of agreement between three different mania rating scales and a depression rating scale. *J Affect Disord* (2016) 197:1–7. doi: 10.1016/j.jad.2016.02.064
80. Yatham LN, Vieta E, Goodwin GM, Bourin M, de Bodinat C, Laredo J, et al. Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *Br J Psychiatry* (2016a) 208(1):78–86. doi: 10.1192/bjp.bp.114.147587
81. Yatham LN, Beaulieu S, Schaffer A, Kauer-Sant'Anna M, Kapczinski F, Lafer B, et al. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: A CANMAT randomized double-blind trial. *Mol Psychiatry* (2016b) 21(8):1050–6. doi: 10.1038/mp.2015.158
82. Ahn SW, Baek JH, Yang SY, Kim Y, Cho Y, Choi Y, et al. Long-term response to mood stabilizer treatment and its clinical correlates in patients with bipolar disorders: a retrospective observational study. *Int J Bipolar Disord* (2017) 5(1):24. doi: 10.1186/s40345-017-0093-5
83. Garriga M, Solé E, González-Pinto A, Selva-Vera G, Arranz B, Amann BL, et al. Efficacy of quetiapine XR vs. placebo as concomitant treatment to mood stabilizers in the control of subthreshold symptoms of bipolar disorder: Results from a pilot, randomized controlled trial. *Eur Neuropsychopharmacol* (2017) 27(10):959–69. doi: 10.1016/j.euroneuro.2017.08.429
84. Perugi G, Vannucchi G, Barbuti M, Maccariello G, De Bartolomeis A, Fagiolini A, et al. Outcome and predictors of remission in bipolar-I patients experiencing manic episode and treated with oral antipsychotics and/or mood stabilizers: a prospective observational study in Italy. *Int Clin Psychopharmacol* (2018) 33(3):131–9. doi: 10.1097/YIC.0000000000000211
85. Bauer M, Glenn T, Alda M, Bauer R, Grof P, Marsh W, et al. Trajectories of adherence to mood stabilizers in patients with bipolar disorder. *Int J Bipolar Disord* (2019) 7(1):19. doi: 10.1186/s40345-019-0154-z
86. Hafeman DM, Rooks B, Merranko J, Liao F, Gill MK, Goldstein TR, et al. Lithium versus other mood stabilizing medications in a longitudinal study of bipolar youth. *J Am Acad Child Adolesc Psychiatry* (2019), S0890–8567(19)31399-1. doi: 10.1016/j.jaac.2019.06.013
87. Steardo L, Fabrazzo M, Sampogna G, Monteleone AM, D'Agostino G, Monteleone P, et al. Impaired glucose metabolism in bipolar patients and response to mood stabilizer treatments. *J Affect Disord* (2019) 245:174–9. doi: 10.1016/j.jad.2018.10.360
88. Tournier M, Neumann A, Pambrun E, Weill A, Chaffiol JP, Alla F, et al. Conventional mood stabilizers and/or second-generation antipsychotic drugs in bipolar disorders: A population-based comparison of risk of treatment failure. *J Affect Disord* (2019) 257:412–20. doi: 10.1016/j.jad.2019.07.054
89. Tavormina G. Bipolar disorders and bipolarity: the notion of the "mixity". *Psychiatr Danub* (2019) 31(Suppl 3):S434–7.
90. Tavormina G. An approach to treat bipolar disorders mixed states. *Psychiatr Danub* (2016) 28(Suppl-1):9–12.
91. Etain B, Lajnef M, Henry C, Aubin V, Azorin JM, Bellivier F, et al. FACE-BD Clinical Coordinating Center (FondaMental Foundation); FACE-BD Data Coordinating Center (FondaMental Foundation); FACE-BD Clinical Sites and Principal Collaborators in France. Childhood trauma, dimensions of psychopathology and the clinical expression of bipolar disorders: A pathway analysis. *J Psychiatr Res* (2017) 95:37–45. doi: 10.1016/j.jpsychires.2017.07.013
93. Rapinesi C, Serata D, Del Casale A, Simonetti A, Milioni M, Mazzarini L, et al. Successful and rapid response to electroconvulsive therapy of a suicidal patient with comorbid bipolar I disorder and histrionic personality disorder. *J ECT* (2012) 28(1):57–8. doi: 10.1097/YCT.0b013e3182218c8c
94. Rapinesi C, Del Casale A, Di Pietro S, Ferri VR, Piacentino D, Sani G, et al. Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder. *Neurosci Lett* (2016) 629:(43–47.
92. Bersani FS, Girardi N, Sanna L, Mazzarini L, Santucci C, Kotzalidis GD, et al. Deep transcranial magnetic stimulation for treatment-resistant bipolar depression: a case report of acute and maintenance efficacy. *Neurocase* (2013) 19(5):451–7. doi: 10.1080/13554794.2012.690429

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 07 May 2020
doi: 10.3389/fpsyt.2020.00377

Lithium Treatment Over the Lifespan in Bipolar Disorders

Constantin Volkmann[1]*, *Tom Bschor*[2,3] *and Stephan Köhler*[1]

[1] Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Berlin, Germany, [2] Department of Psychiatry, Schlosspark Hospital Berlin, Germany, [3] Department of Psychiatry and Psychotherapy, University Hospital, Technical University of Dresden, Dresden, Germany

Lithium has been the treatment of choice for patients with bipolar disorder (BD) for nearly 70 years. It is recommended by all relevant guidelines as a first-line treatment for maintenance therapy. In this review, we outline the current state of evidence for lithium in the treatment of BD over the lifespan. First, we summarize the evidence on efficacy in general, from relapse prevention to acute anti-manic treatment and its role in treating mood episodes with mixed features and bipolar depression. As patients are often treated for many years and different aspects have to be considered in different phases of life, we discuss the particularities of lithium in the treatment of paediatric BD, in older aged individuals and in pregnant women. Lastly, we discuss the evidence on lithium's proposed suicide-preventive effects, the dangers of rapid discontinuation and lithium's adverse effects, particularly with regard to long-term treatment.

Keywords: bipolar disorder, lithium, efficacy, lifespan, suicidality, discontinuation

OPEN ACCESS

Edited by:
Janusz K. Rybakowski, Poznan University of Medical Sciences, Poland

Reviewed by:
Leonardo Tondo, Centro Lucio Bini, Italy
Giuseppe Tavormina, Independent Researcher, Provaglio d'Iseo, Italy

***Correspondence:**
Constantin Volkmann
constantin.volkmann@charite.de

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *25 February 2020*
Accepted: *15 April 2020*
Published: *07 May 2020*

Citation:
Volkmann C, Bschor T and Köhler S (2020) Lithium Treatment Over the Lifespan in Bipolar Disorders. Front. Psychiatry 11:377. doi: 10.3389/fpsyt.2020.00377

BACKGROUND

Bipolar disorder (BD) is an episodic illness with a very heterogeneous clinical course. It usually presents as a severe, chronic, and disabling condition characterized by mood alterations between euthymia, major depression, and (hypo-)mania. The estimated lifetime prevalence ranges from 0.6% to 2.4% worldwide (1, 2). BD is usually a lifelong disease, hence requiring lifelong treatment strategies. One of the major pharmacological agents in the treatment of BD is lithium. It remains the gold standard in preventing recurrences in BD I (mania and depressive episodes) and BD II (hypomania and depressive episodes) and is effective in the treatment of mania. Additionally, the proposed anti-suicide effect of lithium is unique and potentially of high relevance in the treatment of BD over the lifespan, as patients with BD suffer from high suicide rates (3). Over the last decades, other substances such as second generation antipsychotics (SGA) and anticonvulsants have been prescribed more frequently and there has been a tendency to avoid lithium in the treatment of BD. Reasons may be the overestimation of potential side effects as compared to other substances by professionals and patients alike, despite the highly problematic metabolic profile of antipsychotics (e.g., Olanzapine), particularly over the lifespan (4).

This narrative review focuses on lithium-treatment over the lifespan in BD and gives a summary of its effectiveness, side effects, and treatment recommendations with regard to specific treatment conditions and subtypes of BD. Furthermore, we discuss the risk of lithium-discontinuation, which is an important topic in the treatment of BD over the lifespan.

EFFICACY OF LITHIUM IN BD

The pharmacological treatment of BD has several goals. Lithium is the agent of the "first hour" in the treatment of BD and has been used over decades in all phases of the disease. Lithium treatment aims at the prevention of relapses and is used in the treatment of acute episodes, such as mania, depression, and specific subtypes, such as mood episodes with mixed features or rapid cycling (RC) (see below). Especially with regard to the lifespan, the efficacy of lithium in special treatment conditions, such as BD in paediatric and older aged patients and BD during pregnancy and postpartum are of high relevance. For each of these conditions, different recommendations are available from different treatment guidelines (5). The German S3 guidelines also recommends lithium as the first choice of treatment for patients with high risk for suicidality (6). First, we give a short summary of the general effects of lithium in mania, depression, and maintenance treatment of BD.

Lithium in Maintenance Treatment

Preventing new episodes in BD is essential with regard to quality of life, participation in society and preventing long-term disability. Lithium remains the gold standard in achieving this goal. It is effective in both type I and type II BD (e.g., (5)). Only for lithium, randomized controlled trials (RCTs) without an "enriched design", favoring the substance to be investigated, have been performed (7, 8). Several meta-analyses of randomized placebo-controlled, long-term trials could verify that lithium significantly reduces the risk of new episodes (mania and depression) compared to placebo (e.g., (9–12)). A Cochrane review found the risk of any relapse to be 36% for lithium and 61% for Placebo over the course of 1 year, corresponding to an absolute risk reduction of 25% [NNT = 4, (13)]. Kessing et al. as well as Hayes et al. found lithium monotherapy to be superior to monotherapy with other maintenance mood stabilizers in real life conditions (14, 15). This is reflected by its status as the first-line drug in many international guidelines (5). For optimal efficacy in long-term treatment of BD, target serum levels should generally be around 0.6–0.8 mmol/L, while specific treatment situations and patients may require slightly higher or lower lithium levels (16).

Lithium in Treatment of Mania

While manic episodes are often the most impressive part of BD, their duration is usually shorter compared to that of other disease phases in both BD-I and BD-II. A number of pharmacological agents have been investigated and have proven their efficacy in the treatment of mania, including lithium (17). The network meta-analysis by Cipriani et al. found an effect size of 0.40 SMD, indicating a moderately sized effect, which is comparable to other anti-manic agents (18). For example, lithium showed a comparable efficacy to quetiapine in a 12-week RCT (19). Despite its proven anti-manic properties, lithium has lost some of its relevance in the treatment of mania in the recent years, partly due to the large number of SGAs that have been licensed for this indication. Reasons for favoring SGAs over lithium include the shorter time of dosage increase and sedation, a common side effect of SGAs that is often welcomed during manic agitation. Further potential disadvantages of lithium include the small therapeutic window and hence the necessity for repeated serum level controls (20). In addition, no parenteral application is available for lithium. Notwithstanding these limitations, lithium should be considered as a first-line therapy for manic episodes, as long-term phase-prophylactic treatment is almost always required afterward, for which lithium is considered the first choice. In the treatment of manic episodes, higher levels of 0.8 to 1.2 mmol/L are required in order to achieve optimal response.

Lithium in Treatment of Bipolar Depression

Bipolar depression is the predominant pole in BD type I and type II and responsible for a large number of suicides. The suicide rate is 20-times above that of the general-population (21), which is considerably larger than that of unipolar depression (22). Bipolar depression is also associated with a high rate of morbidity and mortality due to comorbid somatic disorders (23). However, treatment of bipolar depression is challenging for clinicians, as the classical treatment strategies of unipolar depression (antidepressants, lithium) show small(er), if any, effects (24). The lack of effectiveness of antidepressants in BD has been the topic of an ongoing controversy (25, 26). There is evidence that antidepressants may worsen the course of the disease in patients with mixed symptoms or RC by increasing the switch risk or causing tachyphylaxis after repeated antidepressant drug exposures (27).

Similarly, the available data strongly doubt the effectiveness of lithium in treating bipolar depression. The large EMBOLDEN I study found that lithium was not more effective than placebo in treating bipolar depression (28). In an open-label RCT comparing venlafaxine and lithium in bipolar depression in BD type II, lithium was significantly less effective than the antidepressant (29). However, relatively low lithium serum levels are a possible limitation of this and several other trials investigating lithium in the treatment of bipolar depression. Albeit the lack of evidence supporting lithium monotherapy in the treatment of bipolar depression, there are substantial differences in international treatment guidelines with regard to the role of lithium in bipolar depression (30). Some guidelines, such as the CANMAT guidelines (31), still regard lithium as a first line treatment option in bipolar depression. These guidelines argue that lithium should be considered in the acute treatment of bipolar depression due to its central role as a mood stabilizer, its effectiveness in preventing mania and the proposed anti-suicide effect. These guidelines highlight the low number of studies investigating lithium in bipolar depression and the limitations of these studies. Contrarily, the German S3 guideline does not recommend the use of lithium monotherapy in the treatment of bipolar depression (6). The WFSBP guideline agrees with that recommendation and emphasizes the combination therapy of lithium with other agents in bipolar depression (32).

LITHIUM IN EPISODES WITH MIXED FEATURES AND RAPID CYCLING

BD, especially in the lifelong course, is typically characterized by recurring mood episodes of opposite polarity. However, patients may also experience episodes in which depressive and manic symptoms co-occur. These phases were traditionally called mixed states or mixed episodes. The DSM-5 substituted these terms by the so-called "mixed specifier", which indicates the presence of mixed symptoms in either (hypo-)manic or depressive episodes (33). Patients with mixed features in the course of their illness have a considerably higher risk to commit suicide and higher rates of (psychiatric) comorbidities (e.g., anxiety disorders, substance dependence and personality disorders). They suffer from high rates of relapses and experience a larger number of new episodes compared to BD patients without mixed symptoms (34).

Treatment of patients suffering from affective episodes with mixed features is particularly demanding for clinicians, especially as there is a lack of RCTs investigating these patients. The available data on the effectiveness of lithium in mood episodes with mixed symptoms are inconclusive (33, 35). In patients with a manic episode and additional depressive symptoms, lithium was found to be less effective than valproate (36).

Studies investigating the effectiveness of lithium in the maintenance therapy found it to be less effective in patients with mixed symptoms than in patients with "pure" mania. However, episodes with mixed features may generally be more difficult to treat than classic episodes. A *post hoc* analysis of lithium in "dysphoric mania" even found lithium not to be more effective than placebo (37). However, there are several shortcomings of all of these studies, for example the post-doc design and limitations with regard to the patient population. Given the high rates of suicidality during episodes with mixed symptoms and the anti-suicide properties of lithium, it should not be ignored as a pharmacological treatment-option in these patients. However, (more) positive data (mainly based on *post hoc* analyses) are available for SGAs and valproate in the treatment of BD with mixed features.

Another clinical phenotype of BD is the concept of RC. RC is defined as a course of BD that includes at least four distinct mood episodes (including major depressive, manic, hypomanic, with or without mixed features) occurring within a 12-month period. RC has a lifetime prevalence of 5 to 33 % among BD patients, which emphasizes its clinical relevance (38, 39). Patients with RC suffer from a higher burden of symptoms, higher rates of suicide attempts and completed suicides and they are frequently suffering from other psychiatric comorbidities over the lifespan of BD (40, 41). Patients with RC show a prolonged and complex course of their disease and high rates of treatment failure compared to patients without RC (42). Risk factors that are associated with the onset of RC are female gender, hypothyroidism, and antidepressant medication (43).

Only very little data on the treatment of RC are available from randomized clinical trials. Naturalistic and non-controlled studies suggest that lithium is less effective in patients with RC than in those without (44). However, all available treatments show lower effectiveness in patients with RC and lithium may show better efficacy than other mood stabilizers except for valproate (45). In a re-analysis of patients with BP II receiving venlafaxine and lithium, however, there were no differences in response or relapse rates between patients with or without RC (46). In a study from Suppes et al., no differences could be found between lithium and lamotrigine in reducing depressive symptoms in patients with bipolar depression and RC (47). Regarding long-term treatment of BD and RC, lithium has been investigated in a prospective trial (cross-over design, duration of 2 years) in comparison to carbamazepine or the combination of both (48). Lithium monotherapy was inferior to the combination therapy in patients with a history of RC, while there was no difference to carbamazepine monotherapy. In addition, lithium monotherapy was equally effective in comparison to a combination treatment of lithium and valproate in RC (relapse rates) and in comparison to valproate monotherapy (49).

LITHIUM IN PAEDIATRIC BIPOLAR DISORDERS

BD often begins in adolescence (50) and usually requires lifelong treatment including pharmacotherapy and psychosocial interventions (51). It is important to distinguish between paediatric and adult BD when choosing the appropriate medication, as side effects may affect patients of different age groups differentially.

Lithium has been approved for the acute and maintenance treatment of mixed and manic episodes of BD I in children and adolescents (age from 7 to 17 years) by the FDA. The effectiveness of lithium in paediatric patients has been demonstrated by numerous studies [e.g., (52, 53)].

In young patients with BD, the risks and benefits of pharmacological (long-term) treatment have to be balanced even more carefully, as the longer duration of exposure to the medication poses particular risks of adverse events. Before starting lithium treatment, standard examinations such as baseline laboratory checks of thyroid hormones, creatinine, blood salts, and calcium levels should be performed. The monitoring of lithium-levels and of other blood parameters is comparable to that of adults. As in all BD patients but especially in paediatric BD, the spectrum of lithium adverse effects should be thoroughly discussed, especially with regard to lithium intoxication. In adolescents, adequate hydration during the summer and during high levels of physical activity are important concerns the patient should be informed of. Cases of significant dehydration (such as due to emesis or diarrhoea) can make a dose reduction or pausing of the medication necessary. Like in adults, thyroid hormone status has to be closely monitored, as lithium may lead to hypothyroidism requiring the substitution of thyroid hormones (54). In paediatric BD, acute and long-term treatment with lithium seems to have relatively little effect on body weight (53, 55)

and may therefore be preferred to antipsychotics with their unfavorable metabolic profile. Serious side effects of lithium in paediatric BD, which have been reported and therefore must be recognized, are suicidal ideation, change of blood cell count, and neurological side effects (54).

Dosing Strategies in Paediatric BD

The elimination half-time of lithium is significantly shorter and the clearance of lithium significantly higher in paediatric patients. Therefore, Landersdorfer et al. (56) recommend a twice-daily dosing of lithium to achieve acceptable blood concentrations. Data are missing for once-daily dosing of lithium in paediatric BD and is thus not recommended.

To summarize, lithium is an effective treatment strategy in the treatment of paediatric BD in different phases of the disease, in mixed and manic episodes and in the maintenance phase.

LITHIUM USE IN PREGNANT AND POSTPARTUM WOMEN WITH BD

Women with BD are at an elevated risk of recurrence during the peripartum and postpartum period with relapse rates as high as 40–70% (57, 58). Recent research suggests that lithium discontinuation may be responsible for the elevated relapse risk during pregnancy, as pregnancy itself only has a small or even no effect on relapse rates in BD (57, 59). A majority of pregnant women with BD decide to self-discontinue lithium or even have problems getting a prescription for lithium (60, 61). There is a high variability in the available information and recommendations regarding lithium treatment during pregnancy (62). While lithium is the most recommended agent in BD during pregnancy, there is a lack of high-quality data. Observational studies support the use of lithium in the postpartum period in relapse prevention (58). However, the benefits of relapse prevention have to be weighed against potential adverse effects on mother and child (63).

One major fear is the assumed teratogenicity of lithium during pregnancy, especially the risk of Ebstein's anomaly. In one of the largest cohort studies, Paterno et al. found that lithium intake during the first trimester is associated with an increased risk of cardiac malformations. In this study the adjusted risk ratio for cardiac malformations between exposed and non-exposed infants was 1.65 (95% confidence interval [CI], 1.02 to 2.68) and it showed a dose-dependent relationship. Nevertheless, the effect size was lower than previously assumed, with an absolute risk increase of 1.25% (64). In a meta-analysis by Munk-Olsen (65), lithium intake during pregnancy did not correlate with complications during pregnancy or delivery. However, the authors reported an increased risk for "cardiovascular defects, neural tube defects, hypospadias, and epispadias (OR 1.71), but not for major cardiac malformations (e.g., Ebstein's anomaly)". For a detailed overview, we recommend the review of Hermann et al. (62).

Several experts recommend continuing lithium in patients with BD I who have been stable on lithium to prevent relapse or even mood instability. Nonetheless, a critical discussion should be held with the patient that involves the risks, benefits, and alternatives for treatment during pregnancy and postpartum. Changing of medication during pregnancy and postpartum should be avoided when possible (62). Patients continuing taking lithium should take a reduced dosage or even stop taking lithium in the critical period of heart development (4 to 12 weeks). However, lithium should never be discontinued abruptly. An increase in the GFR and an expansion of the blood volume occurring during pregnancy can cause a decrease in lithium levels during the first and second trimesters (66). Therefore, the lithium dosage may have to be increased in order to ensure sufficient lithium levels (67). Most guidelines propose to check lithium levels every 2 to 4 weeks, for the last trimester a weekly check is recommended (63, 66, 68, 69). Further monitoring is needed if patients develop preeclampsia, hyperemesis gravidarum, or suffer from fever. During the first trimester and concurrent lithium treatment, foetal ultrasound should be performed to check for cardiac malformations (63, 70, 71).

Lithium and Breastfeeding

There is a controversial debate on whether or not lithium should be continued during breastfeeding, since studies investigating its effects on the child are scarce (70). As there is an increased chance of a recurrence of BD with lithium discontinuation in general (57) and during the postpartum period in particular, a change of treatment regimen for breastfeeding is not the first choice. In support of this, Bergink (72) could verify that patients with a new episode of BD during postpartum taking lithium had fewer recurrences after 9-month postpartum compared to patients receiving an antipsychotic treatment. Most of the guidelines conclude with a negative benefit-risk ratio for breastfeeding during lithium treatment (63, 70).

LITHIUM IN OLDER AGE BIPOLAR DISORDER

Patients aged 60 years and older account for a quarter of all BD patients (73). Nonetheless, pharmacological and non-pharmacological treatment strategies in these individuals are hardly studied in RCTs (74). BD patients in older age have a significantly reduced life expectancy of up to 15 to 20 years. They are at a higher risk of suffering from metabolic syndrome, cardiovascular diseases, general renal diseases and cognitive decline (75–77) compared to the general population. The lower life expectancy means that older patients may be exposed to prophylactic medication for a shorter period of time than younger patients, potentially translating to a reduced risk of long-term side effects (e.g., with regard to kidney function). Based on the available data, there are treatment recommendations for BD in older age in international treatment guidelines (31).

Lithium is considered the first line medication in older aged patients with BD in the maintenance treatment. It is recommended for the prevention of depression and mania given the evidence from adult studies, but also because the

largest number of studies has been conducted for lithium in geriatric patients (73). However, due to concerns regarding tolerability and adverse events, lithium is prescribed less frequently in older individuals, although it is usually well tolerated by most of these patients (78, 79).

The randomized controlled GERI–BD trial investigated the efficacy and tolerability of lithium and divalproex in the treatment of mania in older age (60 years and above). Target serum concentrations were 0.80–0.99 mEq/L for lithium and 80–99 μm/L for valproate.

In this trial, lithium and valproic acid demonstrated to be equally effective in the 3-week follow-up (74) but lithium was more effective in reducing manic symptoms after the 9-week follow-up (74). Lithium and valproate showed a comparable frequency of side effects and were generally tolerated, providing evidence for lithium and valproate to be relatively safe with few adverse effects in BD in older adults.

Special Considerations for Using Lithium in Older Age

It is recommended that therapeutic lithium levels should be lower in patients with BD and older age (31, 80, 81). Dehydration is common in older patients and should be prevented, particularly if lithium is prescribed. Special attention should be paid, if other substances are prescribed that carry a risk of increasing lithium blood levels. Medications that should be prescribed carefully under these circumstances are diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), but also non-steroidal anti-inflammatory drugs (NSAIDs). Lithium blood levels and renal parameters should be checked regularly, especially at the beginning of the treatment (82, 83).

The recommended lithium levels in BD patients in older age are 0.4–0.8 mmol/L (31). For depressive episodes and maintenance therapy, serum concentrations are recommended to be low as 0.4–0.6 mmol/L (9). The recommended serum levels for the treatment of mania are indicated at 0.4–0.8 mmol/L for ages 60–79 years and a bit lower (0.4–0.7 mmol/L) for patients with the age of 80 and above (80). This is reasonable as lithium levels higher than 0.8 mmol/L may cause neurocognitive and neurological symptoms (84) and renal side effects (85). Long-term treatment with lithium is associated with a reduction of the GFR and a twofold increased risk of chronic kidney disease (86). Patients with BD in older age are consequently at a higher risk of these adverse effects after having taken lithium for several years (78). Lithium levels and renal function should therefore be controlled every 3 months in patients aged 65 and above.

SIDE EFFECTS OF LITHIUM OVER THE LIFESPAN

Lithium treatment is associated with a number of undesired side-effects that involve different organ systems. Gastro-intestinal complaints such as nausea, vomiting, and diarrhoea are relatively common. Nausea affects around 10–20% of patients, particularly in the early phase of treatment and often diminishes with longer treatment duration (87). Fine hand tremor is reported by about 25% of patients treated with lithium (88), the absolute risk increase was 9.6% compared to placebo in short-term trials [NNH = 10, (89)]. Clinically, it presents as postural tremor and its frequency and intensity correlate with lithium serum levels (90). Management mainly includes dose reduction. Pharmacological management with propranolol is recommended only in cases of severe tremor, as beta-blockers may introduce other side-effects (91).

The risk of hypothyroidism is increased 5.78-fold compared to placebo (92) and lithium may lead to increased blood calcium and parathyroid hormone levels (93). TSH and calcium levels should therefore be monitored regularly; hypothyroidism can be managed by levothyroxine substitution and is no reason for discontinuing lithium.

Cardiological harms may also arise from lithium treatment. In a recent review, the most common ECG abnormality was T wave inversion. Further alterations include QT prolongation and ventricular tachyarrhythmias (94).

Renal complications are another important concern in lithium-treated patients. A reduced concentration ability of the kidneys is associated with longer treatment duration (95) and is found in 54% to 73% of patients (95, 96). With lithium treatment, an excess decline of 15% in the kidney's ability to concentrate urine is found compared to untreated controls (92). However, as these results stem from observational data, they have to be interpreted with caution. A reduced concentration ability can manifest as a nephrogenic diabetes insipidus (NDI), clinically characterized by polyuria and polydipsia. Patients with NDI are at higher risk of lithium intoxication and should therefore be monitored more closely (97). Early detection is recommended and involves the assessment of "urine volume, frequency of urination, nycturia, thirst, and fluid intake". Several treatment options have been suggested with limited evidence (97). In almost all cases, NDI is reversible when lithium is stopped.

With long-term use, lithium can cause chronic tubulo-interstitial nephritis, which is characterized by a decrease in the glomerular filtration rate (GFR) and may lead to chronic kidney disease (lithium nephropathy) (97, 98). While a detrimental effect of lithium on the kidneys seems certain, it remains unclear to which extend the observed decline in GFR is due to age-related renal impairment. A reduction in GFR of 0–5 ml/min is seen over 1 year and the risk of renal failure has been estimated to be about 0.5% compared to 0.2% in controls (92). A clinically relevant impairment of the renal function does usually not occur before at least 15 years of lithium treatment (99). Due to a lack of long-term studies, the evidence on lithium nephropathy is scarce and no clear recommendations regarding its management exist (97). If the kidney function is impaired, reducing the dosage or stopping lithium treatment may be necessary. Unlike NDI, renal failure may not be reversible upon lithium discontinuation.

A potential negative effect of lithium on cognition has been debated for many years. Typical complaints of lithium-treated individuals involve lethargy, fatigue, lack of mental clarity, and

an inability to concentrate (100). Cognitive side effects may be a reason for non-adherence to lithium treatment (101). While BD is associated with cognitive dysfunctions, it remains unclear, to which extend these arise due to the illness or the treatment. A recent narrative review concluded that lithium may improve some cognitive functions while deteriorating others (102). Lithium negatively affects "immediate verbal learning and memory (SMD 0.29, 95% CI 0.07 to 0.51), creativity (SMD 0.34, 95% CI 0.00 to 0.68) and psychomotor performance (SMD 0.62, 95% CI 0.27 to 0.97)", although these findings are based on relatively few patients (103). Lithium-induced hypothyroidism may be partly responsible for these cognitive deficits that can thus be counter-acted by levothyroxine substitution (104). In contrast, evidence from preclinical (105, 106) and clinical research (107) suggests that lithium may have beneficial effects on the incidence and progression of dementia. In support of this, a large population-based study found a negative correlation between lithium intake and dementia incidence (108). Patients with BD have a higher risk of developing dementia compared to the general population and lithium may be protective in these patients (109).These findings are based mainly on correlational data, however, and thus need confirmation by randomized trials.

A well-known and often unpleasant side-effect is weight gain. It is seen more often than with placebo (OR 1.89, 95% CI 1.27 to 2.82, p=0.002). Bowden et al. reported an average increase in body weight of 6 kg after a treatment duration of 1 year. Interestingly, weight gain was only observed in patients that already were obese at the beginning of the study. Among non-obese people, no such weight gain was observed (110).

Serum levels of lithium have to be closely monitored to avoid lithium intoxication, particularly in the elderly. Lithium intoxication is characterized by confusion, gross tremor (as opposed to a fine tremor as a typical side effect with therapeutic serum levels), ataxia, falls, convulsions, and gastrointestinal symptoms such as vomiting and diarrhoea. A retrospective cohort study found it to occur in around 1 in 100 person-years (111). Among 1,340 patients that were followed for 17 years, no deaths due to lithium intoxication were reported. Management includes stopping lithium, giving water (per os or parenterally), haemodialysis, and forced diuresis (111).

There are a few contraindications that need to be considered before initiating lithium treatment. These include cardiac pre-conditions such as certain types of arrythmias (e.g., Brugada syndrome), previous or current myocardial infarction and kidney failure.

LITHIUM AND SUICIDALITY

The life expectancy of patients with BD is reduced by about 10 years compared to the general population (112) and the mortality gap seems to be increasing rather than decreasing over the years (113). A major cause of death is suicide, which is around 20–30-fold more frequent than in the general population (114). Around 25–50% of patients with BD attempt suicide at some point in their life and around 15% of patients die of suicide (115). The prevention of suicides is therefore a pivotal goal in the treatment of BD.

Lithium has been associated with a reduced suicide risk in patients with affective disorders including BD in a number of studies with varying methodology (116–118). Long-term studies suggest a strong suicide-preventing effect with suicides being 82% less frequent during lithium treatment (119). The studies supporting this suicide-preventing effect often include observational data, however, which are prone to bias. Adherence to lithium treatment and lower risk for suicidal behavior may correlate spuriously and may at least in part not be causally related (120). Lithium treatment is likely to be introduced when patients are at their worst, followed by a period of improvement. The increase in suicide risk after discontinuation of lithium treatment may be due to rebound depression or withdrawal effects. Additionally, patients may stop their lithium medication because their health is deteriorating, while continuously adhering to their medication when they are doing well.

More reliable evidence comes from RCTs. The largest meta-analysis investigating lithium and suicidality in RCTs found a reduction in suicides from 6/241 in the placebo group to 0/244 in the lithium group, corresponding to an absolute risk reduction of 2.5% [NNT = 40, (3)]. Only one trial did not use a withdrawal design, which may introduce bias due to withdrawal effects in the placebo group. This 1-year trial reported three suicides in the placebo arm and 0 suicides in the lithium arm, making the estimate more uncertain (121)

A relationship between lithium concentrations in tap water and a reduced suicide risk has even been postulated multiple times (122), which a more recent study did not replicate (122). The mechanism by which lithium may reduce suicides is hypothesized to be the reduction of impulsive and aggressive behavior in bipolar and depressed patients. By some authors, it is thought to have a specific anti-suicide effect exceeding its mood stabilizing properties (123).

As suicides are a special case of death, all-cause mortality seems a more relevant outcome, unless deaths of other causes (such as due to lithium intoxication or kidney failure) are favored over suicides. Investigating this, Cipriani et al. included eight RCTs with 782 patients and found a reduction in all-cause mortality in the lithium group of 2.31% over an average of around 81.5 weeks (Absolute risk: 5/392 (1.28%) vs. 14/392 (3.59%), absolute risk reduction: 2.31%, corresponding to an NNT = 43). This risk reduction was rather uncertain, however, with a wide 95% confidence interval for the odds ratio of 0.15 to 0.95.

It is possible that the mortality rate of patients treated with lithium is not constant over time. Specifically, lithium-induced deaths due to harms such as kidney failure may result after year-long exposures, thereby possibly reducing the overall benefit on mortality.

As the absolute risk reduction is rather small, it seems uncertain, if lithium reduces overall mortality over a course of years, which is the usual duration of treatment.

DISCONTINUATION OF LITHIUM

Psychiatric patients, including patients with BD, often stop medication, e.g., due to concepts of their illness and treatment that differ from those of their physicians. A lack of insight into being ill is another reason. Furthermore, as lithium treatment is associated with adverse effects and the long-term effects on the body are insufficiently understood, many patients stop their lithium medication due to unwanted effects. The most common reasons are diarrhoea, tremor, diabetes insipidus, creatinine increase, and weight gain (124). Furthermore, lithium nephropathy can make discontinuation of lithium necessary.

Abrupt lithium discontinuation in patients stabilized on the medication is associated with severe adverse effects, such as suicidal behavior (59). In a study investigating this issue, 3 of 18 patients relapsed within 4 days after discontinuation, two of which had been stable on lithium for as long as 42 and 58 months (125). In a study of 64 patients with BD that were investigated in a naturalistic setting, the relapse risk increased from 53.3% to 94.1% (NNH = 2.5) from gradual (2–4 weeks) to rapid (< 2 weeks) discontinuation over 5 years (126). Similar results were found in a randomized trial of 161 bipolar patients. Abrupt discontinuation (1–14 days) led to a 20-fold increase in relapse rates as compared to gradual reduction (15–30 days) over a course of 3 years (37% vs. 1.8%, $p < 0.0001$, (59)). The median time to recurrence was decreased from 14.0 months to 2.5 months (127). The same pattern of increased relapse rates is seen in pregnant women (128).

The risk of relapse after abrupt discontinuation seems to exceed the risk before starting lithium treatment and may thus be considered an iatrogenic harm (rebound phenomenon, (129). It is therefore strongly recommended to discontinue lithium very slowly. Whether a gradual withdrawal over more than 4 weeks is more beneficial has not been investigated to date.

It is likely that rebound after discontinuation undermines the validity of relapse prevention trials, in which stabilized patients are withdrawn from lithium within a few weeks before being randomized to placebo (129). The benefit of lithium could thus be smaller than generally assumed.

If lithium discontinuation is followed by a relapse, patients may want to reinstate lithium medication. Reintroduction of lithium after discontinuation does not seem to affect treatment efficacy (130), as had been speculated by some authors in the past (131).

CONCLUSIONS

BD is a debilitating illness with an often chronic clinical course that usually requires lifelong treatment. Lithium has been used for treating BD for many years since the discovery of its antimanic properties in 1949 (132). Notwithstanding the introduction of other therapeutic agents that have led to a reduction in prescription of lithium in the past decades (133), it still remains the gold standard in the treatment of BD, particularly over the lifespan with the highest efficacy in the maintenance treatment. The proposed suicide-preventing effect of lithium is unique, while possibly being less substantiated than previously thought. It is an efficacious medication in the acute treatment of mania, while lacking efficacy in the treatment of bipolar depression. Lithium can be used for the treatment of BD in all age groups. It is effective in paediatric BD and can be used, with caution, during pregnancy. Lithium use is generally not recommended during breastfeeding, however. Older aged patients with BD also benefit from lithium, while the serum levels are recommended to be rather lower than in younger adults. Lithium is generally well tolerated. However, adverse events, such as hypothyroidism, renal dysfunctions, and cognitive side effects have to be weighed against the benefits. Special care is strongly recommended when discontinuing lithium, as rapid withdrawal may lead to severe side-effects.

In sum, lithium remains an effective and generally tolerable therapeutic agent for BD. Every clinically active psychiatrist should be able to handle lithium comfortably, such that the harms are minimized and the benefits outweigh the risks. We hope that this review helps guide practitioners and patients alike.

AUTHOR CONTRIBUTIONS

CV and SK drafted and wrote the manuscript. TB provided a critical revision of the article.

FUNDING

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité – Universitätsmedizin Berlin.

REFERENCES

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* (2016) 387 (10027):1561–72. doi: 10.1016/S0140-6736(15)00241-X
2. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* (2011) 68(3):241–51. doi: 10.1001/archgenpsychiatry.2011.12
3. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* (2013) 346:f3646. doi: 10.1136/bmj.f3646
4. Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, et al. Clinical use of lithium salts: guide for users and prescribers. *Int J Bipolar Disord* (2019) 7 (1):16. doi: 10.1186/s40345-019-0151-2
5. Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. *J Affect Disord* (2017) 217:266–80. doi: 10.1016/j.jad.2017.03.052
6. DGBS and DGPPN. S3-Leitlinie zur Diagnostik und Therapie Bipolarer Störungen. *Langversion* (2019). [cited 2.0; Available from: www.leitlinie-bipolar.de.
7. Licht RW. Lithium: still a major option in the management of bipolar disorder. *CNS Neurosci Ther* (2012) 18(3):219–26. doi: 10.1111/j.1755-5949.2011.00260.x

8. Bschor T, Baethge C, Grunze H, Lewitzka U, Scherk H, Severus E, et al. [German S3 guidelines on bipolar disorders-first update 2019 : What is new in pharmacotherapy?]. *Nervenarzt* (2020). doi: 10.1007/s00115-019-00852-5
9. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord* (2014) 2:15. doi: 10.1186/s40345-014-0015-8
10. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* (2004) 161(2):217–22. doi: 10.1176/appi.ajp.161.2.217
11. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* (2014) 1(5):351–9. doi: 10.1016/S2215-0366(14)70314-1
12. Vieta E, Gunther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol* (2011) 14(8):1029–49. doi: 10.1017/S1461145711000885
13. Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *Cochrane Database Syst Rev* (2001) 2001(3):CD003013. doi: 10.1002/14651858.CD003013
14. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. *Bipolar Disord* (2018) 20:419–31. doi: 10.1111/bdi.12623
15. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. *World Psychiatry* (2016) 15(1):53–8. doi: 10.1002/wps.20298
16. Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. *Bipolar Disord* (2019) 21(5):394–409. doi: 10.1111/bdi.12805
17. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. *J Clin Psychiatry* (1998) 59 Suppl 6:13–9; discussion 20.
18. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet* (2011) 378(9799):1306–15. doi: 10.1016/S0140-6736(11)60873-8
19. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* (2005) 66(1):111–21. doi: 10.4088/JCP.v66n0116
20. Vieta E, Sanchez-Moreno J. Acute and long-term treatment of mania. *Dialogues Clin Neurosci* (2008) 10(2):165–79.
21. Baldessarini RJ, Tondo L, Pinna M, Nunez N, Vazquez GH. Suicidal risk factors in major affective disorders. *Br J Psychiatry* (2019) p:1–6. doi: 10.1192/bjp.2019.167
22. Coryell W, Andreasen NC, Endicott J, Keller M. The significance of past mania or hypomania in the course and outcome of major depression. *Am J Psychiatry* (1987) 144(3):309–15. doi: 10.1176/ajp.144.3.309
23. Baldessarini RJ, Vazquez GH, Tondo L. Bipolar depression: a major unsolved challenge. *Int J Bipolar Disord* (2020) 8(1):1. doi: 10.1186/s40345-019-0160-1
24. Köhler S, Gaus S, Bschor T. The challenge of treatment in bipolar depression: evidence from clinical guidelines, treatment recommendations and complex treatment situations. *Pharmacopsychiatry* (2014) 47(2):53–9. doi: 10.1055/s-0033-1364004
25. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry* (2016) 3(12):1138–46. doi: 10.1016/S2215-0366(16)30264-4
26. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* (2013) 170(11):1249–62. doi: 10.1176/appi.ajp.2013.13020185
27. Amsterdam JD, Shults J. Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode? *J Affect Disord* (2009) 115(1-2):234–40. doi: 10.1016/j.jad.2008.07.007
28. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* (2010) 71(2):150–62. doi: 10.4088/JCP.08m04995gre
29. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. *J Clin Psychopharmacol* (2008) 28(2):171–81. doi: 10.1097/JCP.0b013e318166c4e6
30. Kelly T. Lithium and the Woozle effect. *Bipolar Disord* (2019) 21(4):302–8. doi: 10.1111/bdi.12753
31. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* (2018) 20(2):97–170. doi: 10.1111/bdi.12609
32. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* (2010) 11(2):81–109. doi: 10.3109/15622970903555881
33. Betzler F, Stover LA, Sterzer P, Kohler S. Mixed states in bipolar disorder - changes in DSM-5 and current treatment recommendations. *Int J Psychiatry Clin Pract* (2017) 21(4):244–58. doi: 10.1080/13651501.2017.1311921
34. Swann AC, Lafer B, Perugi G, Frye MA, Bauer M, Bahk WM, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry* (2013) 170(1):31–42. doi: 10.1176/appi.ajp.2012.12030301
35. Chakrabarty T, Keramatian K, Yatham LN. Treatment of Mixed Features in Bipolar Disorder: an Updated View. *Curr Psychiatry Rep* (2020) 22(3):15. doi: 10.1007/s11920-020-1137-6
36. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, et al. Depression during mania. Treatment response to lithium or divalproex. *Arch Gen Psychiatry* (1997) 54(1):37–42. doi: 10.1001/archpsyc.1997.01830130041008
37. Bowden CL, Collins MA, McElroy SL, Calabrese JR, Swann AC, Weisler RH, et al. Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. *Neuropsychopharmacology* (2005) 30(10):1932–9. doi: 10.1038/sj.npp.1300788
38. Carvalho AF, Dimellis D, Gonda X, Vieta E, McLntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder: a systematic review. *J Clin Psychiatry* (2014) 75(6):e578–86. doi: 10.4088/JCP.13r08905
39. Köhler S, Friedel E, Stamm T. [Rapid Cycling in Bipolar Disorders: Symptoms, Background and Treatment Recommendations]. *Fortschr Neurol Psychiatr* (2017) 85(4):199–211. doi: 10.1055/s-0042-121258
40. Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PEJr., et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am J Psychiatry* (2005) 162(7):1273–80. doi: 10.1176/appi.ajp.162.7.1273
41. Cruz N, Vieta E, Comes M, Haro JM, Reed C, Bertsch J, et al. Rapid-cycling bipolar I disorder: course and treatment outcome of a large sample across Europe. *J Psychiatr Res* (2008) 42(13):1068–75. doi: 10.1016/j.jpsychires.2007.12.004
42. Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. *Acta Psychiatr Scand* (2019) 140(2):94–115. doi: 10.1111/acps.13062
43. Valenti M, Pacchiarotti I, Undurraga J, Bonnin CM, Popovic D, Goikolea JM, et al. Risk factors for rapid cycling in bipolar disorder. *Bipolar Disord* (2015) 17(5):549–59. doi: 10.1111/bdi.12288

44. Post RM, Leverich GS, Kupka R, Keck PEJr., McElroy SL, Altshuler LL, et al. Clinical correlates of sustained response to individual drugs used in naturalistic treatment of patients with bipolar disorder. *Compr Psychiatry* (2016) 66:146–56. doi: 10.1016/j.comppsych.2016.01.009
45. Tondo L, Hennen J, Baldessarini RJ. Rapid-cycling bipolar disorder: effects of long-term treatments. *Acta Psychiatr Scand* (2003) 108(1):4–14. doi: 10.1034/j.1600-0447.2003.00126.x
46. Lorenzo-Luaces L, Amsterdam JD, Soeller I, DeRubeis RJ. Rapid versus non-rapid cycling bipolar II depression: response to venlafaxine and lithium and hypomanic risk. *Acta Psychiatr Scand* (2016) 133(6):459–69. doi: 10.1111/acps.12557
47. Suppes T, Marangell LB, Bernstein IH, Kelly DI, Fischer EG, Zboyan HA, et al. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. *J Affect Disord* (2008) 111(2-3):334–43. doi: 10.1016/j.jad.2008.02.004
48. Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* (1997) 58(11):470–8. doi: 10.4088/JCP.v58n1102
49. Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* (2005) 162 (11):2152–61. doi: 10.1176/appi.ajp.162.11.2152
50. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* (2004) 55(9):875–81. doi: 10.1016/j.biopsych.2004.01.022
51. Goldstein BI, Birmaher B, Carlson GA, DelBello MP, Findling RL, Fristad M, et al. The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. *Bipolar Disord* (2017) 19(7):524–43. doi: 10.1111/bdi.12556
52. Findling RL, McNamara NK, Pavuluri M, Frazier JA, Rynn M, Scheffer R, et al. Lithium for the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Discontinuation Study. *J Am Acad Child Adolesc Psychiatry* (2019) 58(2):287–296 e4. doi: 10.1016/j.jaac.2018.07.901
53. Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, et al. Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study. *Pediatrics* (2015) 136(5):885–94. doi: 10.1542/peds.2015-0743
54. Findling RL, Kafantaris V, Pavuluri M, McNamara NK, McClellan J, Frazier JA, et al. Dosing strategies for lithium monotherapy in children and adolescents with bipolar I disorder. *J Child Adolesc Psychopharmacol* (2011) 21(3):195–205. doi: 10.1089/cap.2010.0084
55. Sun AY, Woods S, Findling RL, Stepanova E. Safety considerations in the psychopharmacology of pediatric bipolar disorder. *Expert Opin Drug Saf* (2019) 18(9):777–94. doi: 10.1080/14740338.2019.1637416
56. Landersdorfer CB, Findling RL, Frazier JA, Kafantaris V, Kirkpatrick CM. Lithium in Paediatric Patients with Bipolar Disorder: Implications for Selection of Dosage Regimens via Population Pharmacokinetics/Pharmacodynamics. *Clin Pharmacokinet* (2017) 56(1):77–90. doi: 10.1007/s40262-016-0430-3
57. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* (2007) 164(12):1817–24; quiz 1923. doi: 10.1176/appi.ajp.2007.06101639
58. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. *Am J Psychiatry* (2016) 173(2):117–27. doi: 10.1176/appi.ajp.2015.15010124
59. Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. *Bipolar Disord* (1999) 1(1):17–24. doi: 10.1034/j.1399-5618.1999.10106.x
60. Broeks SC, Thisted Horsdal H, Glejsted Ingstrup K, Gasse C. Psychopharmacological drug utilization patterns in pregnant women with bipolar disorder - A nationwide register-based study. *J Affect Disord* (2017) 210:158–65. doi: 10.1016/j.jad.2016.12.001
61. McCrea RL, Nazareth I, Evans SJ, Osborn DP, Pinfold V, Cowen PJ, et al. Lithium prescribing during pregnancy: a UK primary care database study. *PLoS One* (2015) 10(3):e0121024. doi: 10.1371/journal.pone.0121024
62. Hermann A, Gorun A, Benudis A. Lithium Use and Non-use for Pregnant and Postpartum Women with Bipolar Disorder. *Curr Psychiatry Rep* (2019) 21(11):114. doi: 10.1007/s11920-019-1103-3
63. Poels EMP, Bijma HH, Galbally M, Bergink V. Lithium during pregnancy and after delivery: a review. *Int J Bipolar Disord* (2018) 6(1):26. doi: 10.1186/s40345-018-0135-7
64. Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. *N Engl J Med* (2017) 376(23):2245–54. doi: 10.1056/NEJMoa1612222
65. Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. *Lancet Psychiatry* (2018) 5(8):644–52. doi: 10.1016/S2215-0366(18)30180-9
66. Wesseloo R, Wierdsma AI, van Kamp IL, Munk-Olsen T, Hoogendijk WJG, Kushner SA, et al. Lithium dosing strategies during pregnancy and the postpartum period. *Br J Psychiatry* (2017) 211(1):31–6. doi: 10.1192/bjp.bp.116.192799
67. Westin AA, Brekke M, Molden E, Skogvoll E, Aadal M, Spigset O. Changes in drug disposition of lithium during pregnancy: a retrospective observational study of patient data from two routine therapeutic drug monitoring services in Norway. *BMJ Open* (2017) 7(3):e015738. doi: 10.1136/bmjopen-2016-015738
68. Deligiannidis KM. Therapeutic drug monitoring in pregnant and postpartum women: recommendations for SSRIs, lamotrigine, and lithium. *J Clin Psychiatry* (2010) 71(5):649–50. doi: 10.4088/JCP.10ac06132gre
69. Ward S, Wisner KL. Collaborative management of women with bipolar disorder during pregnancy and postpartum: pharmacologic considerations. *J Midwifery Womens Health* (2007) 52(1):3–13. doi: 10.1016/j.jmwh.2006.09.002
70. Galbally M, Roberts M, Buist A, Perinatal Psychotropic Review G. Mood stabilizers in pregnancy: a systematic review. *Aust N Z J Psychiatry* (2010) 44 (11):967–77. doi: 10.3109/00048674.2010.506637
71. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, et al. Management of bipolar disorder during pregnancy and the postpartum period. *Am J Psychiatry* (2004) 161(4):608–20. doi: 10.1176/appi.ajp.161.4.608
72. Bergink V, Burgerhout KM, Koorengevel KM, Kamperman AM, Hoogendijk WJ, Lambregtse-van den Berg MP, et al. Treatment of psychosis and mania in the postpartum period. *Am J Psychiatry* (2015) 172(2):115–23. doi: 10.1176/appi.ajp.2014.13121652
73. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord* (2015) 17(7):689–704. doi: 10.1111/bdi.12331
74. Young RC, Mulsant BH, Sajatovic M, Gildengers AG, Gyulai L, Al Jurdi RK, et al. GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder. *Am J Psychiatry* (2017) 174(11):1086–93. doi: 10.1176/appi.ajp.2017.15050657
75. Forty L, Ulanova A, Jones L, Jones I, Gordon-Smith K, Fraser C, et al. Comorbid medical illness in bipolar disorder. *Br J Psychiatry* (2014) 205 (6):465–72. doi: 10.1192/bjp.bp.114.152249
76. Gildengers AG, Whyte EM, Drayer RA, Soreca I, Fagiolini A, Kilbourne AM, et al. Medical burden in late-life bipolar and major depressive disorders. *Am J Geriatr Psychiatry* (2008) 16(3):194–200. doi: 10.1097/JGP.0b013e318157c5b1
77. Yu C, Sylvestre JD, Segal M, Looper KJ, Rej S. Predictors of psychiatric re-hospitalization in older adults with severe mental illness. *Int J Geriatr Psychiatry* (2015) 30(11):1114–9. doi: 10.1002/gps.4361
78. Rej S, Herrmann N, Shulman K, Fischer HD, Fung K, Gruneir A. Current psychotropic medication prescribing patterns in late-life bipolar disorder. *Int J Geriatr Psychiatry* (2017) 32(12):1459–65. doi: 10.1002/gps.4635
79. Shulman KI, Rochon P, Sykora K, Anderson G, Mamdani M, Bronskill S, et al. Changing prescription patterns for lithium and valproic acid in old age:

shifting practice without evidence. *BMJ* (2003) 326(7396):960–1. doi: 10.1136/bmj.326.7396.960
80. Shulman KI, Almeida OP, Herrmann N, Schaffer A, Strejilevich SA, Paternoster C, et al. Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report. *Bipolar Disord* (2019) 21(2):117–23. doi: 10.1111/bdi.12714
81. Sun M, Herrmann N, Shulman KI. Lithium Toxicity in Older Adults: a Systematic Review of Case Reports. *Clin Drug Invest* (2018) 38(3):201–9. doi: 10.1007/s40261-017-0598-9
82. Juurlink DN, Mamdani MM, Kopp A, Rochon PA, Shulman KI, Redelmeier DA. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc* (2004) 52(5):794–8. doi: 10.1111/j.1532-5415.2004.52221.x
83. Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults–a systematic review. *J Geriatr Psychiatry Neurol* (2012) 25 (1):51–61. doi: 10.1177/0891988712436690
84. Forester BP, Streeter CC, Berlow YA, Tian H, Wardrop M, Finn CT, et al. Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: a lithium-7 magnetic resonance spectroscopy study. *Am J Geriatr Psychiatry* (2009) 17(1):13–23. doi: 10.1097/JGP.0b013e318172b3d0
85. Rej S, Beaulieu S, Segal M, Low NC, Mucsi I, Holcroft C, et al. Lithium dosing and serum concentrations across the age spectrum: from early adulthood to the tenth decade of life. *Drugs Aging* (2014) 31(12):911–6. doi: 10.1007/s40266-014-0221-1
86. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* (2015) 386(9992):461–8. doi: 10.1016/S0140-6736(14)61842-0
87. Schou M, Baastrup PC, Grof P, Weis P, Angst J. Pharmacological and clinical problems of lithium prophylaxis. *Br J Psychiatry* (1970) 116(535):615–9. doi: 10.1192/bjp.116.535.615
88. Gelenberg AJ, Jefferson JW. Lithium tremor. *J Clin Psychiatry* (1995) 56 (7):283–7.
89. McKnight RF, de La Motte de Broons de Vauvert S, Chesney E, Amit BH, Geddes J, Cipriani A. Lithium for acute mania. *Cochrane Database Syst Rev* (2019) 6:CD004048. doi: 10.1002/14651858.CD004048.pub4
90. Vestergaard P, Poulstrup I, Schou M. Prospective studies on a lithium cohort. 3. Tremor, weight gain, diarrhea, psychological complaints. *Acta Psychiatr Scand* (1988) 78(4):434–41. doi: 10.1111/j.1600-0447.1988.tb06363.x
91. Baek JH, Kinrys G, Nierenberg AA. Lithium tremor revisited: pathophysiology and treatment. *Acta Psychiatr Scand* (2014) 129(1):17–23. doi: 10.1111/acps.12171
92. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* (2012) 379(9817):721–8. doi: 10.1016/S0140-6736(11)61516-X
93. Twigt BA, Houweling BM, Vriens MR, Regeer EJ, Kupka RW, Rinkes IH, et al. Hypercalcemia in patients with bipolar disorder treated with lithium: a cross-sectional study. *Int J Bipolar Disord* (2013) 1:18. doi: 10.1186/2194-7511-1-18
94. Mehta N, Vannozzi R. Lithium-induced electrocardiographic changes: A complete review. *Clin Cardiol* (2017) 40(12):1363–7. doi: 10.1002/clc.22822
95. van Melick EJ, Meinders AE, Hoffman TO, Egberts TC. Renal effects of long-term lithium therapy in the elderly: a cross-sectional study. *Int J Geriatr Psychiatry* (2008) 23(7):685–92. doi: 10.1002/gps.1961
96. Boton R, Gaviria M, Batlle DC. Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. *Am J Kidney Dis* (1987) 10(5):329–45. doi: 10.1016/S0272-6386(87)80098-7
97. Schoot TS, Molmans THJ, Grootens KP, Kerckhoffs APM. Systematic review and practical guideline for the prevention and management of the renal side effects of lithium therapy. *Eur Neuropsychopharmacol* (2019) 31:16–32. doi: 10.1016/j.euroneuro.2019.11.006
98. Kripalani M, Shawcross J, Reilly J, Main J. Lithium and chronic kidney disease. *BMJ* (2009) 339:b2452. doi: 10.1136/bmj.b2452
99. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, et al. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. *Int J Bipolar Disord* (2017) 5(1):27. doi: 10.1186/s40345-017-0096-2
100. Judd LL. Effect of lithium on mood, cognition, and personality function in normal subjects. *Arch Gen Psychiatry* (1979) 36(8 Spec No):860–6. doi: 10.1001/archpsyc.1979.01780080034010
101. Johnson FR, Ozdemir S, Manjunath R, Hauber AB, Burch SP, Thompson TR. Factors that affect adherence to bipolar disorder treatments: a stated-preference approach. *Med Care* (2007) 45(6):545–52. doi: 10.1097/MLR.0b013e318040ad90
102. Xu N, Huggon B, Saunders KEA. Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment. *CNS Drugs* (2020) 34(1):29–46. doi: 10.1007/s40263-019-00688-2
103. Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. *J Clin Psychiatry* (2009) 70 (11):1588–97. doi: 10.4088/JCP.08r04972
104. Tremont G, Stern RA. Minimizing the cognitive effects of lithium therapy and electroconvulsive therapy using thyroid hormone. *Int J Neuropsychopharmacol* (2000) 3(2):175–86. doi: 10.1017/S1461145700001838
105. Wilson EN, Do Carmo S, Iulita MF, Hall H, Ducatenzeiler A, Marks AR, et al. BACE1 inhibition by microdose lithium formulation NP03 rescues memory loss and early stage amyloid neuropathology. *Transl Psychiatry* (2017) 7(8):e1190. doi: 10.1038/tp.2017.169
106. Wilson EN, Do Carmo S, Welikovitch LA, Hall H, Aguilar LF, Foret MK, et al. NP03, a Microdose Lithium Formulation, Blunts Early Amyloid Post-Plaque Neuropathology in McGill-R-Thy1-APP Alzheimer-Like Transgenic Rats. *J Alzheimers Dis* (2020) 73(2):723–39. doi: 10.3233/JAD-190862
107. Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry* (2011) 198(5):351–6. doi: 10.1192/bjp.bp.110.080044
108. Kessing LV, Gerds TA, Knudsen NN, Jorgensen LF, Kristiansen SM, Voutchkova D, et al. Association of Lithium in Drinking Water With the Incidence of Dementia. *JAMA Psychiatry* (2017) 74(10):1005–10. doi: 10.1001/jamapsychiatry.2017.2362
109. Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, de Azevedo Cardoso T. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. *Acta Psychiatr Scand* (2020). doi: 10.1111/acps.13153
110. Bowden CL, Calabrese JR, Ketter TA, Sachs GS, White RL, Thompson TR. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *Am J Psychiatry* (2006) 163(7):1199–201. doi: 10.1176/ajp.2006.163.7.1199
111. Ott M, Stegmayr B, Salander Renberg E, Werneke U. Lithium intoxication: Incidence, clinical course and renal function - a population-based retrospective cohort study. *J Psychopharmacol* (2016) 30(10):1008–19. doi: 10.1177/0269881116652577
112. Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. *Bipolar Disord* (2015) 17(5):543–8. doi: 10.1111/bdi.12296
113. Ösby U, Brandt L, Correia N, Ekbom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* (2001) 58(9):844–50. doi: 10.1001/archpsyc.58.9.844
114. Plans L, Barrot C, Nieto E, Rios J, Schulze TG, Papiol S, et al. Association between completed suicide and bipolar disorder: A systematic review of the literature. *J Affect Disord* (2019) 242:111–22. doi: 10.1016/j.jad.2018.08.054
115. Tondo L, Isacsson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and prevention. *CNS Drugs* (2003) 17(7):491–511. doi: 10.2165/00023210-200317070-00003
116. Baldessarini RJ, Tondo L. Suicide risk and treatments for patients with bipolar disorder. *JAMA* (2003) 290(11):1517–9. doi: 10.1001/jama.290.11.1517
117. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord* (2006) 8(5 Pt 2):625–39. doi: 10.1111/j.1399-5618.2006.00344.x
118. Lewitzka U, Severus E, Bauer R, Ritter P, Muller-Oerlinghausen B, Bauer M. The suicide prevention effect of lithium: more than 20 years of evidence-a narrative review. *Int J Bipolar Disord* (2015) 3(1):32. doi: 10.1186/s40345-015-0032-2
119. Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* (2001) 104(3):163–72. doi: 10.1034/j.1600-0447.2001.00464.x
120. Coryell W, Arndt S, Turvey C, Endicott J, Solomon D, Mueller T, et al. Lithium and suicidal behavior in major affective disorder: a case-control

study. *Acta Psychiatr Scand* (2001) 104(3):193–7. doi: 10.1034/j.1600-0447.2001.00338.x
121. Borjesson J, Gotzsche PC. Effect of lithium on suicide and mortality in mood disorders: A systematic review. *Int J Risk Saf Med* (2019) 30(3):155–66. doi: 10.3233/JRS-190058
122. Vita A, De Peri L, Sacchetti E. Lithium in drinking water and suicide prevention: a review of the evidence. *Int Clin Psychopharmacol* (2015) 30 (1):1–5. doi: 10.1097/YIC.0000000000000048
123. Ahrens B, Muller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect? *Pharmacopsychiatry* (2001) 34(4):132–6. doi: 10.1055/s-2001-15878
124. Ohlund L, Ott M, Oja S, Bergqvist M, Lundqvist R, Sandlund M, et al. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. *BMC Psychiatry* (2018) 18(1):37. doi: 10.1186/s12888-018-1895-4
125. Christodoulou GN, Lykouras EP. Abrupt lithium discontinuation in manic-depressive patients. *Acta Psychiatr Scand* (1982) 65(5):310–4. doi: 10.1111/j.1600-0447.1982.tb00852.x
126. Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* (1993) 50(6):448–55. doi: 10.1001/archpsyc.1993.01820180046005
127. Baldessarini RJ, Tondo L, Floris G, Rudas N. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. *Am J Psychiatry* (1997) 154(4):551–3. doi: 10.1176/ajp.154.4.551
128. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *Am J Psychiatry* (2000) 157(2):179–84. doi: 10.1176/appi.ajp.157.2.179
129. Baldessarini RJ, Tondo L. Effects of Treatment Discontinuation in Clinical Psychopharmacology. *Psychother Psychosom* (2019) 88(2):65–70. doi: 10.1159/000497334
130. Tondo L, Baldessarini RJ, Floris G, Rudas N. Effectiveness of restarting lithium treatment after its discontinuation in bipolar I and bipolar II disorders. *Am J Psychiatry* (1997) 154(4):548–50. doi: 10.1176/ajp.154.4.548
131. Post RM, Leverich GS, Altshuler L, Mikalauskas K. Lithium-discontinuation-induced refractoriness: preliminary observations. *Am J Psychiatry* (1992) 149 (12):1727–9. doi: 10.1176/ajp.149.12.1727
132. Cade JF. Lithium salts in the treatment of psychotic excitement. 1949. *Bull World Health Organ* (2000) 78(4):518–20.
133. Blanco C, Laje G, Olfson M, Marcus SC, Pincus HA. Trends in the treatment of bipolar disorder by outpatient psychiatrists. *Am J Psychiatry* (2002) 159 (6):1005–10. doi: 10.1176/appi.ajp.159.6.1005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

STUDY PROTOCOL
published: 15 May 2020
doi: 10.3389/fpsyt.2020.00435

Efficacy, Safety, and Tolerability of Theta-Burst Stimulation in Mixed Depression: Design, Rationale, and Objectives of a Randomized, Double-Blinded, Sham-Controlled Trial

Diego Freitas Tavares, Carla Garcia Rodrigues dos Santos, Leandro Da Costa Lane Valiengo, Izio Klein, Lucas Borrione, Pamela Marques Forte, Andre R. Brunoni and Ricardo Alberto Moreno*

Department of Psychiatry, University of São Paulo, São Paulo, Brazil

OPEN ACCESS

Edited by:
Mario F. Juruena, King's College London, United Kingdom

Reviewed by:
Giuseppe Tavormina, Independent Researcher, Provaglio d'Iseo, Italy
Eduardo Pondé de Sena, Universidade Federal da Bahia, Brazil

***Correspondence:**
Diego Freitas Tavares
diego.tavares@hc.fm.usp.br

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *30 October 2019*
Accepted: *28 April 2020*
Published: *15 May 2020*

Citation:
Tavares DF, dos Santos CGR, Valiengo LDCL, Klein I, Borrione L, Forte PM, Brunoni AR and Moreno RA (2020) Efficacy, Safety, and Tolerability of Theta-Burst Stimulation in Mixed Depression: Design, Rationale, and Objectives of a Randomized, Double-Blinded, Sham-Controlled Trial. Front. Psychiatry 11:435. doi: 10.3389/fpsyt.2020.00435

Introduction: Mixed-specifier mood disorders are probably a different subgroup in terms of response to treatment, socio-demographic parameters, course, and family history. Here we describe the rationale and design of a clinical trial aimed to test the efficacy, safety, and tolerability of a non-pharmacological treatment known as theta-burst stimulation (TBS) for treating the mixed depressive episodes of both bipolar (I or II), and unipolar depression.

Methods: The study is designed as a randomized, sham-controlled, double-blinded clinical trial evaluating TBS for the treatment of moderate or severe major depressive episodes with mixed features of patients receiving at least one first or second-line pharmacological treatment for depressive episodes without adequate response. Ninety adult (18 to 65 years old) patients will be enrolled and submitted to 6-week (comprising 5 consecutive days a week sessions for the first 3 weeks and then 2 days a week for a further 3 week) of inhibitory followed by excitatory TBS in dorsolateral prefrontal cortex. Participants will be assessed using clinical and neuropsychological tests before and after the intervention. The primary outcome is change in Montgomery–Åsberg Depression Scale (MADRS) score over time and across groups. Cognitive parameters will also be assessed with neuropsychological tests.

Results: The clinical results will provide evidence about TBS as an adjunctive treatment for mixed depression treatment and neuropsychological parameters will contribute toward an improved understanding the effects of TBS in cognition.

Conclusion: Our results could introduce a novel therapeutic technique for mixed depressive episodes of both bipolar and unipolar disorders.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT04123301; date of registration: 10/10/2019; URL: https://clinicaltrials.gov/ct2/show/NCT04123301?term=NCT04123301&rank=1.

Keywords: depression, bipolar disorder, transcranial stimulation, mixed states/episodes, randomized controlled (clinical) trial

INTRODUCTION

Although overlapping depressive and (hypo) manic symptoms in mood disorder have been identified from the incipient descriptions of manic-depressive illness (1), current classifications have only appeared in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in 1994 under the name of "mixed state" in which the complete manic syndrome and complete depressive syndrome would simultaneously occur in type I bipolar disorder (BD) patient (2). Important studies carried out last decade (3–9) in different forms of overlapping depressive, manic, and hypomanic symptoms have supported the concept of mood episode with mixed features of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), that can be applied to any episode of BD I or II, but also of major depressive episode of major depressive disorder (MDD) (10). The mixed features specifier at DSM-5 is characterized by the presence of at least three symptoms of the opposite pole of the predominant mood episode (**Table 1**) (11), excluding the "DIP symptoms": distractibility (D), irritability (I), and psychomotor agitation (P), with the preliminary justification that such symptoms have been described in both (hypo)manic and the depressive episodes in the current classifications. Studies prior to (7–9) and later (12–15) to the publication of the DSM-5 demonstrate that the exclusion of "DIP symptoms" is not corroborated by scientific evidence. The presence of mixed features in any mood episode, especially the depressive episodes, has been associated with higher comorbidities, higher relapse rates, worse clinical outcomes, and higher suicide risk in BD patients and has been evaluated in several studies (16–20), although it has not yet been adequately studied in depressive episodes with mixed features of MDD. A recent review (21) showed that the percentage of mixed features ranged from 4.3% (22) to 58.6% (23) in BD and from 0% (22) to 34% (23) in MDD, much depending on each study criteria. These extremely wide variations may be due to the low sensitivity of the mixed feature specifier adopted by the DSM-5 (5.1%) (24).

Transdiagnostic approaches aim to identify factors that occur regardless of the diagnostic construct that may play a role in initiating and/or maintaining different disorders. According to transdiagnostic approaches risk factors for a specific disorder may also confer risk for other disorders, especially those that share symptoms. Rather than examining risk factors for each specific disorder, this paradigm suggests that a better approach to understand the pathophysiology would be to focus on transdiagnostic factors that may contribute to the development of many forms of psychopathology (25, 26). Mixed features in the context of different mood disorders go in the same direction as this approach. Another aspect that has been recently studied and which meets these transdiagnostic approaches is the alteration of biological rhythms in mood disorders (27). Changes in chronobiological rhythms have been described in both MDD and BD (28). The investigation of changes in biological rhythms in depression with mixed features of MDD or BD has not been adequately investigated (29, 30).

Repetitive transcranial magnetic stimulation (rTMS) is widely known treatment option for MDD (31). A recent rTMS meta-analysis in the treatment of depressive episodes indicates that the technique yields statistically significant results improving 30% of patients receiving active excitatory rTMS compared to 10% of patients receiving sham treatment (analysis based in 29 randomized, double-blind, and controlled clinical trials) (32). Recently, a new form of rTMS, the theta-burst mode stimulation (TBS) was introduced and appears to produce at least similar effects on brain activity than standard rTMS (33–36). In addition to greater efficacy, the reduced duration of administration may be another advantage of TBS compared to conventional rTMS procedure, standard TMS sessions last about 45 min, whereas TBS requires less than 10 min of stimulation (33, 37). There are two types of TBS stimulation: intermittent (iTBS) and continuous (cTBS), with facilitating and inhibitory effects, respectively (36). Recent evidence is growing about TBS use in treatment resistant depression (38). Despite the growing number of studies on BD neuroimaging in recent years, the brain regions involved in mood dysregulation in episodes with mixed features have been poorly studied. If some neurofunctional abnormalities appear to be independent of mood state, others appear to be preferentially associated with mania or depression involving the amygdala and other limbic regions, as well as frontal ventral regions, with possible hemispheric lateralization of these anomalies according to mood state patient (36). The few mixed state neuroimaging studies so far support the hypothesis

TABLE 1 | Depression with mixed features specifier (DSM-5).

Mixed depression (3 or more of the following during a major depressive episode):
(1) expansive or elevated mood;
(2) increased self-esteem or grandiosity;
(3) more talkative than usual or speaking pressure;
(4) flight of ideas or subjective sensation that thoughts are running;
(5) increased energy or goal-directed activity (socially, at work or at school);
(6) increased or excessive involvement in activities with high potential for bad consequences (eg, rampant shopping, sexual indiscretion, unwise business investments);
(7) reduced need for sleep (feeling rested despite sleeping less than usual).

DSM-5, 5th edition of the Diagnostic and Statistical Manual of Mental Disorders.

of lateralization of brain abnormalities in relation to bipolar symptomatology, suggesting that neurofunctional abnormalities preferably located in the frontal and limbic areas of the right hemisphere may be associated with the depressive component whereas abnormalities similar left regions would be associated with the manic component (39). Few studies have evaluated the efficacy of TMS in mixed depressive states alone. A recent open study has shown that low frequency (inhibitory) of repetitive (non-TBS) TMS on the right dorsolateral prefrontal cortex (DLPFC) for 3 weeks led to a response and remission rate of 46% and 28%, respectively, in depressive episodes with mixed features of type I BD (40). On the other hand, a study with TBS modality showed that bilateral stimulation (right cTBS and left iTBS) produced greater results in treating major depressive episodes of MDD than unilateral stimulation (41).

As the DSM-5 definition of mixed features has been recently published, treatment guidelines that provide recommendations for treating mixed episodes are still limited (42). Some authors suggest that data from clinical trials using mixed episodes defined by DSM-IV-TR may guide the treatment of mood episodes with mixed features defined by DSM-5, but with certain caveats (42). The DSM-IV definition of mixed episodes was restrictive and as such cannot be applied to the current definition of mixed states in DSM-5, with the caveat that the current definition does not yet understand DIP symptoms and that recent studies shows that DIP symptoms are likely to be cardinal symptoms of mixed states (17). In addition, these previous studies were conducted in patients with bipolar I disorder, whose results cannot be applied to mixed states of BD II and MDD (43). Mixed specifier of mood disorders (TB and MDD) are probably a different subgroup in terms of clinical response to treatment, socio-demographic parameters, course (frequency of recurrences, predominant polarity, etc.), and family history (44).

The main objective of this study is to evaluate the efficacy and safety of TBS as an add-on treatment for mood stabilizers (in BD I and II) or antidepressants (in MDD) in moderate and severe major depressive episodes with mixed features. Therefore, TBS will be combined to pharmacological treatments of patients who are adequately treated with first or second-line drugs to treat a mixed depressive episode of either MDD (antidepressants) or BD (mood stabilizers), according to CANMAT, and still present with moderate or severe mixed depression. In addition, the study aims to evaluate the impact of restrictive (without "DIP symptoms") and broad (considering "DIP symptoms") criteria on treatment-related factors and other clinical features.

METHODS

Design and Study Population

This will be a randomized, double-blind, sham-controlled, 6-week clinical trial, comprising 5 consecutive days a week sessions for the first 3 weeks and then 2 days a week (interval at least 1 day between sessions) for a further 3 weeks of active or sham TBS. The study will be conducted at the Institute of Psychiatry of the School of Medicine of the University of Sao Paulo (HCFMUSP). The study will be conducted in accordance with the principles established by the Declaration of Helsinki (45) and the American Document of Good Clinical Practice (46). This protocol have been published in www.clinicaltrials.gov with the number NCT04123301.

Ninety adult patients aged 18 to 65 years with a diagnosis of type I BD, type II BD or MDD in moderate or severe depressive episode (according to DSM-5 criteria) with mixed features (according to DSM-5 criteria plus symptoms of distractibility, irritability and psychomotor agitation). The diagnosis will be confirmed by the Portuguese version of the structured interview of DSM-IV (Structured Clinical Interview—SCID IV) (47) modified with the DSM-5 criteria and specifiers without the exclusion of symptoms distractibility, irritability, and psychomotor agitation, since there isn't a Portuguese version of the SCID of DSM-5. Recruitment strategies will include referrals from other doctors and advertising at internet and newspapers. Participants will be randomized using a computer generated list for one of two intervention groups (in a 1:1 ratio) to the active or sham TBS group. Allocation masking will be done by sequentially numbered cards that will determine which group each patient belongs to. The card determines whether the coil to be used will produce active or sham stimulation. A person not directly involved in the clinical trial will be responsible for delivering the sham or true coil according to randomization, remembering that the coils are physically identical and have similar sound properties and stimuli. Participants and staff will be unaware of the status of allocation groups.

Inclusion and Exclusion Criteria

Eligibility criteria is the presence of manic polarity symptoms during a moderate or severe depressive episode of BD I, BD II or MDD. We set the Montgomery–Åsberg Depression Rating Scale (MADRS) (48) with a score between 20 and 34 points for the definition of moderate major depressive episode and above 34 points for severe major depressive episode. The definition of major depressive episode with mixed features will be performed using the Young Mania Rating Scale (YMRS) (49) with ≥1 point on three or more items according to criteria used in the International Mood Disorders Collaborative Project (12) and consist with other definitions of depression with mixed features (50–53). Patients will be included in any appropriate pharmacological regimen (first or second line) according to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines to treat a major depressive episode of MDD or BD (I or II) (54, 55) and still have mixed depressive symptoms, so that TBS will be applied as an add-on treatment. We will not make adjustments to patient treatments, we will only enroll patients that are already on a stable psychopharmacological regimen (at least one month) of first or second line according to CANMAT but with no response/remission or partial response (still meeting inclusion criteria). The pharmacological regimen should be maintained on the same schedule and dosage from the beginning to the end of the study and patients will not be in a psychotherapy regimen. Drugs such as benzodiazepines will only be allowed at low doses (less than 3 mg per day of lorazepam or equivalent). Exclusion criteria will be: concomitant diagnosis of other neuropsychiatric disorders such as: schizophrenia,

dementias, mental retardation, organic mental disorder, or epilepsy; psychotic depression; acute suicide ideation (assessed by interview and clinical evaluation); suspected or confirmed pregnancy; women in breastfeeding; severe or unstable clinical disease; specific contraindications to TBS (previous epileptic seizures; change in electroencephalogram at some point in life; previous stroke; previous severe TBI (with neurosurgery); metallic object on head (except mouth) as projectile piece, surgical clip, welding fragments; any implanted device (cardiac pacemaker, intravenous catheter). Personality, anxiety, and substance use disorders will be allowed as comorbidity provided the primary diagnosis is BD or MDD.

Clinical assessments will be conducted weekly until the end of week 3 and thereafter a final assessment will be conducted at the end of week 6. Adverse events will be evaluated every day during the first week and then once a week until the end of the week 6. The neuropsychological assessment battery will be applied before the patient is stimulated and at the end of the week 6 of intervention (**Table 2**).

Study Hypothesis

The main hypothesis of this study is that the active TBS on the right and left DLPFC in patients with mixed depression can produce a greater and statistically significant reduction in the primary outcome scale (MADRS) compared to sham TBS. Other aims of the study will be evaluate: TBS safety and tolerability; socio-demographic and clinical profiles; impact of DSM-5 mixed features with and without DIP symptoms; impact of DSM-5 anxiety features; impact of biological rhythms in mixed depression; impact of impulsivity on mixed depression; and impact of mixed depression in functionality.

TABLE 2 | Measurement outcomes over time.

Scales	Baseline	End of week 1	End of week 2	End of week 3	End of week 6
SCID I/P modified	X				
MADRS	X	X	X	X	X
YMRS	X	X	X	X	X
WHOQOL-bref	X	X	X	X	X
BIS-11	X	X	X	X	X
CGI-S	X	X	X	X	X
GAF	X	X	X	X	X
HAM-A	X	X	X	X	X
BRIAN	X	X	X	X	X
Morningness–Eveningness Questionnaire	X				
TMS' Typical side Effects Scale	X	X	X	X	X
UKU-SERS	X	X	X	X	X
Neuropsychological Assessment	X				X

SCID, Structured Clinical Interview; MADRS, Montgomery–Åsberg Depression Scale; YMRS, Young Mania Rating Scale; WHOQOL, World Health Organization questionnaire; BIS-11, Barratt Impulsivity Scale; GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Scale; BRIAN, Biological Rhythm Interview of Assessment in Neuropsychiatry; TMS, transcranial magnetic stimulation; UKU-SERS, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; CGI-S, Clinical global impression - Severity.

Measurement of Variables and Outcomes

This study will analyze:

1. Socio-demographic variables: age, gender, marital status, number of children, years of education, income status;
2. Clinical features along the life: medical and psychiatric comorbidities, daily consumption of coffee or black tea or energy drink or cola or tobacco, family history of mood disorder, psychotherapy at the moment, electroconvulsive therapy in the past, number of mood episodes, number of previous hospitalizations, predominant polarity (manic, hypomanic or depressive), previous depressions specifier (melancholic or atypical), past of psychotic depression;
3. Depressive symptoms at the present episode: depressed mood, anhedonia, increase or reduction in appetite, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue/loss of energy, impulse reduction such as indecision, procrastination, abulia, excessive or inappropriate guilt, low concentration, thoughts of death, suicidal thoughts or suicide attempts);
4. DSM-5 mixed features (hypomanic symptoms during depression): reduced need for sleep, acceleration of thoughts or flight of ideas, grandiosity or high self-esteem, increased energy or directed activity, pressure to speak or flight of ideas, increased impulsivity (sex, expenses/gifts/donations; games/bets; mobile use/internet use, drugs, stimulant substances as coffee, energy drink or amphetamines, smoke, abuse of painkillers, anxiolytics, muscle relaxing drugs and hypnotics, food compulsion, love obsession, excessive jealousy, impulsive change of look, tattoos and piercings, work or study compulsion) without and with DIP symptoms (distractibility, irritability and psychomotor agitation);
5. DSM-5 anxious features: apprehensive expectation, tension or worry, feeling restless, difficulty concentrating on worrying thoughts, fear that something terrible might happen, feeling that you can lose control of yourself;
6. Other suggestive symptoms of mixed depression: intensification of depressed mood characterized by anguish, distress, despair or restlessness, high mood lability, hyper reactivity to environmental stressors, sleep-wake cycle dysregulation characterized by difficulty turning off at night and getting out of bed in the morning, auto-aggressiveness or self-mutilation.

Primary outcome will be change in MADRS from baseline to week 3. Secondary outcomes will be: change in YMRS at the end of week 3 and 6 of treatment; response rates (50% or more of reduction in MADRS at the end of weeks 3 and 6 of treatment); remission rates (MADRS <11 (56) at the end of weeks 3 and 6 of treatment); change in anxious symptoms assessed by Hamilton Anxiety Scale (HAM-A) (57) at the end of weeks 3 and 6 of treatment; change in overall clinical impression assessed by Global Clinical Impression of Severity (GCI-S) (58) and Global Assessment of Functioning (GAF) (59) at the end of weeks 3 and 6 of treatment; change of functionality assessed by abbreviated version of the World Health Organization questionnaire (WHOQOL) (60) at the end of weeks 3 and 6 of treatment;

change of biological rhythms assessed by the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN) (61) at the end of weeks 3 and 6 of treatment; change of impulsivity assessed by Barratt Impulsivity Scale (BIS-11) (62) at the end of weeks 3 and 6 of treatment; association between the chronotype assessed by Morningness–Eveningness Questionnaire (63) and the severity of mixed depression assessed by MADRS; and change in neuropsychological battery parameters before and at the end of the intervention (6 weeks).

Serious adverse events associated with the technique such as seizures is very rare if standardized pacing parameters are used (64). The most commonly observed side effects are facial muscle contractions, mild headache and facial pain. Other side effects include tinnitus, dizziness and nausea (65). To assess side effects, we will use a standardized scale by our service that tracks common side effects in transcranial magnetic stimulation (headache, cervical pain, physical tension, scalp pain, scalp burning, dizziness, nausea, hearing impairment, difficulty of concentration, mental confusion, positive mood, negative mood, convulsion). Data will be quantified for the presence of symptoms (1—absent, 2—mild, 3—moderate, and 4—strong) and for the relationship that the patient attributes to the stimulation (1—none, 2—remote, 3 – possible, 4—probable, and 5—definitive). Concomitantly we will assess side effects by the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU-SERS) (66). This scale assesses side effects related to psychiatric symptoms, neurological symptoms, autonomic symptoms, and other symptoms. The severity of each item varies in levels from 0 to 3. Blinding efficacy will be assessed at the end of week 6 by asking TBS appliers and participants about their allocation group.

Randomization and Allocation

The randomization list will be created through the website www.randomization.com and a block randomization will be performed to allow the permutation of the order and size of the blocks. Each patient allocation will be performed using opaque envelopes, sealed and labeled with a random number assigned to the participant. Envelopes tell you if the participant receives active or sham treatment, according to the code on envelope.

Intervention

TBS sessions will be performed using MagPro X100 TMS device (Magventure, Lucernemarken, Denmark) and Cool-B65 A/P (Magventure, Lucernemarken, Denmark) coil. An identical butterfly coil for both active and sham stimulation will be used. The coil will be positioned over the DLPFC and the cortical location will be obtained through anatomical measurements (F3 and F4 positions determined by the 10–20 Electroencephalographic International System) on the right and left. As most mixed depressive episodes are resistant to drug treatment and there are no clinical trials evaluating TBS specifically in mixed depressive episodes so far, we replied a study protocol (41) that evaluated TBS in resistant major depressive episodes of MDD. The bilateral TBS sections will be applied in the following order: first inhibitory stimulation—cTBS—in the right DLPFC followed by excitatory stimulation—iTBS—in the left DLPFC with the following parameters: in cTBS bursts of three pulses at 50 Hz (20-ms interval between stimuli) will be applied continuously for 120 s totaling 1800 pulses in the right DLPFC and iTBS bursts of three pulses at 50 Hz (20-ms interval between stimuli) will be applied for 2-s duration repeated every 10 s for a total time of 570 s also totaling 1800 pulses in the left DLPFC, both with 80% of visual motor threshold (64). We will use a magnetic stimulator device (MagVenture©, United States) in study mode for double-blind trials. Participants will perform one session a day over five consecutive days (Monday to Friday) at the first, second and third weeks and then sessions 2 days a week, with an interval of at least 1 day between sessions, for a further 3 weeks of active or sham TBS.

Blinding

As this is a double-blind study, both the investigators who will perform the clinical evaluations, the researchers who will perform the TBS sessions, and the participants will not be aware of the treatment given to each participant until the end of the study.

Sample Size Calculation

There are no studies on mixed depression using neuromodulation techniques, so that we used a study that used a similar methodology (bilateral TBS) (41) for treatment-resistant unipolar depression that found a reduction of 52.5% of the depression scale for the active group and a reduction of 17.4% of the depression scale for sham group ($F/X^2 = 6.166$). The sample size calculation took into account this measure of effect size obtained in the study cited and was performed with Stata® Statistical Software. The total number of participants we calculated was 82 participants, taking into account 90% power and 5% alpha. As this is a long term study we estimate a dropout rate of 10%, similar to recent studies in this field (37). Thus, we will need to recruit 90 patients, 45 participants in each group (active versus sham).

Statistical Analysis

Statistical analyses will be performed using Stata® (67) and the Statistical Package for the Social Sciences—SPSS® (68). The overall significance level for this study will be 0.05 using two-tailed tests. The study results will be analyzed for two patient populations: the intention-to-treat (ITT(and the per-protocol (PP) analysis set. The ITT set will include all subjects who met the study eligibility criteria and received at least one week active/sham TBS treatment. The PP population thus will include all subjects from the ITT set who receive the protocol-specified treatment and complete the 6-week treatment regimen or withdrew before completion per the study protocol. Comparisons of baseline demographic and clinical characteristics and safety assessments will be performed on the ITT analysis set. The primary efficacy analysis will be performed using the PP analysis set.

Comparisons of baseline demographic and clinical characteristics between the study groups will be performed to ensure that the groups are balanced at baseline and that the randomization is successful. For comparison of means (continuous variables), the two-sample t-test or a nonparametric equivalent will

be used. For comparison of proportions (categorical variables), the chi-square test or Fisher's exact test will be used, as appropriate. The change in MADRS total score from baseline to week 3 (primary endpoint) will be compared between the treatment groups using a linear mixed model (69) with a continuous dependent variable (MADRS score) to measure the primary outcome. For primary outcome subject will be the random effect and the fixed factors will be intervention (sham × active). Secondary outcomes will also follow the same pattern and the scales' scores will be the random effect and the fixed factors will be intervention (sham × active). Since patients will be taking different medications and dosages, the defined daily dose (DDD) will be used in the statistical analysis. This enables the inclusion of several medications and doses in the model, as medication groups (e.g., antidepressants, anticonvulsants, etc.).

Cognitive Assessments

Participants will be assessed before the TBS sessions and at week 6 with the Psychology Experiment Building Language tests (PEBL) (70) and the E-prime Software (Psychology Software Tools Inc.) (71) using the following tests: Trial Making Test (TMT-A, TMT-B), PEBL computer version (70); Digits test, PEBL computerized version (70); Berg's Wisconsin 64 Card Sorting Test, PEBL computerized version (70); Iowa Test, PEBL computerized version (70); Tower of London Test, PEBL computerized version (70); Cued Emotional Control Test (CECT), E-Prime Software (71); and Internal Shift Task (IST), E-Prime Software (71). Neuropsychological assessment will be applied by trained, blinded neuropsychologists in relation to treatment groups. The assessments will occur at the baseline and at the end of the sixth week after the beginning of the study, with the purpose of evaluating the cognitive performance, with and without emotional valence (cold and hot cognition), for cognitive domains such as: working memory, cognitive flexibility, decision making, processing speed, attention, and inhibitory control (72). An assessment battery of approximately one and a half hours was planned, with the possibility of a 15-min break at half time.

Reasons for Withdrawal or Termination

Patients will be withdrawn from the study if they meet one or more of the following criteria:

(1) Leave the study on their own accord;

(2) Two consecutive visits OR three or more non-consecutive visits;

(3) Have severe clinical or psychiatric events (at clinical assessment) during the study:.

These criteria will be analyzed on a case-by-case basis according to the clinical assessment that the psychiatrist may be considering. Examples of serious clinical events are: neurological deficits, cardiovascular deficits, endocrine decompensation, loss of consciousness, syncope; and others. Examples of serious psychiatric events are: suicidal ideation, suicide attempt, autoaggressiveness (self-mutilation), hetero-agressivity, severe anxiety, severe psychosis, etc.

(4) Serious adverse effects (at clinical assessment) during the study:

These criteria will be analyzed on a case-by-case basis according to the clinical assessment that the psychiatrist may be considering. Examples of serious adverse effects: severe or frequent headaches, severe cervical pain, severe scalp pain, severe scalp burning, severe dizziness, severe nausea, and seizures.

(5) Worsening of depressive (>25% on the MADRS) or manic (>50% on the YMRS) symptomatology at the end of each week of treatment.

Patients with worsening scores on depressive symptom scales (increase on MADRS scores greater than 25%) or manic symptoms (increase on YMRS scores greater than 50%) at the end of each intervention week (compared to the previous week).

Patients who discontinue the study will be referred to the psychiatrist who referred the study for appropriate follow-up and management of the disease.

DISCUSSION

Here we provided the study protocol of a randomized controlled trial (RCT) that will evaluate the efficacy of TBS for the treatment of mixed depression of both bipolar and unipolar disorders. To the best of our knowledge, this is the first study in this field. Will be applied 21 sessions of bilateral TBS, comprising first inhibitory stimulation delivered by cTBS in the right DLPFC followed by excitatory stimulation delivered by iTBS in the left DLPFC, totalizing 3600 pulses. We performed sample size calculation based on the effect size found in the most similar clinical trial found in literature (41). The CANMAT guidelines provide the first- and second-line adequate treatments to treat both unipolar and bipolar depression (55). So far, there is no scientific recommendations to treat mixed depression. So that, we will include patients in a regular use (at least 30 days) of a first or second-line treatment of a CANMAT treatment and still presents with a moderate or severe major depressive episode. Patients with different drug treatments will be included, which will significantly increase the external validity of the results (73).

Previous studies indicate that mixed features population have distinct clinical and treatment response characteristics and has been associated with higher comorbidities, higher relapse rates, worse clinical outcomes, and higher suicide risk (51, 74, 75). We defined the MADRS (48) to assess depression symptoms and YMRS (49) to assess maniac symptoms. While some studies defined mixed depression considering YMRS ≥ 4 points (51, 74), recent data suggests that YMRS with ≥ 1 point on three or more items according are appropriate to classify this issue (12). Although any RCT with TBS has been performed so far in mixed depression, one clinical trial evaluated the efficacy of bilateral TBS in refractory non-mixed depression (41). Our RCT differs from this one in several ways, including a larger sample size (90 vs. 60) and comprising mixed depression presentation of both BD and MDD. In addition to the primary outcome that will assess the efficacy of TBS in mixed depression, this study will evaluate the effect of this technique on anxious symptoms, impulsivity, biological rhythms, functionality, quality of life, and cognition, the latter through a computerized neuropsychological battery.

We are aware that our study has some limitations. The current study will be an add-on TBS study, in spite of the randomized and sham-controlled design. It has been reported that add-on repetitive TMS treatment could enhance the clinical responses to antidepressants (76), therefore, the observed responses to TBS could partly result from modulation of the effects of the medications that patients were using during the TBS treatment. However, before we have solid evidence to support the antidepressant efficacy of TBS, the add-on design is more ethically sounded and could provide more real-life data. The concomitant medications will not be allowed to be changed and will be their original medication regimen which they had failed to respond to. Someone could consider mixed sample (BDI, BDII and unipolar depression) a limitations of the study, however last decade evidence corroborated the change that occurred in the DSM-5 in which the old mood episode called "mixed state" (only allowed in bipolar I disorder) was removed and changed into a mood specifier that can be applied to major depressive episodes of both bipolar I disorder, bipolar II disorder, and MDD (unipolar depression). This change suggests that the major depressive episodes of these diseases are similar in terms of clinical presentation, so much that the specifier "with mixed features" (mixed depression) can be attributed to all of them. The fact that these are different diseases might not affect the treatment of the acute depressive episode, similar to what we observe in antidepressants use to treat acute depression of MDD, bipolar II disorder and even bipolar I disorder (protected by mood stabilizers) (55). Thus, consolidating a recent transdiagnostic approach to psychiatric diseases, our objective is also to verify whether the same clinical presentation (mixed depression) could be treated in the same way with TBS regardless of the diagnosis, since all patients will be in a moderate or severe mixed depression.

CONCLUSION

This study will investigate the efficacy of TBS for the treatment of mixed depression using a randomized, double-blinded, sham-controlled design. Both clinical information and standardized scales will contribute to best understand of mixed depression and their relationship with treatment. At the time of submission, recruitment has not been completed.

ETHICS STATEMENT

The protocol has been presented and approved by to the Research Ethics Committee HCFMUSP (CAAE: 80237017.6.0000.0068 Register number: 2.733.369). All enrolled subjects will consent to participate through an Informed Consent Form.

AUTHOR CONTRIBUTIONS

Conceived and designed the clinical trial: DT, AB, RM. Wrote the first draft of the manuscript: DT. Contributed to the writing of the manuscript: AB, RM. Study execution: DT, CS, LV, IK, LB, PF.

FUNDING

Research Foundation Support Agency of the state of Sao Paulo (FAPESP): Process: 2017/19237-1. Period: July, 2018 to June, 2020.

ACKNOWLEDGMENTS

MagVenture Inc. provided a sham stimulation coil to be used in this study. There is no other role of MagVenture regarding the protocol and the execution of this study.

REFERENCES

1. Trede K, Salvatore P, Baethge C, Gerhard A, Maggini C, Baldessarini RJ. Manic-depressive illness: evolution in Kraepelin's Textbook, 1883–1926. *Harvard Rev Psychiatry* (2005) 13(3):155–78. doi: 10.1080/10673220500174833
2. Jorge MR. Manual diagnóstico e estatístico de transtornos mentais: texto revisado: DSM-IV-TR. In: *Manual diagnóstico e estatístico de transtornos mentais: texto revisado: DSM-IV-TR.* Artmed (2002).
3. Benazzi F. Age at onset of bipolar II depressive mixed state. *Psychiatry Res* (2001) 103(2-3):229–35. doi: 10.1016/S0165-1781(01)00258-X
4. Bertschy G, Gervasoni N, Favre S, Liberek C, Ragama-Pardos E, Aubry JM, et al. Phenomenology of mixed states: a principal component analysis study. *Bipolar Disord* (2007) 9(8):907–12. doi: 10.1111/j.1399-5618.2007.00462.x
5. Koukopoulos A, Sani G, Koukopoulos A, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. *Acta Psychiatr Scand* (2007) 115:50–7. doi: 10.1111/j.1600-0447.2007.00963.x
6. Angst J, Azorin J-M, Bowden CL, Perugi G, Vieta E, Gamma A, et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry* (2011) 68(8):791–9. doi: 10.1001/archgenpsychiatry.2011.87
7. Swann AC, Steinberg JL, Lijffijt M, Moeller GF. Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features. *World Psychiatry* (2009) 8(3):166–72. doi: 10.1002/j.2051-5545.2009.tb00245.x
8. Judd LL, Schettler PJ, Akiskal H, Coryell W, Fawcett J, Fiedorowicz JG, et al. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. *J Affect Disord* (2012) 138(3):440–8. doi: 10.1016/j.jad.2011.12.046
9. Pae C-U, Vöhringer PA, Holtzman NS, Thommi SB, Patkar A, Gilmer W, et al. Mixed depression: a study of its phenomenology and relation to treatment response. *J Affect Disord* (2012) 136(3):1059–61. doi: 10.1016/j.jad.2011.11.024
10. Association A. *DSM-5: Manual diagnóstico e estatístico de transtornos mentais*. Artmed Publisher (2014).
11. Malhi GS, Fritz K, Allwang C, Burston N, Cocks C, Devlin J, et al. Are manic symptoms that 'dip'into depression the essence of mixed features? *J Affect Disord* (2016) 192:104–8. doi: 10.1016/j.jad.2015.12.009
12. McIntyre RS, Soczynska JK, Cha DS, Woldeyohannes HO, Dale RS, Alsuwaidan MT, et al. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and

bipolar disorder: results from the International Mood Disorders Collaborative Project. *J Affect Disord* (2015) 172:259–64. doi: 10.1016/j.jad.2014.09.026
13. Perugi G, Angst J, Azorin J-M, Bowden CL, Mosolov S, Reis J, et al. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry* (2015) 76(3):e351–8. doi: 10.4088/JCP.14m09092
14. Targum SD, Suppes T, Pendergrass JC, Lee S, Silva R, Cucchiaro J, et al. Major depressive disorder with subthreshold hypomania (mixed features): clinical characteristics of patients entered in a multiregional, placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* (2016) 68:9–14. doi: 10.1016/j.pnpbp.2016.02.007
15. Miller S, Suppes T, Mintz J, Hellemann G, Frye MA, McElroy SL, et al. Mixed depression in bipolar disorder: prevalence rate and clinical correlates during naturalistic follow-up in the Stanley Bipolar Network. *Am J Psychiatry* (2016) 173(10):1015–23. doi: 10.1176/appi.ajp.2016.15091119
16. Seo H-J, Wang H-R, Jun T-Y, Woo YS, Bahk W-M. Factors related to suicidal behavior in patients with bipolar disorder: the effect of mixed features on suicidality. *Gen Hosp Psychiatry* (2016) 39:91–6. doi: 10.1016/j.genhosppsych.2015.12.005
17. Shim IH, Woo YS, Bahk W-M. Prevalence rates and clinical implications of bipolar disorder "with mixed features" as defined by DSM-5. *J Affect Disord* (2015) 173:120–5. doi: 10.1016/j.jad.2014.10.061
18. Tavormina G. A long term clinical diagnostic-therapeutic evaluation of 30 case reports of bipolar spectrum mixed states. *Psychiatria Danubina* (2013) 25:190–3.
19. Perugi G, Medda P, Swann AC, Reis J, Rizzato S, Mauri M. Phenomenological subtypes of severe bipolar mixed states: a factor analytic study. *Compr Psychiatry* (2014) 55(4):799–806. doi: 10.1016/j.comppsych.2014.01.012
20. Tavormina G. Bipolar disorders and bipolarity: the notion of the" mixity". *Psychiatria Danubina* (2019) 31(Suppl 3):434–7.
21. Verdolini N, Agius M, Ferranti L, Moretti P, Piselli M, Quartesan R. The state of the art of the DSM-5 "with mixed features" specifier. *Sci World J* (2015) 2015:78–84. doi: 10.1155/2015/757258
22. McIntyre R, Tohen M, Berk M, Zhao J, Weiller E. DSM-5 mixed specifier for manic episodes: evaluating the effect of depressive features on severity and treatment outcome using asenapine clinical trial data. *J Affect Disord* (2013) 150(2):378–83. doi: 10.1016/j.jad.2013.04.025
23. Hergueta T, Weiller E. Evaluating depressive symptoms in hypomanic and manic episodes using a structured diagnostic tool: validation of a new Mini International Neuropsychiatric Interview (MINI) module for the DSM-5'With Mixed Features' specifier. *Int J Bipolar Disord* (2013) 1(1):21. doi: 10.1186/2194-7511-1-21
24. Takeshima M, Oka T. DSM-5-defined 'mixed features' and B enazzi's mixed depression: Which is practically useful to discriminate bipolar disorder from unipolar depression in patients with depression? *Psychiatry Clin Neurosci* (2015) 69(2):109–16. doi: 10.1111/pcn.12213
25. Fernandez KC, Jazaieri H, Gross JJ. Emotion regulation: a transdiagnostic perspective on a new RDoC domain. *Cogn Ther Res* (2016) 40(3):426–40. doi: 10.1007/s10608-016-9772-2
26. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* (2010) 167(7):748–51. doi: 10.1176/appi.ajp.2010.09091379
27. Çalıyurt O. Role of chronobiology as a transdisciplinary field of research: Its applications in treating mood disorders. *Balkan Med J* (2017) 34(6):514–21. doi: 10.4274/balkanmedj.2017.1280
28. Talih F, Gebara NY, Andary FS, Mondello S, Kobeissy F, Ferri R. Delayed sleep phase syndrome and bipolar disorder: Pathogenesis and available common biomarkers. *Sleep Med Rev* (2018) 41:133–40. doi: 10.1016/j.smrv.2018.02.002
29. Quante M, Kaplan ER, Rueschman M, Cailler M, Buxton OM, Redline S. Practical considerations in using accelerometers to assess physical activity, sedentary behavior, and sleep. *Sleep Health* (2015) 1(4):275–84. doi: 10.1016/j.sleh.2015.09.002
30. Tazawa Y, Wada M, Mitsukura Y, Takamiya A, Kitazawa M, Yoshimura M, et al. Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis. *J Affect Disord* (2019) 253:257–69 doi: 10.1016/j.jad.2019.04.087
31. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* (2020) 131(2):474–528. doi: 10.1016/j.clinph.2019.11.002
32. Berlim M, Van den Eynde F, Tovar-Perdomo S, Daskalakis Z. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *psychol Med* (2014) 44(2):225–39. doi: 10.1017/S0033291713000512
33. Schwippel T, Schroeder PA, Fallgatter AJ, Plewnia C. Clinical review: The therapeutic use of theta-burst stimulation in mental disorders and tinnitus. *Prog Neuropsychopharmacol Biol Psychiatry* (2019) 92:285–300 doi: 10.1016/j.pnpbp.2019.01.014
34. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet* (2018) 391(10131):1683–92. doi: 10.1016/S0140-6736(18)30295-2
35. Cao X, Deng C, Su X, Guo Y. Response and remission rates following high-frequency vs. low-frequency repetitive transcranial magnetic stimulation (rTMS) over right DLPFC for treating major depressive disorder (MDD): a meta-analysis of randomized, double-blind trials. *Front Psychiatry* (2018) 9:413. doi: 10.3389/fpsyt.2018.00413
36. Li C-T, Chen M-H, Juan C-H, Liu R-S, Lin W-C, Bai Y-M, et al. Effects of prefrontal theta-burst stimulation on brain function in treatment-resistant depression: a randomized sham-controlled neuroimaging study. *Brain Stimul* (2018) 11(5):1054–62. doi: 10.1016/j.brs.2018.04.014
37. Fitzgerald PB, Hoy KE, Elliot D, McQueen RS, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. *Neuropsychopharmacology* (2018) 43(7):1565–72. doi: 10.1038/s41386-018-0009-9
38. Fitzgerald PB, Chen L, Richardson K, Daskalakis ZJ, Hoy KE. A pilot investigation of an intensive theta burst stimulation protocol for patients with treatment resistant depression. *Brain Stimul* (2020) 13(1):137–44. doi: 10.1016/j.brs.2019.08.013
39. Kaladjian A, Belzeaux R, Micoulaud-Franchi J, Cermolacce M, Fakra E, Azorin J. Mixed states and neuroimaging. *L'Encephale* (2013) 39:S162–6. doi: 10.1016/S0013-7006(13)70116-7
40. Pallanti S, Grassi G, Antonini S, Quercioli L, Salvadori E, Hollander E. rTMS in resistant mixed states: An exploratory study. *J Affect Disord* (2014) 157:66–71. doi: 10.1016/j.jad.2013.12.024
41. Li C-T, Chen M-H, Juan C-H, Huang H-H, Chen L-F, Hsieh J-C, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain* (2014) 137(7):2088–98. doi: 10.1093/brain/awu109
42. Fagiolini A, Coluccia A, Maina G, Forgione RN, Goracci A, Cuomo A, et al. Diagnosis, epidemiology and management of mixed states in bipolar disorder. *CNS Drugs* (2015) 29(9):725–40. doi: 10.1007/s40263-015-0275-6
43. Rosenblat JD, McIntyre RS. Treatment recommendations for DSM-5–defined mixed features. *CNS Spectr* (2017) 22(2):147–54. doi: 10.1017/S1092852916000432
44. Vázquez GH, Lolich M, Cabrera C, Jokic R, Kolar D, Tondo L, et al. Mixed symptoms in major depressive and bipolar disorders: A systematic review. *J Affect Disord* (2018) 225:756–60. doi: 10.1016/j.jad.2017.09.006
45. Williams JR. The Declaration of Helsinki and public health. *Bull World Health Organ* (2008) 86:650–2. doi: 10.2471/BLT.08.050955
46. Castelein S, Houtjes W, Roodbol P, Knegtering H. Good clinical practice and the maintenance of ethical standards in medical research: advice for junior researchers working in mental health care. *Tijdschr Psychiatr* (2014) 56(8):533–8.
47. Del-Ben CM, Vilela JAA, Crippa JADS, Hallak JEC, Labate CM, Zuardi AW. Confiabilidade da" Entrevista Clínica Estruturada para o DSM-IV-Versão Clínica" traduzida para o português. *Braz J Psychiatry* (2001) 23(3):156–9. doi: 10.1590/S1516-44462001000300008
48. Duarte-Guerra LS, Gorenstein C, Paiva-Medeiros PF, Santo MA, Neto FL, Wang Y-P. Clinical utility of the Montgomery-Åsberg Depression Rating Scale for the detection of depression among bariatric surgery candidates. *BMC Psychiatry* (2016) 16(1):119. doi: 10.1186/s12888-016-0823-8
49. Vilela J, Crippa JADS, Del-Ben CM, Loureiro SR. Reliability and validity of a Portuguese version of the Young Mania Rating Scale. *Braz J Med Biol Res* (2005) 38(9):1429–39. doi: 10.1590/S0100-879X2005000900019

50. Swann AC, Lafer B, Perugi G, Frye MA, Bauer M, Bahk W-M, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry* (2013) 170(1):31–42. doi: 10.1176/appi.ajp.2012.12030301
51. Tohen M, Kanba S, McIntyre RS, Fujikoshi S, Katagiri H. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. *J Affect Disord* (2014) 164:57–62. doi: 10.1016/j.jad.2014.04.003
52. Azorin J-M, Kaladjian A, Adida M, Fakra E, Belzeaux R, Hantouche E, et al. Self-assessment and characteristics of mixed depression in the French national EPIDEP study. *J Affect Disord* (2012) 143(1-3):109–17. doi: 10.1016/j.jad.2012.05.036
53. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* (2009) 166 (2):173–81. doi: 10.1176/appi.ajp.2008.08050746
54. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. *Can J Psychiatry* (2016) 61 (9):540–60. doi: 10.1177/0706743716659417
55. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* (2013) 15(1):1–44. doi: 10.1111/bdi.12025
56. Hawley C, Gale T, Sivakumaran Tgroup HNR. Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disord* (2002) 72 (2):177–84. doi: 10.1016/S0165-0327(01)00451-7
57. Freire MÁ, Figueiredo VLMD, Gomide A, Jansen K, Silva RAD, Magalhães PVDS, et al. Escala Hamilton: estudo das características psicométricas em uma amostra do sul do Brasil. *J Bras Psiquiatr* (2014) 63(4):281–9. doi: 10.1590/0047-2085000000036
58. Guy W. *Assessment manual for psychopharmacology, revised*. Rockville, MD: DEW (1976) p. 341–50.
59. Jones SH, Thornicroft G, Coffey M, Dunn G. A brief mental health outcome scale: Reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* (1995) 166(5):654–9. doi: 10.1192/bjp.166.5.654
60. Fleck M, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida" WHOQOL-bref". *Rev Saúde Pública* (2000) 34(2):178–83. doi: 10.1590/S0034-89102000000200012
61. Giglio LMF, da Silva Magalhães PV, Andreazza AC, Walz JC, Jakobson L, Rucci P, et al. Development and use of a biological rhythm interview. *J Affect Disord* (2009) 118(1-3):161–5. doi: 10.1016/j.jad.2009.01.018
62. Malloy-Diniz LF, Mattos P, Leite WB, Abreu N, Coutinho G, Paula JJD, et al. Tradução e adaptação cultural da Barratt Impulsiveness Scale (BIS-11) para aplicação em adultos brasileiros. *J Bras Psiquiatr* (2010) 59(2):99–105. doi: 10.1590/S0047-20852010000200004
63. Silva CFD, Silvério JMA, Rodrigues PJF, Pandeirada J, Fernandes SM, Macedo FBD, et al. The Portuguese version of the Horne and Ostberg morningness-eveningness questionnaire: Its role in education and psychology. *Revista Psicologia e Educação* (2002) 1 (1–2):39–50.
64. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *J Clin Neurophysiol* (2011) 28(1):67. doi: 10.1097/WNP.0b013e318205135f
65. Sayar GH, Ozten E, Tan O, Tarhan N. Transcranial magnetic stimulation for treating depression in elderly patients. *Neuropsychiatr Dis Treat* (2013) 9:501. doi: 10.2147/NDT.S44241
66. Lingjaerde O, Ahlfors U, Bech P, Dencker S, Elgen K. The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand* (1987) 76:1–100. doi: 10.1111/j.1600-0447.1987.tb10566.x
67. StataCorp L. Stata data analysis and statistical Software. *Spec Ed Rel* (2007) 10:733.
68. Kirkpatrick L, Feeney B. *A simple guide to IBM SPSS: for version 20.0*. Wadsworth Publishing (2012).
69. West BT, Welch KB, Galecki AT. *Linear mixed models: a practical guide using statistical software*. CRC Press, Boa Ration (2014).
70. Piper BJ, Mueller ST, Geerken AR, Dixon KL, Kroliczak G, Olsen RH, et al. Reliability and validity of neurobehavioral function on the Psychology Experimental Building Language test battery in young adults. *PeerJ* (2015) 3:e1460. doi: 10.7717/peerj.1460
71. Schneider W, Eschmann A, Zuccolotto A. *E-Prime (Version 2.0. 8.90)*. Pittsburgh, PA: Psychology Software Tools. Inc (2002).
72. Vanderhasselt M-A, Brunoni AR, Loeys T, Boggio PS, De Raedt R. Nosce te ipsum–Socrates revisited? Controlling momentary ruminative self-referent thoughts by neuromodulation of emotional working memory. *Neuropsychologia* (2013) 51(13):2581–9. doi: 10.1016/j.neuropsychologia.2013.08.011
73. Heale R, Twycross A. Validity and reliability in quantitative studies. *Evidence-Based Nurs* (2015) 18(3):66–7. doi: 10.1136/eb-2015-102129
74. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PEJr., et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry* (2009) 166(2):164–72. doi: 10.1176/appi.ajp.2008.08030322
75. McIntyre RS, Cucchiaro J, Pikalov A, Kroger H, Loebel A. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *J Clin Psychiatry* (2015) 76(4):398–405. doi: 10.4088/JCP.14m09410
76. Berlim MT, den Eynde Van F, Daskalakis ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. *J Clin Psychiatry* (2013) 74(2):e122–9. doi: 10.4088/JCP.12r07996

Conflict of Interest: DT: worked as speaker and produced scientific source during the last 2 years for the following pharmaceutical companies: Cristália, Aché and Torrent. AB: receives grants from the 2012 FAPESP Young Research Award from the São Paulo State Foundation (Grant No. 20911-5), the Brain and Behavior Research Foundation (Grant No. 20493), and a National Council for Scientific and Technological Development Grant (CNPq, Grant No. 470904). RM: acted as a consultant, received honoraria or scientific educational grant funding or conducted clinical research sponsored by companies with developments in the area of bipolar and depressive disorders (Servier, Jansen, Daiichi Sankyo Brasil Farmacêutica Ltda., Grupo EMS, Aché, Cristália, Torrent, Abbott, GlaxoSmithKline, Pfizerf); receives research grants from the Research Foundation Support Agency of the State of Sao Paulo, Brazil (FAPESP); and receives a research productivity grant from the National Research Council – Brazil (CNPq).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 11 June 2020
doi: 10.3389/fpsyt.2020.00500

Depression Preceding Diagnosis of Bipolar Disorder

Claire O'Donovan and Martin Alda *

Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

This paper focuses on depression that precedes an onset of manifest bipolar disorder as early stage bipolar disorder. First, we review how to pragmatically identify the clinical characteristics of patients presenting with an episode of depression who subsequently go on to develop episodes of mania or hypomania. The existing literature shows a strong consensus: accurate identification of depression with early onset and recurrent course with multiple episodes, subthreshold hypomanic and/or mixed symptoms, and family history of bipolar disorder or completed suicide have been shown by multiple authors as signs pointing to bipolar diagnosis. This contrasts with relatively limited information available to guide management of such "pre-bipolar" (pre-declared bipolar) patients, especially those in the adult age range. Default assumption of unipolar depression at this stage carries significant risk. Antidepressants are still the most common pharmacological treatment used, but clinicians need to be aware of their potential harm. In some patients with unrecognized bipolar depression, antidepressants can not only produce switch to (hypo)mania, but also mixed symptoms, or worsening of depression with an increased risk of suicide. We review pragmatic management strategies in the literature beyond clinical guidelines that can be considered for this at-risk group encompassing the more recent child and adolescent literature. In the future, genetic research could make the early identification of bipolar depression easier by generating informative markers and polygenic risk scores.

Keywords: bipolar disorder, family history (FH), early onset, mixed depression, staging, adverse response to antidepressants, mood stabilizers, polarity at onset

OPEN ACCESS

Edited by:
Dina Popovic,
Sheba Medical Center, Israel

Reviewed by:
Liz Forty,
Cardiff University, United Kingdom
Gabriele Sani,
Università Cattolica del Sacro Cuore, Italy

***Correspondence:**
Martin Alda
malda@dal.ca

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *25 February 2020*
Accepted: *18 May 2020*
Published: *11 June 2020*

Citation:
O'Donovan C and Alda M (2020) Depression Preceding Diagnosis of Bipolar Disorder. Front. Psychiatry 11:500. doi: 10.3389/fpsyt.2020.00500

INTRODUCTION

Of people presenting with an episode of major depression, a certain proportion may in reality be suffering from depression that is of bipolar type. This could be for several reasons: 1) in many if not most cases bipolar disorder starts with symptoms of depression and first hypomania/mania may not appear until years later; 2) depression is considered a part of the bipolar genetic spectrum and thus some forms of depression are conceivably variants of bipolar disorder, particularly in those with a strong family history; and 3) previous episodes of hypomania or even mania may be missed in some patients.

In this paper we will deal with the first two possibilities acknowledging that we currently mostly misidentify first episode and early stage bipolar disorder (BD) when it presents as depression ("pre-bipolar depression" meaning depression before it is realized that it is bipolar by virtue of an ensuing

hypo/manic episode) by defaulting to unipolar disorder. We will review the literature relevant for the best identification of depressive episodes in probable early stages of bipolar disorder that is prior to manifest (hypo) mania and suggest a pragmatic cost/benefit approach to management that handles uncertainty of final diagnosis to come.

POLARITY AT ONSET AND INTERVAL FROM FIRST DEPRESSION TO FIRST MANIA

Depressive episodes are common at the onset of bipolar disorder as shown in both retrospective and prospective studies. The proportion of those with a depressive index episode varies between different studies, but consistently is over 50% (range of 50%–80%). Family data suggest that the polarity at onset is possibly a heritable trait and may identify separate genetic subtypes of bipolar disorder (BD) (1).

The advantage of retrospective studies is usually their large sample size. On the other hand, they are prone to recall bias and especially less severe episodes are more difficult to remember. For this reason, prospective follow-up of young people at risk of bipolar disorder is valuable in mapping the early course more accurately. Repeated careful clinical assessments allow for detection of less severe mood states that might be overlooked in retrospect. Several such long-term cohort studies are described in the literature and practically all document high rates of depressive onsets. For instance, in the Canadian high-risk study major depression was reported as the initial episode in 58% of at-risk individuals and depressive disorder not otherwise specified (NOS) in another 19% while the remaining 23% of onsets were divided between mania, hypomania, and cyclothymia (2). Similarly, in the Dutch bipolar offspring cohort, 108 participants were followed for 12 years. At the second assessment, 15 out of 17 who had a diagnosis of bipolar disorder had an index episode of depression or dysthymia that preceded the first (hypo)mania by an average of 5.6 ± 4.4 years (3). In the Pittsburgh high-risk study, 25 out of 36 offspring diagnosed with bipolar disorder had a previous history of depression (4). And finally, several other high-risk studies that reported cross-sectional prevalence of mood disorders found especially high rates of depression in children of parents with bipolar disorder, reviewed by Vandeleur (5). See also a review of high-risk studies, prospective and retrospective by Vieta et al. (6).

Some studies suggest that there is also a difference in the manifestation of early depression depending on the family history. In the Pittsburgh high-risk study, those at risk of bipolar disorder had depression that was more severe with more prominent atypical symptoms, especially hypersomnia, fatigue, psychomotor retardation, and sense of hopelessness (7).

A related variable describing the early course of BD is the interval from first depression to mania or hypomania. This also tends to vary considerably both within and between studies. Thus, Berk et al. (8) reported an average of 7.6 ± 8.7 years and Cha et al. 5.6 ± 6.1 years (9). In both cases the interval is not only lengthy, but also highly variable between individuals. Murru et al. found the duration of untreated illness over 6 years on average and those with a longer untreated interval had more typically younger onset, predominantly depressive polarity, more chronic course, and more frequent comorbid conditions (10).

CONVERSION FROM MAJOR DEPRESSION TO BIPOLAR DISORDER

Another group of observations relate to longitudinal cohorts of people initially diagnosed with major depression. Given a sufficient length of follow-up, a certain proportion of them will convert to bipolar I or bipolar II disorder. The longest such observation comes from the Zurich cohort of Jules Angst. He and colleagues showed that after an initial somewhat steeper rate of conversion, from the 5th year onward the proportion of those who developed a manic episode was about 1% per year and hypomanias occurred at a rate of 0.5% per year (11). Coryell et al. (12) observed conversion to mania and hypomania each in about 5% of patients previously diagnosed with depression and followed for 10 years. These rates are only marginally lower than the Angst data. In another long-term prospective cohort of patients with major depression followed for an average of 17.5 years, the rate of new onsets of mania was 7.5% and hypomania in 12.2%. The risk was associated with symptoms of psychosis and subthreshold hypomanic symptoms during the depressive episodes as well as early onset of depression (13). In a population cohort of 3012 young community participants, 3.6% of people with an initial depression were re-diagnosed with bipolar disorder after a period of up to 10 years, but the risk was substantially higher at 9% in those with onset of depression before the age of 17 (14). Finally, in a large population database study, the cumulative incidence of conversion was 8.4% over an average of 7.7 ± 5.4 years with the strongest predictors being the parental diagnosis of BD, psychotic depression, prior diagnosis of psychosis, and inpatient treatment for the index episode (15).

BIPOLAR DEPRESSION IN ABSENCE OF (HYPO)MANIA

However, not all with bipolar depression ever develop a manic episode. In some of them family history of BD is an indication that their depression is of a different type. Blacker and Tsuang estimated that about two-thirds of unipolar relatives of bipolar probands in fact had bipolar depression (16). It is to be noted that the distinction between this group and those that convert is somewhat artificial. The length of follow-up is clearly an issue—cf. the Zurich study in which some patients changed their diagnosis even after 50 years (11).

IDENTIFICATION OF CLINICAL FEATURES THAT CAN HELP IDENTIFY PRE-BIPOLAR DEPRESSION

In the above sections we discussed the features of depressive episodes that, in retrospect, preceded a confirmed diagnosis of bipolar disorder or differentiated those with established diagnoses of BD versus unipolar depression. Clinicians, however, face a different task. They need to decide whether a patient presenting with depression might be suffering from bipolar depression and if so, what implications this has for clinical management.

There are no definitive criteria or biomarkers for depression preceding first episode hypo/mania and some would argue that it is unipolar depression until it converts. In this view, antidepressant induced switch is a helpful hint to alter course of treatment. The alternative view is that our goal is to better identify probable bipolar disorder at first/early episode depression, particularly in high risk families, cause no harm, and positively impact the long-term course of illness. In this latter approach, a staging strategy to enrich the data collected at a research level and a clinically useful cost/benefit strategy at a clinical level is imperative. One approach to depression at least in youth is to assign no polarity (unipolar or bipolar) until several episodes have occurred but this will not do justice to those who convert late or not at all.

Table 1 provides a summary of clinical variables helpful in distinguishing unipolar and bipolar depression, using a triad of family history, course of illness, and symptoms.

Table 1 also denotes those clinical features that are identifiable for the clinician relying on criteria as per Diagnostic and Statistical Manual (DSM).

ASSESSMENT OF FAMILY HISTORY

Of this triad, the most robust predictor is family history of bipolar disorder, especially in early onset youth. Family history of completed suicide along with male sex are the only known predictors of completed suicide in this group (6). The most valuable course predictors are recurrence and early age of onset of depressive symptoms. The most consistent symptom-related factors are subsyndromal hypo/manic symptoms (mixed symptoms) and mood lability (6).

Family history, like recurrence and age of onset of first symptoms are readily available to the clinician who spends some time. It is often the first piece of information presenting to the treating clinician before any treatment commences. However, poor quality of family history information in routine clinical practice is a frequent critique in the literature (23, 24). While earlier studies endorsed under reporting of indirectly collected family history bipolar, the recent colloquialization of the term "bipolar" has led to concerns in the opposite direction (https://ibpf.org/articles/please-stop-saying-bipolar-when-you-mean-unpredictable-or-broken/accessed2020-02-16) (http://www.vh1.com/news/261723/bipolar-disorder-hollywood-misconceptions/accessed2020-02-16) (25).

Family study of individual family members with structured interviews is the most accurate method for research, with family history from a tool such as the Family History Research Diagnostic Criteria method (FH-RDC) from as many informants as possible providing a more accessible although less sensitive tool (26). Finally, there is some evidence for the Family History Screen which provides information on 15 psychiatric disorders including mania and takes 5–20 min, depending on complexity (27). **Table 2** provides clinical advice on verification of a patient report of family history bipolar disorder.

ASSESSMENT OF COURSE OF ILLNESS

There is little difficulty for the clinician in assessing early onset and recurrent episodic depression along with seasonality and hormonal status, and changes in the course of illness over time as long as attention is paid to past and prospective course in a methodical manner. This is imperative where there is early onset or a family history of bipolar disorder.

Pictorial graphing representation of the episodes can be particularly helpful and the patient can be engaged in the maintenance phase in depicting this (for example, see: https://bipolarnews.org/wp-content/uploads/2010/07/Patient-Retrospective-Manual.pdf accessed 04/27/2020). Unfortunately the use of pictorial graphing of episodes tends to be siloed in the bipolar disorder literature although it is helpful for both unipolar and bipolar illnesses and hence the pictorial representation of

TABLE 1 | Potential predictors of bipolar course in comparison to unipolar course [see also (17–22)].

Symptoms	Course	Family History
Presence of mixed symptoms*	Early age of onset	Bipolar Disorder
Atypical depression*	Abrupt onset/offset	Suicide
Lability of mood	Frequent episodes	Severe mental illness
Psychomotor retardation*	Shorter episodes	
Pathological guilt	Post-partum episode	
Psychotic symptoms	Recurrent episodic	
Hyperthymic/cyclothymic temperament	Treatment resistance	
Catatonia*	Seasonality*	
	Abrupt onset response to antidepressant/increase dose	

These factors are present in some modified form in DSM V; the others require a broader understanding of the psychiatric literature.

TABLE 2 | Factors to consider in assessing family history of hypo/mania from an informant.

Is the person described a biological relative?
Has the person described adequate DSM criteria for hypo/mania?
Has the person described got persistent psychosis?
Is the behavioral manifestation apparent to family consistent with a probable diagnosis of hypo/mania
Has the person described been hospitalized?
Has the person received/responded to ECT?
Has the person described been prescribed lithium or divalproex or carbamazepine or lamotrigine?
Has the person described been prescribed higher dose atypical antipsychotics consistent with treatment of bipolar disorder?
Has the person described been prescribed antidepressant monotherapy long term and done well?
Has the person had serious impairment of function at some stage of their illness?
Has the person described ended their life by suicide or made a serious suicide attempt?

course tends to start with a hypo/manic episode and work backward. Staging models of bipolar disorder which identify depression as prodromal or non-specific or at increased risk of bipolar disorder (i.e. identify it as unipolar depression before it "converts") are evolving and not currently yet of clinical help to the clinician's dilemma (28).

ASSESSMENT OF MIXED SYMPTOMS

The assessment of mixed/hypomanic symptoms interspersed in a depressive episode is at best a challenge for the clinician when looking for guidance from the literature with both broad and narrow interpretations of mixed symptoms, variably defined in DSM and the broader literature, and a more specific unique mixed syndrome most notably propounded by Koukopoulos (29). DSM V mixed symptom specifier is the most restrictive diagnosis requiring three mixed hypomanic symptoms, excluding the overlapping symptoms of psychic and motor agitation, irritability, and distractibility (30). These above excluded symptoms, along with mood lability, the broader–irritability-anger-hostility continuum and an impulsive suicidality are considered the core of mixed state by many others (29, 31–33).

A broad assessment of DSM V criteria for major depression and hypo/mania along with mood lability and an irritability-anger –hostility factor without *a priori* assignment to pole may be most valuable to the clinician in assessing baseline and progression of illness state with or without treatment intervention. Of those tools available for assessment of mixed symptoms, the Zimmerman scale matches DSM V criteria for mixed symptom specifier (34).

Other continuous (between poles) assessment can be used such as using the Young Mania Rating Scale, along with the Montgomery-Asberg Depression Rating Scale (includes the irritability-hostility dimension but does not include lability or impulsivity (35, 36) and various structured interviews such as the Structured Clinical Interview for DSM or The Schedule for Affective Disorders and Schizophrenia).

TABLE 3 | Assessment and monitoring of major depression with family history of bipolar disorder or suicide.

Careful assessment and follow up of family history
Baseline and follow up monitoring of both manic and depressive symptoms
Weekly monitoring for 4 weeks
Bi-weekly monitoring up to 12 weeks
Use of collateral history
Specific attention to suicidality including impulsive suicidality
Specific attention to psychic or motor agitation
Specific attention to the irritability-hostility-aggression continuum
Follow course long term for alteration in course of illness
Referral to psychiatric services, specialty mood disorders clinics where available

There are a large number of other criteria and scales for mixed symptoms which variably include (37–39) and exclude the three overlapping DSM symptoms (39). They also include other symptoms and validate exclusion of some of the more frank manic symptoms of DSM mixed symptom specifier such as euphoria, less commonly found in mixed depression—see the Koukopoulos Mixed Depression Rating Scale (40).

Patients with manic symptoms can be more averse to reporting to the clinician and benefit from self-reporting scales of mania include the Altman scale and the Internal State scale (41, 42).The hypomania checklist (HCL 32) has been used specifically in major depression with mixed features (43). Sachs has published a combined DSM V clinical monitoring form (includes overlapping symptoms) and speaks to the need for careful and detailed assessment and follow-up (44, 45). Other scales include family history of bipolar disorder as a validating criterion, e.g. (46). Summary recommendations for assessment and monitoring are given in **Table 3**.

PRAGMATIC MANAGEMENT OF POSSIBLE/PROBABLE PRE-BIPOLAR DEPRESSION

There is now largely an acceptance that bipolar and unipolar depression are treated differently with overlap for a minority of bipolar I and some bipolar II depressions that may be pharmacogenetically distinct in response to antidepressants (47). It is accepted that bipolar depression with mixed features should not be treated with antidepressants (37, 47). What then of possible pre-bipolar depression/a depression with family history of bipolar disorder or early onset of depression with mixed symptoms or both? Recent clinical Practice Guidelines on major depression have been largely silent on the topic of potential bipolar depression, ignoring familial risk of bipolar disorder as a key consideration (48–51). The exception is the original Royal Australian Guidelines on mood disorders, a merger of unipolar and bipolar illnesses. By virtue of approaching the disorders in this unitary fashion, the management approach views the unipolar depressive episode as either unipolar or unknown bipolar, pays attention to differentiating symptoms and course factors and emphasizes family history of bipolar disorder as raising the "index of suspicion". It emphasizes approaching the diagnosis as provisional to be clarified over time and

acknowledges the possibility of iatrogenic worsening. It also emphasizes the close relationship between highly recurrent episodic depression and bipolar disorder which opens up the exploration for the treating psychiatrist that the episode of depression is unipolar but may respond pharmacologically similar to bipolar depression (52).

In contrast, recent treatment guidelines for children/adolescent depression are much more attentive to factoring family history of bipolar disorder into the assessment, gathering collateral history and providing detailed psychoeducation to families regarding potential bipolar outcomes (53, 54). There are several obvious reasons for this. Firstly, early age of onset is among the more solid predictors of bipolar depression and risk of manic switch in youth is 4.5 times greater than in adults (55). Mixed manic symptoms interspersed with depression are more common in youth (56). It is more firmly accepted that antidepressants can cause harm in adolescent depression with new onset of or increase in irritability, impulsivity and agitation, suicidal thinking, and behavior as well as the broader phenomenology of "activation" (53, 54, 57, 58). There are several long-term prospective cohorts of children with familial risk ongoing, cited above, with attempts to calculate risk of future bipolar course at least over the short term (59). Finally, the assessment of youth typically includes families which alters the perspective.

The more recent guidelines also reflect a significant number of recent studies and reviews in children and adolescents (and occasionally up to age 20) with major depression and family history of bipolar disorder summarized by Angal in a recent case report and review of the literature (56).

The Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Toolkit published in 2018 keeps the clinician aware of potential future bipolar course, advise on frequency of careful monitoring in the first 12 weeks, emphasize supportive but active monitoring in shorter episodes, use of CBT/IPT in milder cases, low dose and slow titration (no increase for 4 weeks from fluoxetine 10 mg), avoidance of tricyclics which are ineffective, and avoidance of venlafaxine which has been associated with more self-harm events. (Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Toolkit: http://www.gladpc.org accessed 2020-02-16).At the same time they make clear that severe episodes needed to be treated aggressively—the most challenging question for those with risk factors for bipolar depression is what pharmacological agent to use.

Some of these tools could be used in a similar fashion for monitoring those with family history of bipolar disorder regardless of age. However, even the youth guidelines do not adequately address the assessment of mixed symptoms in a depressive episode.

There is a need to accurately and thoroughly assess and monitor mixed symptoms particularly in those with major depression and family history positive for bipolar disorder both as initial presentation (pre-antidepressant) and in follow up monitoring. Quite apart from the known risk of manic/hypomanic switch, there is a small but significant literature on the association of antidepressants with worsening of depression, cycling of depression, emergent mixed symptoms, treatment resistance, and suicidality (not limited to youth) in a subgroup of depressed patients with and without potential mixed symptoms (22, 55, 60–66).

We retrospectively studied a small group of confirmed bipolar versus unipolar depressed patients (over 7 years) for earlier history. Family history of bipolar disorder and completed suicide predicted future bipolar course. Early onset depression as well as treatment emergent mixed symptoms, lability, psychomotor activation, and suicidality were significantly more common in the "pre-bipolar group" (60).

Antidepressant worsening is now increasingly accepted as a potential outcome in bipolar depression although still with considerable controversy about their efficacy and potential adverse effects and "tachyphylaxis" (63, 66–73). Serotonin reuptake inhibitors and bupropion are favored over more multimodal antidepressants in the International Society for Bipolar Disorders Guidelines on use of antidepressants in bipolar depression. Antidepressants are contraindicated in mixed bipolar depression and alternative mood stabilizing agents with antidepressant efficacy are considered rather than antidepressants (73).

Antidepressant worsening in child and adolescent depression is also accepted as a possibility in a minority of patients and antidepressants are held second line or for more severe cases and more frequently monitored than in adult guidelines The option of adding a mood stabilizer to the antidepressant is made explicitly in these recent guidelines (Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Toolkit: http://www.gladpc.org accessed 2020-02-16).

Absent from any guideline is recommendation for a systematic assessment of baseline symptomatology and monitoring of outcome, whether "watchful waiting" monitoring the natural transition of illness, or with active specific pharmacological or psychotherapeutic intervention, particularly in relation to mixed symptoms. This can be as simple as assessing all DSM V symptoms of both depression and mania in a good clinical interview, but self-report tools noted above can be of benefit both for education and monitoring and allow also for collateral history for observable changes. The challenge is that there is no accepted definition of mixed symptoms.

SPECIFIC TREATMENTS FOR DEPRESSION WITH FAMILY HISTORY OF BIPOLAR DISORDER

There can be no specific recommendations for this group at this time as all data is extrapolation. Clinicians should be experienced and have a good knowledge of unipolar, bipolar, child and adolescent, youth guidelines, and guidelines for mixed bipolar states and apply where they see fit and change according to treatment response (37, 47–54, 56, 57, 72, 73). Guidelines for first episode psychosis contain limited data on the depression with psychotic features group (6). Guidelines have unfortunately

TABLE 4 | Treatment considerations for major depression with family history of bipolar disorder or suicide.

Consideration of supportive therapy, CBT, IPT, and FFT in milder, shorter depression
Antidepressants may cause harm in this group
Cautious low dose—go slow strategy for antidepressants if used.
Consider lithium especially in those with family history response to lithium/family history suicide
Consider avoiding SNRIs and TCAs
Consider tapering antidepressant if mixed symptoms evolve
Consider adding mood stabilizer
Consider neuromodulation (ECT and with consequent personalized treatment rTMS) in moderate to severe especially mixed depression
Consider lamotrigine or quetiapine as they are used in both unipolar and bipolar depression
Consider ziprasidone or lurasidone augmentation if mixed symptoms

CBT, cognitive behavioral therapy; IPT, Interpersonal Therapy; FFT, Family Focused Therapy; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

siloed data. For example, suggestions for "low dose—go slow" antidepressants in this group is largely borrowed from the child and adolescent guidelines (high risk group) and early psychosis literature (6).

Several recent papers, not reviewed here summarize the limited data on treatment of "unipolar " depression with mixed features (33, 74–77) which may or may not proceed to bipolar disorder or in part have its own signature. As can be seen by the recency of papers quoted, up to date knowledge of the evolving literature is important as guidelines are already outdated.

Table 4 outlines strategies to consider in approaching major depression, family history bipolar disorder—of most importance in youth but remaining important in young adults all the way to old age. These are extrapolated from both unipolar and bipolar guidelines above where the agent is recommended as effective in both unipolar and bipolar depression.

Antidepressants continue to have a presence as indeed some of these cases may have little diathesis to bipolar outcome or respond to antidepressants effectively as do a minority of those with known bipolar depression. The potential *post hoc* fallacy assuming that an antidepressant has been effective has to be balanced against the presumed natural duration of a depressive episode which in pre-bipolar depression can be quite short with abrupt offset. Careful delineation of baseline symptoms of both poles will help identify natural evolution of mixed symptoms or indeed antidepressant worsening, even if preceded by a honeymoon response. The principle of *primum non nocere* is most challenging with antidepressants but the use of potent psychotropics of any kind has to be balanced against the possible benefits of evidence based psychotherapies particularly in milder or earlier onset cases. Inevitably many cases will be severe, and we point to agents, pharmacological and neuromodulatory, that have benefit and/or less harm in either unipolar or bipolar depression either in mono or combined therapy such as quetiapine, lamotrigine and lithium, and electroconvulsive therapy. Repetitive transcranial magnetic stimulation has evidence in both unipolar and bipolar depression but there is report of a very small number of cases of treatment emergent hypo/mania (78). We would urge caution in extrapolating treatment recommendations from DSM IV diagnosed mixed mood which is directed to a mixed manic syndrome rather than depression with some mixed symptoms. Ziprasidone and lurasidone have limited data in mixed depression (35, 36, 77).

Lithium should be considered as a serious contender given its benefit in both recurrent episodic depression and bipolar depression, its neuroprotective effects, and its antisuicidal effects, most especially but not exclusively in those with a family history of lithium response or completed suicide. It has no specific evidence in depression with mixed symptoms, but there appears to be a good case for its use (79). The choice here should be considered in light of proposed predictors of lithium response (family history, especially of lithium-responsive illness, absence of mood incongruent psychosis, and low rates of comorbid conditions (80).

CONCLUSIONS AND FUTURE DIRECTIONS

The existing literature supports the distinction between depression that is likely a manifestation of bipolar disorder and depressive disorder. The most consistent features helpful in such differentiation include early onset, highly recurrent clinical course, family history of bipolar disorder and/or completed suicide, and adverse response to antidepressants. Arguably, these factors are not infallible. It is hoped that in the future, laboratory or brain imaging technologies can contribute further to more accurate diagnosis. One such measure could be based on genome-wide genetic data. It is conceivable that, as more genetic markers of bipolar disorder and depression are discovered, it will be possible to differentiate the subtypes of depression by, for instance, polygenic risk scores. These could be constructed specifically with the goal of capturing genetic differences between unipolar and bipolar depression rather than polygenic scores for each condition alone. Recently, Liebers et al. analyzed polygenic risk score (PRS) differences between UD and BD in 843 BD and 930 UD patients (81). Those with BD had higher PRS for BD and schizophrenia, but both contributed modestly to the overall classification (AUC of 0.64 for either PRS) and only minimally once the authors used clinical profiles for classification. Nevertheless, large datasets are becoming now available to analyze genetic differences between the two types of depression further, see for instance the recent large scale analysis by Coleman et al. (82). How practical such an approach will be remains to be seen. On the one hand, genome-wide analyses point to a significant correlation in genetic liability to major depression and bipolar disorder, on the other hand, the clinical differences give hope that their differentiation at the genetic level should be also possible.

AUTHOR CONTRIBUTIONS

CO'D and MA both reviewed the relevant literature and drafted and revised the manuscript.

FUNDING

The work has been supported by the grant #166098 from the Canadian Institutes of Health Research.

REFERENCES

1. Kassem L, Lopez V, Hedeker D, Steele J, Zandi P, McMahon FJ. Familiality of polarity at illness onset in bipolar affective disorder. *Am J Psychiatry* (2006) 163:1754–9. doi: 10.1176/ajp.2006.163.10.1754
2. Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord* (2007) 9:828–38. doi: 10.1111/j.1399-5618.2007.00421.x
3. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry* (2013) 170:542–9. doi: 10.1176/appi.ajp.2012.12030401
4. Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB, et al. Diagnostic Precursors to Bipolar Disorder in Offspring of Parents With Bipolar Disorder: A Longitudinal Study. *Am J Psychiatry* (2015) 172:638–46. doi: 10.1176/appi.ajp.2014.14010035
5. Vandeleur C, Rothen S, Gholam-Rezaee M, Castelao E, Vidal S, Favre S, et al. Mental disorders in offspring of parents with bipolar and major depressive disorders. *Bipolar Disord* (2012) 14:641–53. doi: 10.1111/j.1399-5618.2012.01048.x
6. Vieta E, Salagre E, Grande I, Carvalho AF , Fernandes BS, Berk M, et al. Early Intervention in Bipolar Disorder. *Am J Psychiatry* (2018) 175:411–26. doi: 10.1176/appi.ajp.2017.17090972
7. Diler RS, Goldstein TR, Hafeman D, Rooks BT, Sakolsky D, Goldstein BI, et al. Characteristics of depression among offspring at high and low familial risk of bipolar disorder. *Bipolar Disord* (2017) 19:344–52. doi: 10.1111/bdi.12508
8. Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, de Castella AR, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. *J Affect Disord* (2007a) 103:181–6. doi: 10.1016/j.jad.2007.01.027
9. Cha B, Kim JH, Ha TH, Chang JS, Ha K. Polarity of the first episode and time to diagnosis of bipolar I disorder. *Psychiatry Investig* (2009) 6:96–101. doi: 10.4306/pi.2009.6.2.96
10. Murru A, Primavera D, Oliva M, Meloni ML, Vieta E, Carpiniello B. The role of comorbidities in duration of untreated illness for bipolar spectrum disorders. *J Affect Disord* (2015) 188:319–23. doi: 10.1016/j.jad.2015.09.009
11. Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* (2005b) 84:149–57. doi: 10.1016/S0165-0327(03)00195-2
12. Coryell W, Endicott J, Maser JD, Keller MB, Leon AC, Akiskal HS. Long-term stability of polarity distinctions in the affective disorders. *Am J Psychiatry* (1995) 152, 3:385–90. doi: 10.1176/ajp.152.3.385
13. Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* (2011) 168:40–8. doi: 10.1176/appi.ajp.2010.10030328
14. Beesdo K, Hofler M, Leibenluft E, Lieb R, Bauer M, Pfennig A. Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life. *Bipolar Disord* (2009) 11:637–49. doi: 10.1111/j.1399-5618.2009.00738.x
15. Musliner KL, Ostergaard SD. Patterns and predictors of conversion to bipolar disorder in 91 587 individuals diagnosed with unipolar depression. *Acta Psychiatr Scand* (2018) 137:422–32. doi: 10.1111/acps.12869
16. Blacker D, Tsuang MT. Unipolar relatives in bipolar pedigrees: are they bipolar? *Psychiatr Genet* (1993) 3:5–16. doi: 10.1002/ajmg.1320480405
17. Moreno C, Hasin DS, Arango C, Oquendo MA, Vieta E, Liu S, et al. Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Bipolar Disord* (2012) 14:271–82. doi: 10.1111/j.1399-5618.2012.01009.x
18. Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* (2005c) 84:149–57. doi: 10.1016/S0165-0327(03)00195-2
19. Perlis RH, Brown E, Baker RW, Nierenberg AA. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. *Am J Psychiatry* (2006) 163:225–31. doi: 10.1176/appi.ajp.163.2.225
20. Ghaemi SN, Bauer M, Cassidy F, Malhi GS, Mitchell P, Phelps J, et al. Diagnostic guidelines for bipolar disorder: a summary of the International Society for Bipolar Disorders Diagnostic Guidelines Task Force Report. *Bipolar Disord* (2008) 10:117–28. doi: 10.1111/j.1399-5618.2007.00556.x
21. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr Bull* (2014) 40:28–38. doi: 10.1093/schbul/sbt114
22. Dudek D, Rybakowski JK, Siwek M, Pawlowski T, Lojko D, Roczen R, et al. Risk factors of treatment resistance in major depression: association with bipolarity. *J Affect Disord* (2010) 126:268–71. doi: 10.1016/j.jad.2010.03.001
23. Swift M. The family history in clinical psychiatric practice. *Am J Psychiatry* (1987) 144:628–9. doi: 10.1176/ajp.144.5.628
24. Baker NJ, Berry SL, Adler LE. Family diagnoses missed on a clinical inpatient service. *Am J Psychiatry* (1987) 144:630–2. doi: 10.1176/ajp.144.5.630
25. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? *J Clin Psychiatry* (2008) 69:935–40. doi: 10.4088/JCP.v69n0608
26. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. *Arch Gen Psychiatry* (1977) 34:1229–35. doi: 10.1001/archpsyc.1977.01770220111013
27. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry* (2000) 57(7):675–82. doi: 10.1001/archpsyc.57.7.675
28. van der Markt A, Klumpers UM, Draisma S, Dols A, Nolen WA, Post RM, et al. Testing a clinical staging model for bipolar disorder using longitudinal life chart data. *Bipolar Disord* (2019) 21:228–34. doi: 10.1111/bdi.12727
29. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand* (2014) 129:4–16. doi: 10.1111/acps.12140
30. American Psychiatric Association. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition*. Arlington, VA: American Psychiatric Association (2013).
31. Vieta E, Valenti M. Mixed states in DSM-5: implications for clinical care, education, and research. *J Affect Disord* (2013) 148:28–36. doi: 10.1016/j.jad.2013.03.007
32. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* (2009) 166:173–81. doi: 10.1176/appi.ajp.2008.08050746
33. Stahl SM, Morrissette DA, Faedda G, Fava M, Goldberg JF, Keck PE, et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr.* (2017) 22:203–19. doi: 10.1017/S1092852917000165
34. Zimmerman M, Chelminski I, Young D, Dalrymple K, Martinez JH. A clinically useful self-report measure of the DSM-5 mixed features specifier of major depressive disorder. *J Affect Disord* (2014) 168:357–62. doi: 10.1016/j.jad.2014.07.021
35. Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *Am J Psychiatry* (2016) 173:400–7. doi: 10.1176/appi.ajp.2015.15060770
36. Patkar AA, Pae CU, Vohringer PA, Mauer S, Narasimhan M, Dalley S, et al. A 13-week, randomized double-blind, placebo-controlled, cross-over trial of

ziprasidone in bipolar spectrum disorder. *J Clin Psychopharmacol* (2015) 35:319–23. doi: 10.1097/JCP.0000000000000323
37. Swann AC, Lafer B, Perugi G, Frye MA, Bauer M, Bahk WM, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness, and diagnosis. *Am J Psychiatry* (2013) 170:31–42. doi: 10.1176/appi.ajp.2012.12030301
38. Berk M, Malhi GS, Cahill C, Carman AC, Hadzi-Pavlovic D, Hawkins MT, et al. The Bipolar Depression Rating Scale (BDRS): its development, validation and utility. *Bipolar Disord* (2007b) 9:571–9. doi: 10.1111/j.1399-5618.2007.00536.x
39. Zimmerman M. Measures of the DSM-5 mixed-features specifier of major depressive disorder. *CNS Spectr*. (2017) 22:196–202. doi: 10.1017/S1092852916000857
40. Sani G, Vohringer PA, Barroilhet SA, Koukopoulos AE, Ghaemi SN. The Koukopoulos Mixed Depression Rating Scale (KMDRS): An International Mood Network (IMN) validation study of a new mixed mood rating scale. *J Affect Disord* (2018) 232:9–16. doi: 10.1016/j.jad.2018.01.025
41. Altman EG, et al. The Altman Self-Rating Mania Scale. *Biol Psychiatry* (1997) 42:948–55. doi: 10.1016/S0006-3223(96)00548-3
42. Bauer MS, Vojta C, Kinosian B, Altshuler L, Glick H. The Internal State Scale: replication of its discriminating abilities in a multisite, public sector sample. *Bipolar Disord* (2000) 2:340–6. doi: 10.1034/j.1399-5618.2000.020409.x
43. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord* (2005a) 88:217–33. doi: 10.1016/j.jad.2005.05.011
44. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. *Bipolar Disord* (2002) 4:323–7. doi: 10.1034/j.1399-5618.2002.01195.x
45. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. *Acta Psychiatr Scand* (2004) Suppl:7–17. doi: 10.1111/j.1600-0447.2004.00409.x
46. Aiken CB, Weisler RH, Sachs GS. The Bipolarity Index: a clinician-rated measure of diagnostic confidence. *J Affect Disord* (2015) 177:59–64. doi: 10.1016/j.jad.2015.02.004
47. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* (2018) 20:97–170. doi: 10.1111/bdi.12609
48. Malhi GS, Outhred T, Hamilton A, Boyce PM, Bryant R, Fitzgerald PB, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Med J Aust* (2018) 208:175–80. doi: 10.5694/mja17.00659
49. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry* (2013) 14:334–85. doi: 10.3109/15622975.2013.804195
50. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* (2015) 29:459–525. doi: 10.1177/0269881115581093
51. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry* (2016) 61:540–60. doi: 10.1177/0706743716659417
52. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N. Z. J Psychiatry* (2015) 49:1087–206. doi: 10.1177/0004867415617657
53. Zuckerbrot RA, Cheung A, Jensen PS, Stein REK, Laraque D. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part I. Practice Preparation, Identification, Assessment, and Initial Management. *Pediatrics* (2018) 141. doi: 10.1542/peds.2017-4081
54. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson RS, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc. Psychiatry* (2007) 46:1503–26. doi: 10.1097/chi.0b013e318145ae1c
55. Baldessarini RJ, Faedda GL, Offidani E, Vazquez GH, Marangoni C, Serra G, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. *J Affect Disord* (2013) 148:129–35. doi: 10.1016/j.jad.2012.10.033
56. Angal S, DelBello M, Zalpuri I, Singh MK. Clinical Conundrum: How do you treat youth with depression and a family history of bipolar disorder? *Bipolar Disord* (2019) 21:383–6. doi: 10.1111/bdi.12788
57. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly. *Can J Psychiatry* (2016) 61:588–603. doi: 10.1177/0706743716659276
58. Luft MJ, Lamy M, Delbello MP, McNamara RK, Strawn JR. Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and Management. *Curr Probl Pediatr Adolesc. Health Care* (2018) 48:50–62. doi: 10.1016/j.cppeds.2017.12.001
59. Delbello MP. A Risk Calculator for Bipolar Disorder in Youth: Improving the Odds for Personalized Prevention and Early Intervention? *J Am Acad Child Adolesc. Psychiatry* (2018) 57:725–7. doi: 10.1016/j.jaac.2018.07.871
60. O'Donovan C, Garnham JS, Hajek T, Alda M. Antidepressant monotherapy in pre-bipolar depression; predictive value and inherent risk. *J Affect. Disord* (2008) 107:293–8. doi: 10.1016/j.jad.2007.08.003
61. Berk M, Dodd S. Are treatment emergent suicidality and decreased response to antidepressants in younger patients due to bipolar disorder being misdiagnosed as unipolar depression? *Med Hypotheses* (2005) 65:39–43. doi: 10.1016/j.mehy.2005.02.010
62. Rihmer Z, Dome P, Gonda X. Antidepressant response and subthreshold bipolarity in "unipolar" major depressive disorder: implications for practice and drug research. *J Clin Psychopharmacol* (2013) 33:449–52. doi: 10.1097/JCP.0b013e318299d2d5
63. Sani G, Napoletano F, Vohringer PA, Sullivan M, Simonetti A, Koukopoulos A, et al. Mixed depression: clinical features and predictors of its onset associated with antidepressant use. *Psychother Psychosom* (2014) 83:213–21. doi: 10.1159/000358808
64. Fava GA. Do antidepressant and antianxiety drugs increase chronicity in affective disorders? *Psychother. Psychosom.* (1994) 61:125–31. doi: 10.1159/000288880
65. Ghaemi SN, Vohringer PA. Athanasios Koukopoulos' Psychiatry: The Primacy of Mania and the Limits of Antidepressants. *Curr Neuropharmacol.* (2017) 15:402–8. doi: 10.2174/1570159X14666160621113432
66. Perugi G, Pacchiarotti I, Mainardi C, Verdolini N, Menculini G, Barbuti M, et al. Patterns of response to antidepressants in major depressive disorder: Drug resistance or worsening of depression are associated with a bipolar diathesis. *Eur Neuropsychopharmacol* (2019) 29:825–34. doi: 10.1016/j.euroneuro.2019.06.001
67. Ruzickova M, Alda M. Antidepressants in bipolar depression: when less is more. *J Psychiatry Neurosci* (2002) 27:312.
68. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* (2007) 164:1348–55. doi: 10.1176/appi.ajp.2007.05122032
69. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry* (2003) 64:123–33. doi: 10.4088/JCP.v64n0204
70. El-Mallakh RS, Ghaemi SN, Sagduyu K, Thase ME, Wisniewski SR, Nierenberg AA, et al. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. *J Affect Disord* (2008) 111:372–7. doi: 10.1016/j.jad.2008.03.025
71. El-Mallakh RS, Vohringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *J Affect Disord* (2015) 184:318–21. doi: 10.1016/j.jad.2015.04.054
72. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin JM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term

treatment of mixed states in bipolar disorder. *World J Biol Psychiatry* (2018) 19:2–58. doi: 10.1080/15622975.2017.1384850
73. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* (2013) 170:1249–62. doi: 10.1176/appi.ajp.2013.13020185
74. Faedda GL, Marangoni C. What is the role of conventional antidepressants in the treatment of major depressive episodes with Mixed Features Specifier? *CNS Spectr.* (2017) 22:120–5. doi: 10.1017/S1092852916000493
75. Shim IH, Bahk WM, Woo YS, Yoon BH. Pharmacological Treatment of Major Depressive Episodes with Mixed Features: A Systematic Review. *Clin Psychopharmacol Neurosci* (2018) 16:376–82. doi: 10.9758/cpn.2018.16.4.376
76. Suppes T, Ostacher M. Mixed features in major depressive disorder: diagnoses and treatments. *CNS Spectr.* (2017) 22:155–60. doi: 10.1017/S1092852917000256
77. Verdolini N, Hidalgo-Mazzei D, Murru A, Pacchiarotti I, Samalin L, Young AH, et al. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines. *Acta Psychiatr Scand* (2018) 138:196–222. doi: 10.1111/acps.12896
78. Rachid F, Moeglin C, Sentissi O. Repetitive Transcranial Magnetic Stimulation (5 and 10 Hz) With Modified Parameters in the Treatment of Resistant Unipolar and Bipolar Depression in a Private Practice Setting. *J Psychiatr Pract* (2017) 23:92–100. doi: 10.1097/PRA.0000000000000213
79. Sani G, Fiorillo A. The use of lithium in mixed states. *CNS Spectr* (in press). doi: 10.1017/S1092852919001184
80. Nunes A, Ardau R, Berghofer A, Bocchetta A, Chillotti C, Deiana V, et al. Prediction of lithium response using clinical data. *Acta Psychiatr Scand* (2020) 141:131–41. doi: 10.1111/acps.13122
81. Liebers DT, Pirooznia M, Ganna A, Goes FS. Discriminating bipolar depression from major depressive disorder with polygenic risk scores. *Psychol Med*. (in press) doi: 10.1017/S003329172000015X
82. Coleman JRI, Gaspar HA, Bryois J, Breen G. The Genetics of the Mood Disorder Spectrum: Genome-wide Association Analyses of More Than 185,000 Cases and 439,000 Controls. *Biol Psychiatry*. (in press) doi: 10.1016/j.biopsych.2019.10.015

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 12 June 2020
doi: 10.3389/fpsyt.2020.00510

The Impact of Subsyndromal Bipolar Symptoms on Patient's Functionality and Quality of Life

Heinz Grunze * *and Christoph Born*

Psychiatrie Schwäbisch Hall and PMU Nuremberg, Nuremberg, Germany

Subsyndromal symptoms have rarely been in the focus of bipolar research. This may be, in part, due to the fact that there is neither a uniform definition nor do they constitute an indication of regulatory and commercial interest. Nevertheless, they do have a decisive impact on the long-term course of bipolar disorder (BD), and the degree of functionality and quality of life (QoL) is more likely determined by their presence or absence than by acute episodes. Summarizing the literature an estimated 20–50% of patients suffer inter-episodically or chronically from subsyndromal BD. The most prominent symptoms that interfere with functionality are subsyndromal depression, disturbances of sleep, and perceived cognitive impairment, whereas anxiety negatively impacts on QoL. In the absence of evidence-based pharmacological treatments for subsyndromal BD, clinical practice adopts guidelines designed for treatment-resistant full-blown episodes of BD, supplemented by cognitive-behavioral, family focused or social-rhythm–based psychotherapies.

Keywords: bipolar disorder, subsyndromal, depression, mania, functionality, quality of life

OPEN ACCESS

Edited by:
Dina Popovic,
Sheba Medical Center, Israel

Reviewed by:
Katherine Gordon-Smith,
University of Worcester,
United Kingdom
Steven Marwaha,
University of Birmingham,
United Kingdom

****Correspondence:***
Heinz Grunze
h.grunze@klinikum-weissenhof.de

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *20 December 2019*
Accepted: *18 May 2020*
Published: *12 June 2020*

Citation:
Grunze H and Born C (2020) The Impact of Subsyndromal Bipolar Symptoms on Patient's Functionality and Quality of Life. Front. Psychiatry 11:510. doi: 10.3389/fpsyt.2020.00510

INTRODUCTION

Reality has taught us that Kraepelin's assumption of full recovery as a decisive distinction between manic-depressive illness and dementia praecox does not hold true in a fair proportion of bipolar patients. Five years after onset of bipolar disorder (BD), at least 13% of patients suffer from a chronic course without remission (1). Persisting subsyndromal symptoms of BD (SSBD) impact on patients functionality and quality of life (QoL), and put them on elevated risk of relapse (2) and an overall more detrimental course of illness with longer duration of illness episodes and more lifetime psychotic symptoms (3). Adapting the dimensional view of BD as proposed by van Os and Kapur (4) subsyndromal symptoms are not necessarily restricted to mood, but may also persist in the domains of cognition and, if present during an acute episode, positive, and negative symptoms. However, little is known about the effects of persisting psychotic symptoms in bipolar patients, the bulk of data points toward subthreshold depression, impaired cognition and disturbed circadian rhythm as the most relevant SSBD (**Figure 1**) (5–8). Both subsyndromal depression and impaired cognition appear to act directly and independently on functionality (5, 8), whereas there is only a moderate indirect effect of sleep disturbances on functioning mediated *via* residual depressive symptoms and perceived cognitive impairments (5). Whereas subsyndromal depressive symptoms

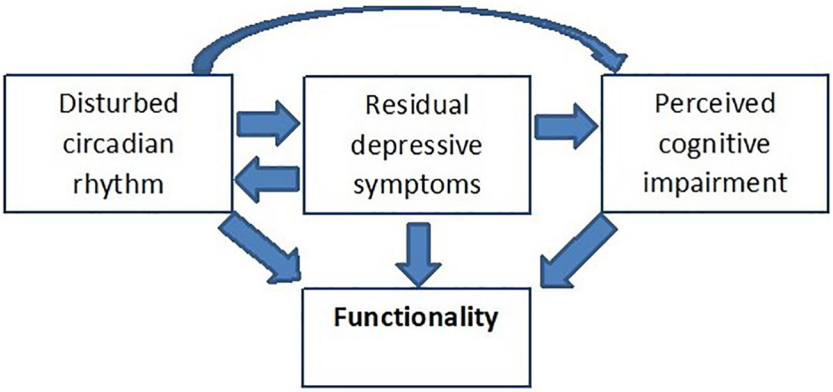


FIGURE 1 | The trias of SSBD, their interaction and impact on functionality. A hypothetical model adapted from (5). Applying a structural equation model (SEM), Samalin et al. (5) demonstrated a significant direct effect of both residual depressive symptoms and perceived cognitive impairment on functionality. In addition, residual depressive symptoms also have a direct effect on perceived cognitive impairment but no significant indirect effect on functioning *via* perceived cognitive impairment. The direct pathway between sleep disturbances and functioning was not significant, however, the SEM confirmed the presence of a moderate indirect effect of sleep disturbances on functioning *via* residual depressive symptoms and perceived cognitive impairments.

might be a crucial driver of psychosocial disability in all age groups, subsyndromal mania may be more abundant in old age bipolar patients than in younger patients (9).

SSBD is a topic that has been neglected for a long time in bipolar research. This may be, in part, due to the fact that there is neither a uniform definition and understanding what constitutes SSBD, nor does SSBD constitute an indication eligible for a marketing claim. However, with recent research on the nature, impact and mostly psychological interventions it appears timely to summarize our—still limited—knowledge.

This review focuses on three topics: Definition and frequency of SSBD, Impact of SSBD on functionality and QoL, and pharmacological and psychological therapies applied in SSBD. The review is not meant to be a complete and systematic review of the topic, it summarizes selected findings on SSBD and its treatment to support clinicians in identifying SSBD and guiding treatment selection. The review is based on a PubMed search covering published articles between 1970 and 2019 with the search terms "Bipolar disorder", "mania", "bipolar depression", combined with either "subsyndromal", "minor", and "chronic". Papers selected for this review are the authors' subjective choice based on perceived novelty and general interest of the findings reported. In addition, reviewers of this article added valuable suggestions on further reports that deserve inclusion. Subsyndromal symptoms in BD may occur as integral part of some bipolar spectrum disorders, e.g., cyclothymia, where mood swings do not satisfy full syndromal criteria, as precursors of a full-blown episode or as residual symptoms after either a manic or depressive episode, sometimes with chronicity (**Figure 2**). Subsyndromal symptoms are observable in a majority of patients during the prodrome of a new manic or depressive episode, with manic episodes having a longer prodrome than depression (10–12). In adolescents, prodromal syndromes may precede a first episodes for years, and their duration and extent might predict

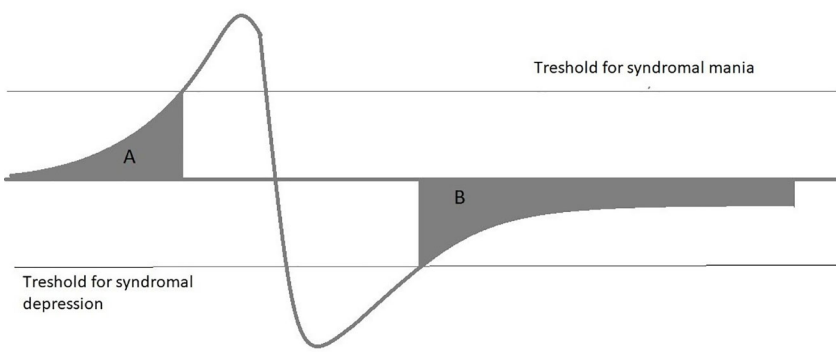


FIGURE 2 | Subsyndromal symptoms in BD may occur as integral part of some bipolar spectrum disorders, e.g., cyclothymia, where mood swings do not fulfil full syndromal criteria, as precursors of a full-blown episode **(A)** or as residual symptoms after either a manic or depressive episode, sometimes with chronicity **(B)**.

later service usage (13). Besides mood and subthreshold psychotic symptoms, anxiety disorders have been identified as a frequent prodromal bipolar symptom (14). The focus of this article, however, is on subsyndromal symptoms in the aftermath of an episode as they do have a pronounced effect on functionality and long-term outcome.

DEFINITION OF SUBSYNDROMAL SYMPTOMS IN BIPOLAR DISORDER

In a past review, Bauer and colleagues identified 77 articles on subsyndromal BD published between 1987 and 2007, and virtually no common definition of subsyndromal mood symptoms was used (15). Until today, there is no uniform, generally accepted and operationalized definition of SSBD. Definitions can be based on being short of syndromal criteria for a major mood episode as defined by Diagnostic and Statistical Manual, 4th edition (DSM IV), e.g., exhibiting at least two, but less than five criteria for a major depressive episode (MDE) ("minor depression") (16). For subsyndromal BD II depression, Benazzi (17) proposed quite restrictive criteria taking also functionality into account: (a) residual depressive symptoms between the last two consecutive MDEs (the DSM-IV longitudinal course specifier "without full interepisode recovery"), (b) residual depressive symptoms lasting more than 2 years, (c) 2–4 MDE symptoms (recorded as present or absent with the Structured Clinical Interview for DSM IV Disorders – Clinician Version (SCID-CV), (d) mild to moderate impairment of functioning [Global Assessment of Functioning (GAF) score 60–70]. The definition by Benazzi et al., however, targets merely subsyndromal depression, but not mania or other domains such as cognition. More frequently, symptomatic rating scales such as the Young Mania Rating scale (YMRS), Mania rating Scale (MRS), Hamilton Depression Rating Scale (HDRS), or Montgomery-Asberg Depression Rating scale (MADRS) (18–20) are used to define both manic and depressive subsyndromal states. The International Society of Bipolar Disorder (ISBD) consensus criteria defines bipolar patients with a YMRS Score 8–14 as subsyndromal manic, and with a HRDS score 8–14 as subsyndromal depressed (21), but other authors allow for a wider range (YMRS 11–20, HRDS 7–17 (20). Finally, some publications equate subsyndromal states with "mild mania (YMRS 5–10)" or "mild depression (HAM-D 7–15) (22).

FREQUENCY OF SUBSYNDROMAL SYMPTOMS IN BIPOLAR DISORDER

A Spanish cohort study over 5 years using ISBD criteria found SSBD in more than 20% of BD patients (23). Applying in another analysis of this study, the wider criteria of De Dios et al. (20) instead of the ISBD criteria increases the percentage of bipolar spectrum patients with subsyndromal symptoms by one-third (36% vs. 22.6%) with a clear preponderance of subsyndromal depression, independent from criteria used (19). Similar figures have been reported from other observational studies (2).

Emerging subsyndromal symptoms are even more frequent in the built-up of an acute episode. Seventy-six percent of BD patients reported subsyndromal, prodromal hypomanic symptoms, and 39% subsyndromal, prodromal depressive symptoms preceding an acute episode (24). Even higher numbers have been reported by Keitner et al. (25) in a BD I cohort study: 78% of the patients reported prodromal depressive symptoms and 87% reported prodromal manic symptoms, and more than half of the patients still exhibits residual symptoms after an acute episode (54% following an MDE and 68% after a manic episode).

However, we have to keep in mind that the definition of subsyndromal states and time criteria vary between studies. Especially, the issue of duration, i.e., how long should symptoms last to satisfy SSBD diagnosis, is critical. SSBD can be rather short if a prodromal state, and lasting in the aftermath of an acute episode. SSBD can be a cross-sectional as well as a longitudinal description of a mood state; cross-sectional if based on rating scale scores at time of examination, e.g., the ISBD criteria (21), short longitudinal if longer than 1 week (22), or lasting longer than 2 years as proposed by Benazzi et al. (17).

Residual depressive symptoms are also abundant in BD II patients, 44.9% of patients have residual symptoms after and MDE despite using restrictive criteria (17). Comparing subsyndromal depressive symptoms in remitted unipolar and bipolar patients, it appears that unipolar patients may have more residual symptoms than bipolar patients, particularly in items related to anxiety and somatic complaints (26).

But even patients who are in remission according to the Clinical Global Impression scale (CGI) are not necessarily free of symptoms and impairment, and are trapped in the gap between remission and recovery. In selected clinical samples receiving optimized treatment, such as the Stanley Foundation Bipolar Network (SFBN) (10) cohort, enduring subsyndromal symptoms, especially of depression, anxiety or physical discomfort, are observable in at least 10% of bipolar patients despite fulfilling formalized criteria of remission (11).

IMPACT ON FUNCTIONALITY

SSBD is not only a predictor of early relapse (27) but also of frequent comorbidities (22), poor functional outcome and low QoL (26, 28–30). Even after a single manic episode, only one out of three patients regains psychosocial functioning at 1-year follow-up (31), suggesting that functional outcomes in BD are impaired from the very beginning. Unfortunately, there is no uniform consensus how to measure psychosocial functioning in BD. The Task Force of the ISBD examined different definitions of psychosocial functioning but without reaching a consensus (21). The task force referred to the definition provided by the International Classification of Functioning, Disability and Health (ICF) (32) in which functioning comprises three

different components: body structures and functions; activities and participation; and personal environmental factors. Moreover, the authors of these guidelines underlined that this construct is probably too complex to be applied to BD, and that besides the ICF, the Functioning Assessment Short Test (FAST) scale (33) might constitute a more practical approach to measure functioning. Another widely used instruments to estimate global functioning is the GAF (34). However, the DSM-5 no longer encourages the use of the GAF. Instead, the use of the self-rated World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) has been recommended (35), but to date little experience exists about its usefulness and applicability in BD.

A SFBN study prospectively evaluated the association between the presence of subsyndromal depressive symptoms in 759 patients with BD and role functioning (28). Subsyndromal depression was operationalized using cut-off scores on the Inventory of Depressive Symptoms-Clinician Rated (IDS-C) and the CGI for Bipolar Disorder (CGI-BP). Patients were divided into three groups: no depression (n = 292, IDS-C score of <13 for the prior 2 weeks), subsyndromal depression (n = 291, IDS-C scores 13 to 27 for the prior 2 weeks), and syndromal depression (n = 179, IDS-C scores > 28 for the prior 2 weeks). To ensure that all subjects were not currently experiencing depressive symptoms as part of a mixed mania, a score of 1 (not ill) on the CGI-BP severity of mania item was also mandatory. Patient functioning in four role domains (work, home duties, family life, and friendships) was assessed using the Life Functioning Questionnaire (LFQ), a 5-min, 14-item, gender-neutral self-report questionnaire designed to assess role function over the preceding month (36). The subsyndromal depressed group was significantly more likely than the no depression group to report impairment at work (64% vs. 31%), with duties at home (75% vs. 38%), in their relationships with family (59% vs. 34%) and friends (56% vs. 18%), and in life functioning overall (70% vs. 32%), and across all domains of role function, the proportion of patients who were impaired were more similar in the subsyndromal and syndromal depression groups than to the no depression group. But not only persistent low mood determines functionality, but also unstable affect, both negative and positive. A study in 27 subjects with BD I examining the prospective influence of inter-episode affect dysregulation on symptoms and functional impairment, and found that mood instability in general during the inter-episode period was associated with greater impairment in home and work functioning (37).

The OPTHYMUM study (29) in 525 BD patients across France chose the converse approach. This cross-sectional study looked into the associations and consequences of low functioning, defined as a GAF score <60. These "low functioning patients" had significantly more frequent emotional subsyndromal symptoms (emotional lability and numbing), disruption of circadian rhythms, sexual disorders, and perceived more cognitive deficits. In addition, they suffered more social and family stigma, were more frequently unemployed and had increased numbers of manic episodes and psychotic symptoms.

The tight association between subsyndromal symptoms and low GAF scores has also been confirmed by McQueen et al. (22) using prospectively collected life charting data from 138 patients with BD. Looking into co-morbidities, SSBD patients were on an even higher risk of eating and anxiety disorders than syndromal patients. A *post hoc* analysis of prospectively collected data by Bennett et al. demonstrated in the SFBN cohort a significant interaction between attention-deficit and anxiety comorbidity and low GAF scores (38). In line with this, a prospective Dutch cohort study demonstrated that subsyndromal anxiety also been impacts on functionality in unipolar depression (39).

In youth with BD-I, a relatively long, predominantly slow-onset mania prodrome appears to be common, including subthreshold manic and depressive psychopathology symptoms (40). Little, however, has been reported about functional prodromal symptoms before a first manic/mixed episode and the diagnosis of a BD. A literature search by Faedda et al. prospectively identified subsyndromal symptoms both of mania and depression as precursors of BD that typically arose years prior to syndromal onset (14). Based on a survey conducted in members of the NDMDA, Hirschfeld and colleagues noted that in majority of patients many domains of social functioning had been already dysfunctional prior to a first BD episode (41), most likely due to subsyndromal symptoms.

In a cross-sectional study of Keitner et al. (25) more than half of the patients disclosed residual symptoms of depression (54%) and mania (68%). However, cognitive symptoms were consistently the most common symptoms reported by patients across studies, and constitute one of the three determinants of functional outcome in the model by Samalin et al. (5). Even when euthymic, compared with people without mood disorders, people with BD have cognitive impairment (42). This may, at least in part, explain why previously able people decline in their functioning (43). In recent years, more sophisticated research has been conducted to objectify the subjective reports of cognitive decline. In the domains of cognition—executive function, attention, processing speed, verbal memory and visual memory—learning memory and executive function may be more impaired than others (44–48). Looking cross-sectionally at psychosocial and occupational function, impaired cognition has a significant effect on both outcomes, whereas residual depressive symptoms seem to impact mainly on psychosocial capabilities (49).

IMPACT ON QUALITY OF LIFE

QoL is a broad construct taken to represent aspects of functioning and satisfaction in occupational, environmental, social, physical, and psychological aspects of life (50).QoL has not only become an increasingly important outcome parameter in clinical trials, but also a target for web-based psychoeducational self-monitoring programs (51, 52). Different scales exist to make the rather holistic and fuzzy defined term "Quality of life" measurable (53). Especially for BD, Michalak and colleagues developed the QoL in Bipolar Disorder (QoL.BD)

scale. It comprises 56 items rated from 1 to 5, evaluating the domains physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, and education. A global score is obtained with higher scores indicating a better QoL, and score below 170 indicates poor QoL (54). A meta-analysis of 66 studies demonstrated significant differences in QoL outcomes between euthymic BD patients and healthy controls with lower QoL in the euthymic patients (55). In a cross-sectional study in 60 clinically stable Bipolar I outpatients with only mild residual symptoms, QoL correlated significantly with resilience, internalized stigma, and, again, residual symptoms of depression. No significant correlations were observed between QoL and residual manic symptoms (56).

The detrimental impact of comorbid anxiety disorders fulfilling full diagnostic criteria on BD has been well established (57). The interaction between anxiety and mood symptoms on a subsyndromal level is still poorly understood and further research is demanded. The few data available suggest that also subsyndromal anxiety has a marked impact on QoL in euthymic bipolar patients. In a cross-sectional Mexican study using the QoL.BD scale and a score of 170 as cut-off for poor QoL, anxious symptoms affected the perceived QoL more than subthreshold symptoms of mania and depression and more than other variables related to the course of BD, such as number of hospitalizations, and even a comorbid diagnosis of full-criteria generalized anxiety disorder (GAD). Of note, subthreshold manic (not depressive) symptoms were in this study the second parameter related to poor QoL (58). **Table 1** summarizes the proven or assumed impact of different subsyndromal symptoms on functionality and QoL. As a limitation, the reader should note that the table reflects the authors' personal views based on the results of their literature search. A full systematic review, and possibly a meta-analytic processing of the results, would be needed and desirable to validate these findings.

But also, somatic malaise has a clear impact on QoL. A large Spanish cohort study using also a cross-sectional design demonstrated that gastrointestinal and somatic symptoms, as well as genital symptoms occur more frequently in SSBD than in the general population (26).

TABLE 1 | Summary of the proposed impact of the different domains of SSBD following an acute episode on functionality and QoL.

Domain of SSBD	Impact on functionality	Impact on QoL
Depression	+++	++
Mania	++	++
Cognition	+++	(+)
Disturbed circadian rhythm	++	+
Psychosis	(+)	?
Comorbid anxiety	++	+++

Note that the table reflects the author's personal view based on the literature cited in this review.

+++, marked impact; ++, moderate impact; +, mild impact; (+), possible impact; ?, unknown.

TREATMENT

Whereas only few treatment studies have targeted SSBD so far, there is some consensus to use similar guidance as for treatment-resistant full blown episodes to eradicate subsyndromal symptoms (59, 60). This includes checking whether the diagnosis is correct, excluding (or treating) psychiatric co-morbidities such as addiction, anxiety and personality disorders, optimization of the medication dose including therapeutic drug monitoring, augmentation and combination strategies, experimental treatments such as ketamine infusion, considering physical treatments such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, or sleep phase advance protocols, reviewing the effectiveness of ongoing psychotherapy, minimizing or eliminating social and occupational distress, and a careful check-up of physical health as organic factors might contribute to persistent symptoms. Some subsyndromal symptoms like anxiety might be targeted with specific drugs normally not used for bipolar core symptoms (61, 62); however, there is some controversy about this approach. The symptom-oriented treatment approach to treat anxiety symptoms with anxiolytics or anti-anxiety drugs has been questioned by the results of a study of Bauer et al. (63). Using naturalistic data, Bauer and co-workers investigated retrospectively the relationship between the use of adjunctive anxiolytics and the time spent in episodes or with SSBD in a *post hoc* analysis of 310 patients with BD. Patients with BD who were taking adjunctive anxiolytics spent significantly more time ill. The authors concluded that, while the study design cannot determine causality, there is an obvious need for controlled studies of a possibly detrimental impact of adjunctive medications for anxiety on the course of BD.

For the prevention and control of subsyndromal symptoms and, by this, preventing relapse lithium levels in the high therapeutic range (0.8–1.0 mmol/l) had been more effective than low-range lithium levels (0.4–0.6 mmol/l). Patients with low-range levels had 2.6 times the risk of major affective relapse as those given lithium for high-range levels, and nearly twice the risk of developing subsyndromal symptoms (24).

The prominent role of lithium in controlling prodromal symptoms of emerging mania or depression has also been confirmed by a *post hoc* analysis of two controlled maintenance studies comparing lithium, lamotrigine, and placebo (64). Compared to placebo, both lithium and lamotrigine treatment significantly delayed emerging subsyndromal symptoms of either polarity and prolongated time from first subsyndromal symptoms to intervention for a full-blown episode. Further analysis showed that this was by large due to suppressing subsyndromal manic or mixed symptoms. On the other hand, lamotrigine appeared to be effective in delaying time from first subsyndromal depressive symptoms to a mood episode (18). The risk of emerging subsyndromal depression or of a MDE in lithium-treated patients might be related to changes in thyroid function. Those lithium-treated BD I patients who needed intervention for depression in these studies had a significantly higher adjusted mean TSH level than those who did not (65).

In the aftermath of an acute episode, switching from different atypical antipsychotics to aripiprazole has been reported to improve subsyndromal symptoms in an observational 24-week study (66). In part, this may also be explained by aripiprazole's lack of anticholinergic effects and its potential antidepressant effects, thus reducing possible medication-induced cognitive and affective impairment.

Specially to overcome functional impairment, cognitive-behavioral, family focused, or social-rhythm–based psychotherapies have been shown to be effective alongside optimized pharmacological treatment (67–69). In a small study with children and adolescents, both omega-3 fatty acid supplementation (Omega3) and individual family psychoeducational psychotherapy (IF-PEP) showed medium-size effects on subsyndromal depression (70). Accumulating evidence suggest that functional remediation may have good potential to boost the recovery process in bipolar patients with subsyndromal symptoms and might be not only more effective than treatment as usual, but also than psychoeducation (71, 72). Case reports suggested that also Eye Movement Desensitization and Reprocessing (EMDR) may positively affect residual bipolar symptoms (73, 74). More recently, a small, 12-week pilot study in patients with SSBD and post-traumatic stress disorder demonstrated that EMDR has significant effects on subsyndromal manic symptoms, and to a lesser degree on subsyndromal depression (75).

DISCUSSION

As a fair estimate, SSBD affects between 20 and 50% of bipolar patients, depending on the definition applied. Especially subsyndromal depression interferes with role functioning in essential domains of normal life, such as work, duties at home and maintaining relationships. Besides residual depression, enduring cognitive impairment in a variety of domains determines psychosocial and occupational outcome. Subsyndromal depression and cognitive decline in SSBD have also been identified as two out of three main driver of low function in a structural equation model as described by Samalin and coworkers, the third one being sleep deprivation (5). Except of one study (58), subsyndromal mania, however, appears not as a main driver of low QoL and functioning, but has been much less investigated than subsyndromal depression. As far as QoL is concerned, anxiety, ranging from just symptoms to full blown comorbid disorder, and physical malaise appear to be inversely related to QoL in BD, including SSBD. However, the potential pathways that might mediate the observed relationships between SSBD and functionality and QoL are still speculative and need further investigation. But in summary, the marked impact of SSBD both on psycho-social functioning and QoL is obvious and well documented in a fair number of studies.

This is in contrast to the relative paucity of treatment studies, which is even more true for pharmacological than for psychological approaches. This may, in part, be due to the absence of an official indication approved by regulatory authorities and, as a consequence, uncertainty about eligibility for reimbursement in some health insurance systems as patients may be categorized as "euthymic". In addition, there is an absence of a generally accepted definition of SSBD and uniform cut-off criteria, that makes it difficult to compare between the few studies available and derive recommendations. If a patient is on lithium, optimizing lithium levels appear to ameliorate subsyndromal mood and cognitive symptoms. Switching to medication that do not add to potential cognitive impairment by anticholinergic side effects might also be a strategy to consider. Recent research, however, clearly pointed out that a tailored psychotherapy might be effective in overcoming SSBD. Especially functional and cognitive remediation seems to be effective, and emerging new techniques as EMDR might add in the future to the treatment portfolio. However, although there is some evidence emerging more recently, more research focus and effort is still needed. Most studies included and mixed both subsyndromal depression and subsyndromal hypomanic patients, without further differentiation of outcomes. More studies looking into the different dimension of SSBD (mania, depression, cognition, psychosis) separately are clearly demanded. Finally, most important, a verified and generally accepted definition of SSBD and its constituents needs to be developed to allow for randomized studies with comparable inclusion/exclusion criteria.

AUTHOR CONTRIBUTIONS

The authors designed the work, conducted the necessary literature search, drafted the manuscript, provide approval for publication, and agree to be accountable for all aspects of the work.

REFERENCES

1. van der Markt A, Klumpers UM, Draisma S, Dols A, Nolen WA, Post RM, et al. Testing a clinical staging model for bipolar disorder using longitudinal life chart data. *BipolarDisord* (2019) 21(3):228–34. doi: 10.1111/bdi.12727
2. Marangell LB. The importance of subsyndromal symptoms in bipolar disorder. *J Clin Psychiatry* (2004) 65 Suppl 10:24–7.
3. Serafini G, Vazquez GH, Gonda X, Pompili M, Rihmer Z, Amore M. Depressive residual symptoms are associated with illness course characteristics in a sample of outpatients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* (2018) 268(8):757–68. doi: 10.1007/s00406-018-0875-5
4. van Os J, Kapur S. Schizophrenia. *Lancet* (2009) 374(9690):635–45. doi: 10.1016/S0140-6736(09)60995-8
5. Samalin L, Boyer L, Murru A, Pacchiarotti I, Reinares M, Bonnin CM, et al. Residual depressive symptoms, sleep disturbance and perceived cognitive impairment as determinants of functioning in patients with bipolar disorder. *J Affect Disord* (2017) 210:280–6. doi: 10.1016/j.jad.2016.12.054
6. Soreca I, Frank E, Kupfer DJ. The phenomenology of bipolar disorder: what drives the high rate of medical burden and determines long-term prognosis? *Depress Anxiety* (2009) 26(1):73–82. doi: 10.1002/da.20521
7. Murru A, Pacchiarotti I, Verdolini N, Reinares M, Torrent C, Geoffroy PA, et al. Modifiable and non-modifiable factors associated with functional impairment

during the inter-episodic periods of bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* (2018) 268(8):749–55. doi: 10.1007/s00406-017-0811-0
8. Roux P, Raust A, Cannavo AS, Aubin V, Aouizerate B, Azorin JM, et al. Associations between residual depressive symptoms, cognition, and functioning in patients with euthymic bipolar disorder: results from the FACE-BD cohort. *Br J Psychiatry* (2017) 211(6):381–7. doi: 10.1192/bjp.bp.117.201335
9. Strejilevich S, Szmulewicz A, Igoa A, Marengo E, Caravotta P, Martino D. Episodic density, subsyndromic symptoms, and mood instability in late-life bipolar disorders: A 5-year follow-up study. *Int J Geriatr Psychiatry* (2019) 34 (7):950–6. doi: 10.1002/gps.5094
10. Sierra P, Livianos L, Arques S, Castello J, Rojo L. Prodromal symptoms to relapse in bipolar disorder. *Aust N Z J Psychiatry* (2007) 41(5):385–91. doi: 10.1080/00048670701266854
11. Jackson A, Cavanagh J, Scott J, Sierra P, Livianos L, Arques S, et al. A systematic review of manic and depressive prodromes Prodromal symptoms to relapse in bipolar disorder. *J Affect Disord* (2003) 74(3):209–17. doi: 10.1016/s0165-0327(02)00266-5
12. Wong G, Lam D, Jackson A, Cavanagh J, Scott J, Sierra P, et al. The development and validation of the coping inventory for prodromes of mania A systematic review of manic and depressive prodromes Prodromal symptoms to relapse in bipolar disorder Life events and the onset of mania. *J Affect Disord* (1999) 53(1):57–65. doi: 10.1016/s0165-0327(98)00096-2
13. Parker G. Predicting onset of bipolar disorder from subsyndromal symptoms: a signal question? *Br J Psychiatry* (2010) 196(2):87–8. doi: 10.1192/bjp.bp.109.074898
14. Faedda GL, Marangoni C, Serra G, Salvatore P, Sani G, Vazquez GH, et al. Precursors of bipolar disorders: a systematic literature review of prospective studies. *J ClinPsychiatry* (2015) 76(5):614–24. doi: 10.4088/JCP.13r08900
15. Bauer M, Glenn T, Grof P, Schmid R, Pfennig A, Whybrow PC. Subsyndromal mood symptoms: a useful concept for maintenance studies of bipolar disorder? *Psychopathology* (2010) 43(1):1–7. doi: 10.1159/000255957
16. Marangell LB, Dennehy EB, Miyahara S, Wisniewski SR, Bauer MS, Rapaport MH, et al. The functional impact of subsyndromal depressive symptoms in bipolar disorder: data from STEP-BD. *JAffectDisord* (2009) 114(1-3):58–67. doi: 10.1016/j.jad.2008.07.006
17. Benazzi F. Prevalence and clinical correlates of residual depressive symptoms in bipolar II disorder. *PsychotherPsychosom* (2001) 70(5):232–8. doi: 10.1159/000056260
18. Frye MA, Yatham LN, Calabrese JR, Bowden CL, Ketter TA, Suppes T, et al. Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *J ClinPsychiatry* (2006) 67(11):1721–8. doi: 10.4088/JCP.v67n1108
19. De Dios C, Agud JL, Ezquiaga E, Garcia-Lopez A, Soler B, Vieta E. Syndromal and subsyndromal illness status and five-year morbidity using criteria of the International Society for Bipolar Disorders compared to alternative criteria. *Psychopathology* (2012) 45(2):102–8. doi: 10.1159/000329740
20. De Dios C, Ezquiaga E, Garcia A, Soler B, Vieta E. Time spent with symptoms in a cohort of bipolar disorder outpatients in Spain: a prospective, 18-month follow-up study. *JAffectDisord* (2010) 125(1-3):74–81. doi: 10.1016/j.jad.2009.12.006
21. Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord* (2009) 11(5):453–73. doi: 10.1111/j.1399-5618.2009.00726.x
22. MacQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. *BipolarDisord* (2003) 5(5):349–55. doi: 10.1034/j.1399-5618.2003.00048.x
23. De Dios C, Ezquiaga E, Agud JL, Vieta E, Soler B, Garcia-Lopez A. Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. *JAffectDisord* (2012) 143(1-3):160–5. doi: 10.1016/j.jad.2012.05.047
24. Keller MB, Lavori PW, Kane JM, Gelenberg AJ, Rosenbaum JF, Walzer EA, et al. Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. *ArchGenPsychiatry* (1992) 49(5):371–6. doi: 10.1001/archpsyc.1992.01820050035005
25. Keitner GI, Solomon DA, Ryan CE, Miller IW, Mallinger A, Kupfer DJ, et al. Prodromal and residual symptoms in bipolar I disorder. *Compr Psychiatry* (1996) 37(5):362–7. doi: 10.1016/s0010-440x(96)90018-8
26. Vieta E, Sanchez-Moreno J, Lahuerta J, Zaragoza S. Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. *JAffectDisord* (2008) 107(1-3):169–74. doi: 10.1016/j.jad.2007.08.007
27. Radua J, Grunze H, Amann BL. Meta-Analysis of the Risk of Subsequent Mood Episodes in Bipolar Disorder. *PsychotherPsychosom* (2017) 86(2):90–8. doi: 10.1159/000449417
28. Altshuler LL, Post RM, Black DO, Keck PEJr., Nolen WA, Frye MA, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. *J Clin Psychiatry* (2006) 67(10):1551–60. doi: 10.4088/JCP.v67n1009
29. Samalin L, Llorca PM, Giordana B, Milhiet V, Yon L, El-Hage W, et al. Residual symptoms and functional performance in a large sample of euthymic bipolar patients in France (the OPTHYMUM study). *J AffectDisord* (2014) 159:94–102. doi: 10.1016/j.jad.2014.02.023
30. Bauer M, Glenn T, Grof P, Rasgon NL, Marsh W, Sagduyu K, et al. Frequency of subsyndromal symptoms and employment status in patients with bipolar disorder. *SOCPSYCHIATRY PSYCHIATREPIDEMIOL* (2009) 44(7):515–22. doi: 10.1007/s00127-008-0464-4
31. Tohen M, Hennen J, Zarate CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *AmJ Psychiatry* (2000) 157 (2):220–8. doi: 10.1176/appi.ajp.157.2.220
32. Organization WH. *International classification of functioning, disability and health : ICF*. Geneva: World Health Organization (2001).
33. Rosa AR, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *ClinPractEpidemiolMentHealth* (2007) 3:5. doi: 10.1186/1745-0179-3-5
34. American Psychiatric A. *Diagnostic and statistical manual of mental disorders*. Washington DC: APA Press (1987).
35. Ustun TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ* (2010) 88(11):815–23. doi: 10.2471/BLT.09.067231
36. Altshuler L, Mintz J, Leight K. The Life Functioning Questionnaire (LFQ): a brief, gender-neutral scale assessing functional outcome. *Psychiatry Res* (2002) 112(2):161–82. doi: 10.1016/s0165-1781(02)00180-4
37. Gershon A, Eidelman P. Inter-episode affective intensity and instability: predictors of depression and functional impairment in bipolar disorder. *J Behav Ther Exp Psychiatry* (2015) 46:14–8. doi: 10.1016/j.jbtep.2014.07.005
38. Bennett F, Hodgetts S, Altshuler L, Close A, Frye M, Grunze H, et al. Predictors of Psychosocial Outcome of Bipolar Disorder: Results from the Stanley Foundation Bipolar Network. *Int J Bipolar Disord* (2019) 7:8. doi: 10.1186/s40345-019-0169-5
39. Karsten J, Penninx BWJH, Verboom CE, Nolen WA, Hartman CA. Course and risk factors of functional impairment in subtreshold depression and anxiety. *Depression Anxiety* (2013) 30(4):386–94. doi: 10.1002/da.22021
40. Correll CU, Hauser M, Penzner JB, Auther AM, Kafantaris V, Saito E, et al. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. *Bipolar Disord* (2014) 16(5):478–92. doi: 10.1111/bdi.12194
41. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* (2003) 64(2):161–74. doi: 10.4088/JCP.v64n0209
42. Martinez-Aran A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord* (2004) 6(3):224–32. doi: 10.1111/j.1399-5618.2004.00111.x
43. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. *PscholMed* (2000) 30(5):1025–36. doi: 10.1017/S0033291799002664

44. Sumiyoshi T, Toyomaki A, Kawano N, Kitajima T, Kusumi I, Ozaki N, et al. Verbal Memory Impairment in Patients with Subsyndromal Bipolar Disorder. *Front Psychiatry* (2017) 8:168. doi: 10.3389/fpsyt.2017.00168
45. Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord* (2007) 9(1-2):103–13. doi: 10.1111/j.1399-5618.2007.00327.x
46. Bonnin CM, Martinez-Aran A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, et al. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. *JAffectDisord* (2010) 121(1-2):156–60. doi: 10.1016/j.jad.2009.05.014
47. Torres IJ, DeFreitas CM, DeFreitas VG, Bond DJ, Kunz M, Honer WG, et al. Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder. *Psychol Med* (2011) 41(5):971–82. doi: 10.1017/s0033291710001613
48. Jimenez-Lopez E, Sanchez-Morla EM, Aparicio AI, Lopez-Villarreal A, Martinez-Vizcaino V, Rodriguez-Jimenez R, et al. Psychosocial functioning in patients with psychotic and non-psychotic bipolar I disorder. A comparative study with individuals with schizophrenia. *J Affect Disord* (2018) 229:177–85. doi: 10.1016/j.jad.2017.12.094
49. Mur M, Portella MJ, Martinez-Aran A, Pifarre J, Vieta E. Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. *Psychopathology* (2009) 42(3):148–56. doi: 10.1159/000207456
50. Morton E, Michalak EE, Murray G. What does quality of life refer to in bipolar disorders research? A systematic review of the construct's definition, usage and measurement. *J Affect Disord* (2017) 212:128–37. doi: 10.1016/j.jad.2017.01.026
51. Fletcher K, Foley F, Murray G. Web-Based Self-Management Programs for Bipolar Disorder: Insights From the Online, Recovery-Oriented Bipolar Individualised Tool Project. *J MedInternetRes* (2018) 20(10):e11160. doi: 10.2196/11160
52. Morton E, Hole R, Murray G, Buzwell S, Michalak E. Experiences of a Web-Based Quality of Life Self-Monitoring Tool for Individuals With Bipolar Disorder: A Qualitative Exploration. *JMIR Ment Health* (2019) 6(12):e16121. doi: 10.2196/16121
53. Murray G, Michalak EE. The quality of life construct in bipolar disorder research and practice: past, present, and possible futures. *Bipolar Disord* (2012) 14(8):793–6. doi: 10.1111/bdi.12016
54. Michalak EE, Murray G. Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. *Bipolar Disord* (2010) 12 (7):727–40. doi: 10.1111/j.1399-5618.2010.00865.x
55. Pascual-Sánchez A, Jenaro C, Montes-Rodríguez JM. Quality of life in euthymic bipolar patients: A systematic review and meta-analysis. *J Affect Disord* (2019) 255:105–15. doi: 10.1016/j.jad.2019.05.032
56. Post F, Pardeller S, Frajo-Apor B, Kemmler G, Sondermann C, Hausmann A, et al. Quality of life in stabilized outpatients with bipolar I disorder: Associations with resilience, internalized stigma, and residual symptoms. *J Affect Disord* (2018) 238:399–404. doi: 10.1016/j.jad.2018.05.055
57. Yapici Eser H, Kacar AS, Kilciksiz CM, Yalçinay-Inan M, Ongur D. Prevalence and Associated Features of Anxiety Disorder Comorbidity in Bipolar Disorder: A Meta-Analysis and Meta-Regression Study. *Front Psychiatry* (2018) 9:229. doi: 10.3389/fpsyt.2018.00229
58. Yoldi-Negrete M, Morera D, Palacios-Cruz L, Camarena B, Ortega H, Castañeda-Franco M, et al. Subsyndromal anxiety: Does it affect the quality of life? A study on euthymic patients with bipolar disorder. *Eur J Psychiatry* (2019) 33(4):159–64. doi: 10.1016/j.ejpsy.2019.06.005
59. Hidalgo-Mazzei D, Berk M, Cipriani A, Cleare AJ, Florio AD, Dietch D, et al. Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. *BrJPsychiatry* (2019) 214(1):27–35. doi: 10.1192/bjp.2018.257
60. Fountoulakis KN. Refractoriness in bipolar disorder: definitions and evidence-based treatment. *CNSNeurosciTher* (2012) 18(3):227–37. doi: 10.1111/j.1755-5949.2011.00259.x
61. Bernhard B, Born C, Seemüller F, Grunze H. Levetiracetam add-on treatment for bipolar patients suffering from subsyndromal symptoms: preliminary data of an open 6-month longitudinal study. *Eur Neuropsychopharmacol* (2005) 15 Suppl 3:416. doi: 10.1016/S0924-977X(05)80844-2
62. Vieta E, Martinez-Aran A, Nieto E, Colom F, Reinares M, Benabarre A, et al. Adjunctive gabapentin treatment of bipolar disorder. *EurPsychiatry* (2000) 15 (7):433–7. doi: 10.1016/S0924-9338(00)00514-9
63. Bauer M, Glenn T, Grof P, Rasgon NL, Marsh W, Sagduyu K, et al. Relationship between adjunctive medications for anxiety and time spent ill in patients with bipolar disorder. *IntJPsychiatry ClinPract* (2009) 13(1):70–7. doi: 10.1080/13651500802450514
64. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* (2004) 65(3):432–41. doi: 10.4088/JCP.v65n0321
65. Frye MA, Yatham L, Ketter TA, Goldberg J, Suppes T, Calabrese JR, et al. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar I maintenance studies. *Acta PsychiatrScand* (2009) 120(1):10–3. doi: 10.1111/j.1600-0447.2008.01343.x
66. Woo YS, Bahk WM, Park YM, Chung S, Yoon BH, Won S, et al. Effects of switching to aripiprazole from current atypical antipsychotics on subsyndromal symptoms and tolerability in patients with bipolar disorder. *Int Clin Psychopharmacol* (2016) 31(5):275–86. doi: 10.1097/yic.0000000000000136
67. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *ArchGenPsychiatry* (2007) 64(4):419–26. doi: 10.1001/archpsyc.64.4.419
68. Gonzalez-Isasi A, Echeburua E, Liminana JM, Gonzalez-Pinto A. Predictors of good outcome in patients with refractory bipolar disorder after a drug or a drug and cognitive-behavioral treatment. *ComprPsychiatry* (2012) 53(3):224–9. doi: 10.1016/j.comppsych.2011.05.001
69. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *AmJ Psychiatry* (2007) 164(9):1340–7. doi: 10.1176/appi.ajp.2007.07020311
70. Fristad MA, Young AS, Vesco AT, Nader ES, Healy KZ, Gardner W, et al. A Randomized Controlled Trial of Individual Family Psychoeducational Psychotherapy and Omega-3 Fatty Acids in Youth with Subsyndromal Bipolar Disorder. *J Child Adolesc Psychopharmacol* (2015) 25(10):764–74. doi: 10.1089/cap.2015.0132
71. Sole B, Bonnin CM, Mayoral M, Amann BL, Torres I, Gonzalez-Pinto A, et al. Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. *Eur Neuropsychopharmacol* (2015) 25(2):257–64. doi: 10.1016/j.euroneuro.2014.05.010
72. Reinares M, Sanchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: what, for whom, and when. *JAffectDisord* (2014) 156:46–55. doi: 10.1016/j.jad.2013.12.017
73. Oh D, Kim D. Eye movement desensitization and reprocessing for posttraumatic stress disorder in bipolar disorder. *Psychiatry Invest* (2014) 11(3):340–1. doi: 10.4306/pi.2014.11.3.340
74. Landin-Romero R, Novo P, Vicens V, McKenna PJ, Santed A, Pomarol-Clotet E, et al. EMDR therapy modulates the default mode network in a subsyndromal, traumatized bipolar patient. *Neuropsychobiology* (2013) 67 (3):181–4. doi: 10.4306/pi.2014.11.3.340
75. Novo P, Landin-Romero R, Radua J, Vicens V, Fernandez I, Garcia F, et al. Eye movement desensitization and reprocessing therapy in subsyndromal bipolar patients with a history of traumatic events: a randomized, controlled pilot-study. *Psychiatry Res* (2014) 219(1):122–8. doi: 10.1016/j.psychres.2014.05.012

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 26 October 2020
doi: 10.3389/fpsyt.2020.552532

Risk Stratification for Bipolar Disorder Using Polygenic Risk Scores Among Young High-Risk Adults

Silvia Biere[1], Thorsten M. Kranz[1], Silke Matura[1], Kristiyana Petrova[1], Fabian Streit[2], Andreas G. Chiocchetti[3], Oliver Grimm[1], Murielle Brum[1], Natalie Brunkhorst-Kanaan[1], Viola Oertel[1], Aliaksandr Malyshau[1], Andrea Pfennig[4], Michael Bauer[4], Thomas G. Schulze[5], Sarah Kittel-Schneider[1,6†] and Andreas Reif[1†]*

[1] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University, Frankfurt, Germany, [2] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim/University of Heidelberg, Mannheim, Germany, [3] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Autism Research and Intervention Center of Excellence Frankfurt, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany, [4] Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Dresden University of Technology, Dresden, Germany, [5] Institute of Psychiatric Phenomics and Genomics, University Hospital Munich, Ludwig-Maximilians-University of Munich, Munich, Germany, [6] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital of Würzburg, University of Würzburg, Würzburg, Germany

OPEN ACCESS

Edited by:
Julian Macoveanu, Copenhagen University Hospital, Denmark

Reviewed by:
Jonathan Richard Iain Coleman, King's College London, United Kingdom
Lone Diana Hørlyck, University of Copenhagen, Denmark

***Correspondence:**
Andreas Reif
andreas.reif@kgu.de

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *16 April 2020*
Accepted: *10 September 2020*
Published: *26 October 2020*

Citation:
Biere S, Kranz TM, Matura S, Petrova K, Streit F, Chiocchetti AG, Grimm O, Brum M, Brunkhorst-Kanaan N, Oertel V, Malyshau A, Pfennig A, Bauer M, Schulze TG, Kittel-Schneider S and Reif A (2020) Risk Stratification for Bipolar Disorder Using Polygenic Risk Scores Among Young High-Risk Adults. Front. Psychiatry 11:552532. doi: 10.3389/fpsyt.2020.552532

Objective: Identifying high-risk groups with an increased genetic liability for bipolar disorder (BD) will provide insights into the etiology of BD and contribute to early detection of BD. We used the BD polygenic risk score (PRS) derived from BD genome-wide association studies (GWAS) to explore how such genetic risk manifests in young, high-risk adults. We postulated that BD-PRS would be associated with risk factors for BD.

Methods: A final sample of 185 young, high-risk German adults (aged 18–35 years) were grouped into three risk groups and compared to a healthy control group (n = 1,100). The risk groups comprised 117 cases with attention deficit hyperactivity disorder (ADHD), 45 with major depressive disorder (MDD), and 23 help-seeking adults with early recognition symptoms [ER: positive family history for BD, (sub)threshold affective symptomatology and/or mood swings, sleeping disorder]. BD-PRS was computed for each participant. Logistic regression models (controlling for sex, age, and the first five ancestry principal components) were used to assess associations of BD-PRS and the high-risk phenotypes.

Results: We observed an association between BD-PRS and combined risk group status (OR = 1.48, $p < 0.001$), ADHD diagnosis (OR = 1.32, $p = 0.009$), MDD diagnosis (OR = 1.96, $p < 0.001$), and ER group status (OR = 1.7, $p = 0.025$; not significant after correction for multiple testing) compared to healthy controls.

Conclusions: In the present study, increased genetic risk for BD was a significant predictor for MDD and ADHD status, but not for ER. These findings support an underlying shared risk for both MDD and BD as well as ADHD and BD. Improving our understanding of the underlying genetic architecture of these phenotypes may aid in early identification and risk stratification.

Keywords: polygenic risk score, bipolar disorder, genetic phenotypes, depression, ADHD, early recognition

INTRODUCTION

Bipolar disorder (BD), which is characterized by recurrent episodes of mania and depression, is a severe and often chronic mental disorder associated with increased premature mortality and disability and reduced quality of life (1, 2). The first symptoms of the disorder occur many years before patients meet full diagnostic criteria, typically in adolescence, which thus marks a high-risk period for BD onset (3, 4). The mean age of onset for BD is between 20 and 30 years, and risk of onset decreases with age thereafter (1, 2). The long interval between early symptoms, correct diagnosis, and adequate treatment (5.8–6.7 years) (5, 6) is associated with a worsened clinical course and a substantial burden of illness (7, 8).

In the early course of BD, mood and drive are often dysregulated (9), which manifests in episodes of (subclinical) depression as well as (sub)threshold hypomania—these increase in severity and frequency during the period until onset (4, 6, 10). While the abovementioned symptoms are difficult to differentiate from normal fluctuations in mood (5), they represent the best predictors for developing BD (4, 10, 11). Additional symptoms include sleep disturbances, fear, anger, and irritability, which often occur in the early course and become more specific and similar to BD symptoms over time (4, 8, 9, 12).

Other difficulties that contribute to misdiagnosis of BD include a high rate of comorbidity and substantial overlap of symptoms between BD and other psychiatric disorders (13). The lifetime prevalence of attention deficit hyperactivity disorder (ADHD) in bipolar patients has been estimated to be around 20% and is thus one of the most common comorbid disorders in BD (14–16). ADHD has an earlier age of onset than BD and is common in relatives and offspring of individuals with BD, which has led to the hypothesis that it may be a precursor of BD (17, 18). However, while there are inconsistent findings regarding a genetic overlap between ADHD and BD (19), recent studies assessing genetic correlations between large-scale genome-wide association studies (GWAS) indicate a modest but significant positive association (12, 18, 20).

In most BD patients, the first episode at the onset of the disorder is a depressive episode, whereas an index mood episode of (hypo-)mania is less likely (21–23). Early age at onset of the first depressive disorder seems to be a prominent risk factor of conversion to BD (24–26). The difficulty in distinguishing BD from major depressive disorder (MDD) before the first (hypo-)manic episode occurs implies that BD diagnosis is often preceded by an initial misdiagnosis of MDD (21). This phenomenon creates the category of the so-called "hidden bipolars." Observed conversion rates from MDD to BD in young adults varies between 2.5 and 15.4% in a follow-up interval of 3–9 years (24, 27, 28). Moreover, studies have provided considerable support for a high shared genetic risk between BD and MDD (29). Family history for BD has been found to be the strongest predictor for conversion (30).

With heritability rates of up to 70% for BD (31), understanding the genetic factors contributing to BD-specific symptoms is crucial to improving diagnosis. Early and accurate diagnosis of BD would aid timely intervention and potentially prevent serious consequential damage. GWAS focusing on the liability for BD have identified shared risk alleles of single-nucleotide polymorphisms (SNPs) between BD and MDD as well as between BD and ADHD (32–35). While individual SNPs have a very small effect on disease risk on their own, a polygenic risk score (PRS), which constitutes a single value estimate of an individual's genetic propensity to a phenotype across a vast array of SNPs, appears to be a promising improvement (36). The PRS is the sum of an individual's genome-wide additive risk for a certain phenotype based on variation in multiple genetic loci and their associated weights from GWAS. Thus, for complex genetic diseases such as BD, PRS are likely to become a valuable predictor for disease risk. PRS using information from disease-associated alleles on current GWAS platforms explain ∼4% of the variation in risk for BD on the liability scale (29, 31). The modest accuracy of PRS is likely due to the highly polygenic nature of psychiatric disorders (37). In the future, higher levels of prediction accuracy may be achieved with predictors estimated from very large discovery samples (38). As GWAS datasets become larger and more diverse, they will have valuable potential for genomic risk prediction (39). Currently, PRS analyses are one of the most widely used approaches to understanding the genetic overlap between disorders, as well as at symptom level in case–control target samples (37).

To improve prognosis or even prevent the development of full-blown BD for affected individuals, there is a clear need to identify causative factors in order to improve diagnosis in the early stages of BD (2, 6). The present study investigates whether BD-PRS is associated with specific prodromal risk groups for BD. Based on previous research, we recruited subjects aged 18–35 belonging to three phenotypic risk groups for BD: Subjects with either ADHD or MDD diagnosis or early recognition (ER) risk factors assessed with the Early Phase Inventory for Bipolar Disorders (EPIbipolar) (13). These groups are being followed up longitudinally to assess the interplay of genetic and clinical predictors for pre-diagnostic risk stratification for BD (40).

MATERIALS AND METHODS

Participants

The study sample comprised 203 high-risk young adults aged 18–35 either diagnosed with ADHD ($n = 128$) or MDD ($n = 51$) or belonging to the ER group ($n = 24$) using standardized instruments (see *Clinical assessments*). Of these, 112 (ADHD = 32, MDD = 56, ER = 24) were recruited as part of the BipoLife substudy "Improving early recognition and intervention in people at-risk of developing bipolar disorder (BD)," which monitors young help-seeking adults over a 3-years period (40, 41). The additional young ADHD adults ($n = 96$) originated from the "Comorbid Conditions of Attention deficit hyperactivity disorders (CoCA)" study, which focuses on the investigation of developmental pathways, genetic and environmental mechanisms that underlie comorbidity of ADHD (42). The control group consisted of 1,223 healthy subjects with no history of psychiatric disorders from the longitudinal resilience assessment (LORA) project (https://lora-studie.de/) investigating the mechanisms involved in the resilience process as they occur in response to the stressors of modern life over a 3-years period (43).

All subjects declared that they understood the experimental procedure and provided written informed consent. The study was undertaken in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki; Rickham, 2013) and approved by the Ethics Committee of the University Hospital Frankfurt am Main, Germany. All subjects were recruited at the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy at the University Hospital Frankfurt.

Clinical Assessments

The inclusion criteria for high-risk subjects were a DSM-IV or DSM-5 diagnosis of either MDD or ADHD or classification into an ER risk group and age in the range of 18–35 years. After an initial screening visit of all participants, the German version of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (44) was carried out with all potential high-risk subjects. Individuals who fulfilled the criteria for a diagnosis of BD, schizoaffective disorder, or schizophrenia as well as those suffering exclusively from substance abuse, anxiety disorder, or obsessive–compulsive disorder were excluded. A comorbid personality disorder was not an exclusion criterion. All remaining subjects were assigned to one of the three risk groups (ADHD, MDD, and ER) depending on diagnosis.

To be assigned to the ADHD risk group, participants needed to fulfill the DSM-5 criteria for ADHD assessed by the DIVA questionnaire (45) and score above the cutoffs in the ADHD self-rating scales (German "ADHS-SB") (46). If available, external evaluation from family members/colleagues for ADHD was also considered. In addition, scores of 30 or above on the short version of the German version of the Wender-Utah-Rating Scale (WURS-k) (47) for retrospective childhood symptoms were required. To be assigned to the MDD risk group, subjects needed to fulfill the criteria for a MDD diagnosis in the SCID-I. For young, help-seeking adults that did not have a confirmed SCID-I diagnosis, the risk assessment tool EPIbipolar was used to assign participants to the ER risk group (13). EPIbipolar operationalizes risk constellations out of the elevated risk factors that are associated with later conversion to BD [(I) positive family history for BD, (II) (sub)threshold affective symptoms, (III) mood swings, (IV) changes in sleep and circadian rhythm, (V) substance misuse or dependence, (VI) impairment in psychosocial functioning, (VII) fearfulness/anxiety, and (VIII) episodic course] and forms risk groups. We assumed that elevated risk might be captured best by including all participants meeting the criteria for the risk categories defined in EPIbipolar (risk group, high-risk group, and ultra-high-risk group) and exclude subjects with no risk group assignment only. Only one participant from the high-risk group, who did not meet the criteria for ADHD or MDD or any of the risk categories defined in EPIbipolar was excluded from the final regression analyses.

Current or past psychiatric symptoms were ascertained in healthy controls to rule out an axis-I disorder (according to DSM-IV and DSM-5, respectively) by semi-structured interview with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (48). All diagnostic interviews were conducted by trained and experienced clinicians.

Genotyping and Quality Control

Genotyping was performed using the Global Screening Array (GSA), Multiple Drops (MD) Version 2.0 at the Life & Brain GmbH Platform Genomics, Bonn, Germany for the 51 MDD and 24 ER subjects. Genotyping of the 128 ADHD cases and 1,223 controls was carried out on a GSA-MD V 1.0 at the Broad Institute in Cambridge, Massachusetts, USA. Quality control of all subjects was performed using PLINK v1.9 (49). SNPs were filtered to exclude those with minor allele frequencies $\leq$0.01, calling rate of $\leq$0.98, variants deviating from Hardy–Weinberg-Equilibrium (HWE) ($p < 1 \times 10^{-6}$), and tri-allelic variants or variants not uniquely mappable. Participants were excluded in case of missingness >0.02, heterozygosity rate > 0.2, and sex mismatch. Filtering for population structure and relatedness was carried out on selected high-quality (HWE $p < 0.02$, MAF >0.2, missingness = 0) SNP set that was LD pruned ($r^2 = 0.1$). In case of cryptically related subjects (pi hat > 0.2), one of the subjects was excluded, preferentially retaining cases. Principal component analysis (PCA) was performed to assess hidden population stratification, and outliers with a $SD > 6$ on one of the first 20 principal components were excluded. After quality control, the datasets were merged and another round of quality control and PCA were carried out as described above.

In total, 141 subjects were excluded from subsequent analyses: 117 subjects were excluded after genetic quality control, 22 subjects were excluded because of missing information on age, and 1 ER subject was excluded for not fulfilling the criteria for ER risk group status (see *Clinical assessments*). The final dataset thus consisted of $N = 1,285$ participants (117 ADHD, 45 MDD, and 23 ER high-risk subjects and 1,100 healthy controls) and 431,828 SNPs.

Polygenic Risk Scores

PRS calculated was performed using the PRSice software version 2.3.1.e with default options [clump-kb 250, clump-p 1.0, clump

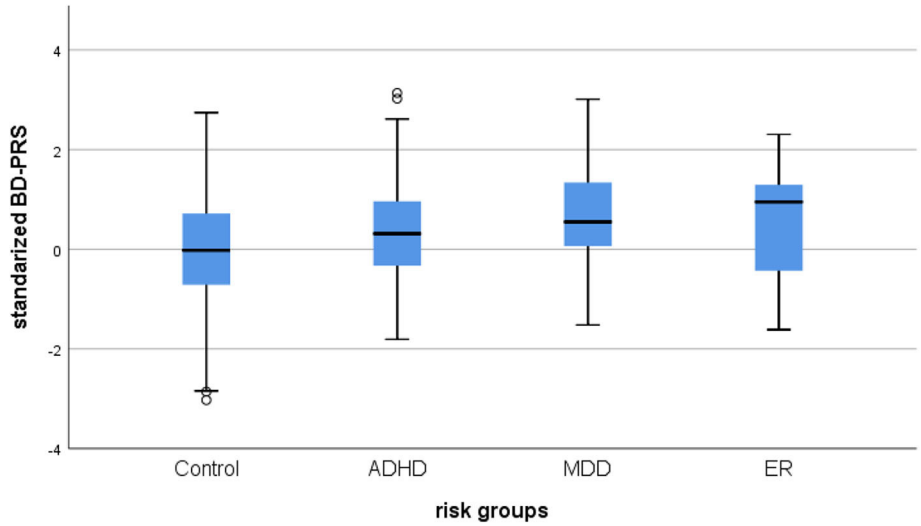


FIGURE 1 | Box plot of the distribution of BD-PRS for BD high-risk groups. Control, healthy control group; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; ER, early recognition; ZScore: BD-PRS, standardized BD-PRS score.

r2 0.1, interval 5e-05, lower 5e-08, stat OR; (50)]. We calculated PRS for BD based on the summary statistic files of the second Psychiatric Genomics Consortium Bipolar Disorder (PGC-BD) GWAS (31), applying INFO score filtering (INFO > 0.8). There was no overlap between the present study sample and the used BD discovery sample. BD-PRS were z-transformed based on the mean and standard deviation observed in the control group. We applied the best-fit function of PRSice, which runs logistic regressions to determine the p-threshold with the largest variance explained by the PRS, assessed as the increment in Nagelkerke's pseudo-R^2 of the full model including BD-PRS and covariates (age, sex, and the first five principal components for population stratification) compared to the null model (only covariates). The best-fit PRS for the combined sample (dependent variable: high-risk vs. control group) was used for further subgroup comparisons. In addition to the incremental R^2 values, we report the incremental R^2 adjusted for the liability scale (onwards referred to as "R2.liability"; –prevalence flag in PRSice2), assuming a more conservative estimated population lifetime prevalence of 2.5% for ADHD in adults (51) and 15% for MDD (52), as well as 17% for ER (unpublished data). For the combined risk group, we applied an average prevalence weighted by the subsample sizes as an approximation of prevalence (7.39%).

Statistics

All further analyses were performed using SPSS 26.0 for Windows (IBM Corp., USA). To examine if BD-PRS (the independent variable) was associated with a specific risk group compared to control status (dependent variable), binary logistic regressions were carried out. Odds ratios (ORs) per standard deviation (SD) increase in BD-PRS are reported. Each regression included sex, age, and the first five principal components (to control for hidden population stratification) as covariates. Uncorrected *p*-values are reported, thus the corresponding Bonferroni-corrected alpha threshold was 0.0125 (correcting for four analyses, i.e. any risk group vs. control, ADHD vs. control, MDD vs. control and ER vs. control).

Given that the sample size was pre-defined at the beginning of the study, we performed a *post-hoc* power analysis to identify the beta error with the given sample size. For the four different binary logistic regressions, we calculated the *post-hoc* statistical power for the estimated population effect sizes with GPower 3.1.9.7 (53) for an population effect of an R^2 of 0.04 (corresponding to a Cohen's d of 0.41) as observed in the PRS analyses in the GWAS by Stahl et al. (31) using the following parameters: Corrected alpha error probability of 0.0125, control group sample size of $n = 1{,}100$, and experimental group sample size of $n = 185$ (combined risk group), $n = 117$ (ADHD), $n = 45$ (MDD), and $n = 23$ (ER), respectively. Power analysis revealed a statistical power of >0.99 for the regression with the combined risk group, and 0.95 (ADHD group), 0.57 (MDD group), and 0.30 (ER group).

RESULTS

Sample Characteristics

The age of the participants (39.4% male, 60.6% female) at the time of the interview ranged from 18 to 82 years, with a mean of 31.39 ($SD = 12.65$) years (**Table 1**).

Risk Group Association With Genetic Risk of BD

BD-PRS score was positively associated with belonging to the combined risk group (OR = 1.48, 95% CI [1.25, 1.76], PRS.R^2 =0.026, PRS.R^2.liability =0.030, $p < 0.001$) vs. controls. Binary logistic regression for the specific subgroups showed BD-PRS

TABLE 1 | Demographic data.

Demographics	ADHD ($N = 117$)	MDD ($N = 45$)	ER ($N = 23$)	Control ($N = 1,100$)
Sex (%)				
Female	41%	64.4%	65.2%	62.6%
Male	59%	35.6%	34.8%	37.4%
Age (years ± SD)	27.21 ± 4.60	25.07 ± 4.83	23.39 ± 4.79	32.30 ± 13.59

Control, healthy control; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; ER, early recognition; SD, standard deviation.

was also associated with ADHD vs. control status (OR = 1.32, 95% CI [1.07, 1.62], PRS.R^2 = 0.011, PRS. R^2.liability = 0.011, $p = 0.009$) and MDD vs. control status (OR = 1.96, 95% CI [1.42, 2.73], PRS.R^2 = 0.050, PRS.R^2.liability = 0.094, $p < 0.001$). A trend was observed for BD-PRS prediction of ER group vs. control status (OR = 1.70, 95% CI [1.07, 2.69], PRS.R^2 = 0.024, PRS R^2.liability = 0.049; $p = 0.025$, see **Figure 1**). Only the association with ER vs. control group status was not significant per the Bonferroni-corrected alpha level of 0.0125. None of the analyzed samples showed hidden population stratification in the first five principal components (PC1–PC5). For a summary of the regression coefficients, see **Table 2**.

DISCUSSION

Summary of Findings

To date, few studies have investigated phenotypes associated with genetic risk of BD utilizing BD-PRS (19, 54). In this study, we uniquely investigated the role of psychopathology and high-risk factors in young adults for the development of BD using BD-PRS scores. Our results provide information about shared genetic risk factors, supporting the hypothesis that BD-PRS might improve the accuracy of BD diagnosis in the early course of illness or prodromal phase. Overall, the results for the combined risk group (ADHD, MDD, and ER) displayed a weak association between the BD-PRS and the respective diagnoses, as made evident by the expected risk-increasing profile (OR = 1.48). In the subgroup analyses, BD-PRS was a significant predictor of both MDD and ADHD diagnosis vs. healthy control status in young adults, but not of ER group status. For MDD as well as ADHD, we observed a weak risk association of BD-PRS and case vs. healthy control status ($OR_{MDD} = 1.96$; $OR_{ADHD} = 1.32$). BD-PRS did not show a significant association with ER group status as per the Bonferroni-corrected significance level, which may be due to the limited statistical power for this comparatively small subsample. The results from our high-risk young adult cohort indicate that the expected shared risk between both MDD and BD and ADHD and BD is considerable. Although the discovery GWAS sample used to calculate BD-PRS in our study is the largest available to date, the predictive power achievable by polygenic scores for BD is still limited. Future, large-scale GWAS will enable better prediction of polygenic risk for developing BD and aid accurate diagnosis.

BD-PRS and MDD

The results of the present study are consistent with and extend previous findings of a strong genetic overlap between BD and MDD (54, 55). From a clinical perspective, one possible explanation for the observed genetic overlap is the high overlap of symptoms between the two disorders with regard to depressive symptoms. However, BD and MDD still differ largely in course of illness, symptomatology and treatment overall. Another potential explanation is that the association between BD-PRS and MDD case status is due to poor assessment of previous hypomanic symptoms in psychiatric patients. That is, a number of patients classified as having MDD in our sample might be misdiagnosed BD patients with undocumented/undetected hypomanic symptoms. However, a recent study showed that BD-PRS was not associated with hypomania (19). In addition, all subjects in our study were diagnosed by experienced raters with the semi-structured clinical interview SCID-I, which is a valid instrument to detect hypomania symptoms.

Instead, the most likely explanation for the observed association of BD-PRS with increased odds of being diagnosed with MDD is that some of our subjects diagnosed with MDD are actually affected by BD, but have not clinically converted to BD yet [i.e., they are "hidden BD patients" (56)]. A major strength of our study is that we focus on young adults, since numerous prior studies have shown that early age of onset for MDD is a predictor of bipolar conversion (24). This is in line with the fact that the index episode for most BD cases is a depressive episode (22–24). However, the unknown degree to which "hidden BD patients" comprise MDD case samples makes it difficult to distinguish between pleiotropy and truly shared biological pathways in the association of genetic risk for BD with MDD. To further investigate this issue and other open questions such as whether BD-PRS decreases with increasing age in MDD cases, large-scale longitudinal studies of conversion rates for individuals diagnosed with MDD are needed.

BD-PRS and ADHD

The association between BD-PRS and ADHD case vs. healthy control status is in line with previous findings of high comorbidity and symptom overlap between the two disorders—especially in the age group assessed in the present study (20). However, as with MDD, there are multiple possible explanations for the observed association in the context of previous findings. It is unclear if the high comorbidity of BD and ADHD is simply a result of misdiagnosis due to similarity of symptom complexes, if it is a true comorbidity or whether ADHD is more likely a prodromal manifestation of BD (13). Given that all diagnoses were given based on the results of semi-structured interviews and standardized instruments based on the DSM-IV and DSM-5 and carried out by trained clinicians, we are confident that misdiagnosis in our sample was very unlikely. It is well-documented that a comorbid diagnosis of ADHD is associated with worse outcomes for BD-affected individuals. BD patients with comorbid ADHD have an earlier

TABLE 2 | Associations of the BD-PRS with risk groups.

Risk group	*β*	*SE*	*P*	*OR*	95% CI	Nagelkerke's R^2 observed	Nagelkerke's R^2 liability
All risk groups (*N* = 185)						0.026	0.030
BD-PRS	0.39	0.087	<0.001*	1.48	1.25–1.76		
Sex	−0.58	0.17	0.001*	0.56	0.41–0.78		
Age	0.066	0.012	<0.001*	0.94	0.92–0.96		
PC 1	−2.596	2.56	0.310	0.075	0.000–11.2		
PC 2	−1.35	2.67	0.615	0.26	0.001–48.9		
PC 3	−0.75	2.86	0.794	0.47	0.002–129		
PC 4	−3.10	2.98	0.298	0.045	0.000–15.5		
PC 5	5.53	2.96	0.062	252	0.76–83,406		
ADHD (*n* = 117)							
BD-PRS	0.28	0.11	0.009*	1.32	1.07–1.62	0.011	0.011
Sex	−0.92	0.20	<0.001*	0.40	0.27–0.59		
Age	−0.048	0.012	<0.001*	0.95	0.93–0.98		
PC 1	−4.23	2.92	0.148	0.02	0.000–4.50		
PC 2	−1269	3.12	0.684	0.28	0.001–128		
PC 3	−0.13	3.44	0.970	0.88	0.001–747		
PC 4	−2.62	3.66	0.474	0.073	0.000–95.0		
PC 5	0.22	3.54	0.951	1.245	0.001–1277		
MDD (*n* = 45)							
BD-PRS	0.68	0.17	<0.001*	1.96	1.42–2.73	0.050	0.094
Sex	0.099	0.31	0.765	1.10	0.58–2.11		
Age	−0.090	0.027	0.001*	0.91	0.87–0.96		
PC 1	2.51	5.02	0.616	12.4	0.001–229298		
PC 2	−4.38	4.76	0.358	0.01	0.000–141		
PC 3	−2.05	5.14	0.689	0.13	0.000–3018		
PC 4	−4.66	5.76	0.419	0.01	0.000–760		
PC 5	15.3	5.72	0.007	4389555	59.7–3.23E+11		
ER (*n* = 23)							
BD-PRS	0.53	0.24	0.025	1.70	1.07–2.69	0.02	0.05
Sex	0.080	0.46	0.862	1.08	0.44–2.66		
Age	−0.17	0.054	0.002*	0.85	0.76–0.94		
PC 1	0.64	7.13	0.928	1.90	0.000–2238258		
PC 2	9.42	8.28	0.255	12377	0.001– 1.38E+11		
PC 3	0.74	8.08	0.927	2.10	0.000–15892441		
PC 4	2.79	7.72	0.718	16	0.000–60807382		
PC 5	15.9	7.86	0.043	8055215	1.64–3.95E+13		

Binary logistic regressions were adjusted for sex, age, and ancestry PCs 1–5. Sex was coded as 1 = male and 2 = female.

**BD-PRS significant after applying the corrected alpha threshold of 0.0125.*

ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; ER, early recognition; CI, confidence interval; PC, principal component.

onset of diagnosed BD, a worse course of illness and a greater burden of other psychiatric comorbid conditions, regardless of whether the ADHD symptoms persist in adulthood or not (14, 57). Duffy (58) proposed that the clinical and biological overlap between BD and ADHD might also be part of a phenotype predicting a specific subtype of BD. In view of the fact that we focused on young adults in our study, our findings might represent a distinct early-onset subtype of BD.

While a recent review only found evidence for a weak association of BD-PRS with ADHD at best (54), various other results support the observed association between BD-PRS and ADHD diagnosis in our study (18–20, 24, 59). However, with regard to the genetic correlation between BD and ADHD, different iterations of the PGC BD-ADHD cross-disorder correlations give different results, and even the correlation between different PGC-BD GWAS phases varies. For example, a larger correlation was observed in Hulzen et al. (20) compared to the later study based on an increased sample by O'Connell et al. (18). In addition, one study has also found evidence for distinct underlying genetic mechanisms (20). Altogether, given the reported genetic

association between BD and ADHD, our findings support the assumption that these disorders share genetic underpinnings. Of interest are similar positive genetic correlations of ADHD with early- and late-onset BD. Further research is needed to disentangle the distinct and shared genetic mechanisms of BD and ADHD.

BD-PRS and ER

Based on the heterogeneity of BD and the unknown composition of risk factors, it is challenging to accurately index individuals with a high propensity to develop BD (23). Most BD patients experience a variety of symptoms, which vary in severity, frequency, and duration and increase until they fulfill full diagnostic criteria (4, 6). However, some risk factors appear to be better indicators than others for propensity to develop BD. The best method to date to quantify risk for BD is the preliminary EPIbipolar (13) used to assign subjects the ER group in this study. Although the risk assessment tool uses key symptom profiles comprising weighted well-documented risk factors associated with later disease manifestation, it is still unclear how well EPIbipolar can measure/predict risk for BD (60). Likewise, EPIbipolar has not yet been tested for an association with BD-PRS. While we could observe a higher average BD-PRS in the ER sample compared to the healthy control group, BD-PRS was not a significant predictor of ER group vs. healthy control status per the corrected significance level. The limited statistical power of this subgroup analysis due to the small sample size of the ER risk group may explain why the weak association did not reach the level of statistical significance. These results underline the need for further research with larger sample sizes, envisaged by BipoLife (40, 41). The dichotomized EPIbipolar threshold for elevated risk used to assign subjects to the ER group (EPIbipolar risk, high-risk and ultra-high-risk group vs. no risk group classification) may also play a role in the negative findings. Exploratory analyses revealed a higher association between the BD-PRS and ER group vs. healthy control status when only subjects who fell into the EPIbipolar high-risk and ultra-high-risk groups were included. Therefore, the lack of association between BD-PRS and ER group status might be a result of an underestimated threshold that leads to an information bias (2, 9). A more stringent threshold for EPIbipolar results and larger sample sizes may enable the detection of an underlying association of BD-PRS with ER BD risk status.

Limitations

A limitation of the present study is the number of participants assessed, particularly when analyzing the three risk groups separately. While our power analysis indicated an adequate power to detect effects as described in the literature for BD case–control samples (31) for the combined risk group, power was limited for analyses of the individual subgroups. In order to detect more subtle effects or investigate the characteristics of subgroups in more detail, larger samples are needed. Another limitation is the predictive power of BD-PRS. While BD-PRS were derived from the largest GWAS of BD to date, substantially larger discovery samples are needed to fully leverage the predictive power of PRS. Additionally, PRS capture only common genetic variations and their effects on risk—rare variants may also play a role in BD risk. We also acknowledge that, by using the best-fit approach implemented in PRSice, the observed variance explained by PRS (pseudo R^2; PRS.R^2.adj = 0.0174038) is likely an overestimation of the true value. Finally, follow-up studies are required to determine how many high-risk participants convert to BD to determine the predictive validity of the BD-PRS associations.

CONCLUSION

In conclusion, we found associations between increased genetic risk for BD and increased odds of MDD and ADHD in young adulthood, but not for odds of ER group status. While PRS only explain a relatively small proportion of the variance of BD, the results of our study indicate that BD-PRS may be still useful for early identification and risk stratification in the future. Currently, the predictive power of psychiatric PRS is still too limited for clinical application (61). However, future, exponentially larger GWAS will substantially increase the signal reliably captured and increase the predictive power of PRS (39). Furthermore, methodological advances of risk scoring methods [e.g., by improved algorithms or inclusion of rare variants, will further improve genetic risk prediction (62)]. Given the comorbidity of MDD and BD, lack of early diagnosis, and the fact that a first onset MDD diagnosis may actually represent an early-onset BD phenotype, further work in longitudinal studies could explore how many high-risk individuals convert to BD. In this regard, it would be interesting to see if those who convert to BD are also those who have a high BD-PRS score. Additionally, a stricter definition of ER status to best reflect conversion risk could contribute to improved BD risk prediction.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because participants of the study did not give permission to publish their genome-wide data, based on obvious conflict with General Data Protection Regulation (OJ L 119, 04.05.2016; cor. OJ L 127, 23.5.2018.; https://gdpr-info.eu/). Requests to access the datasets should be directed to Andreas Reif, Andreas.Reif@kgu.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Frankfurt am Main, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB, KP, SM, OG, MBr, and NB-K: acquisition of data. AR, SK-S, AP, SM, TK, OG, VO, MBa, and TS: critical revision. SB, TK, SK-S, AR, SM, and AP: drafting of manuscript. SB and TK:

analysis and interpretation of data. All authors contributed to the article and approved the submitted version.

FUNDING

The genotyping was funded in part by the Broad Institute in Cambridge, Massachusetts, USA. Early-BipoLife was funded by the Federal Ministry of Education and Research (BMBF, grant number: 01EE1404A) and is part of the BipoLife consortium (local PI AR) described elsewhere (40). This project has also received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 667302. This report reflects only the author's view and the Commission is not responsible for any use that may be made of the information it contains. FS acknowledges support by the German Federal Ministry of Education and Research (BMBF) through the ERA-NET NEURON, SynSchiz—Linking synaptic dysfunction to disease mechanisms in schizophrenia—a multilevel investigation (01EW1810) grant.

ACKNOWLEDGMENTS

We thank all participants of the study for their participation. In addition, we thank the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium (PGC-BIP) for providing access to the relevant data. In particular, we would like to thank Theresia Töpner, Joyce Auer, and Sabine Stanzel for their excellent technical support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.552532/full#supplementary-material

REFERENCES

1. Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord.* (2016) 18:440–50. doi: 10.1111/bdi.12423
2. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. *Therapeut Adv Psychopharmacol.* (2018) 8:251–69. doi: 10.1177/2045125318769235
3. Balsan G, Corcos M. Les troubles maniaco-dépressifs à l'adolescence : aspects cliniques. *Archiv Pediatrie.* (2016) 23:417–23. doi: 10.1016/j.arcped.2015.12.006
4. Van Meter A, Guinart D, Bashir A, Sareen A, Cornblatt BA, Auther A, et al. Bipolar prodrome symptom scale—abbreviated screen for patients: description and validation. *J Affective Disord.* (2019) 249:357–65. doi: 10.1037/t72810-000
5. Dagani J, Signorini G, Nielssen O, Bani M, Pastore A, Girolamo G, et al. Meta-analysis of the Interval between the onset and management of bipolar disorder. *Can J Psychiatry.* (2017) 62:247–58. doi: 10.1177/0706743716656607
6. Leopold K, Ratzer S, Correll CU, Rottmann-Wolf M, Pfeiffer S, Ritter P, et al. Characteristics, symptomatology and naturalistic treatment in individuals at-risk for bipolar disorders: baseline results in the first 180 help-seeking individuals assessed at the dresden high-risk project. *J Affective Disord.* (2014) 152–4:427–33. doi: 10.1016/j.jad.2013.10.009
7. Pfennig A, Conell J, Ritter P, Ritter D, Severus E, Meyer TD, et al. Leitliniengerechte psychiatrisch-psychotherapeutische Behandlung bei bipolaren Störungen: Welche Ressourcen werden dafür benötigt? *Nervenarzt.* (2017) 88:222–33. doi: 10.1007/s00115-016-0083-3
8. Rios AC, Noto MN, Rizzo LB, Mansur R, Martins FE, Grassi-Oliveira R, et al. Early stages of bipolar disorder: characterization and strategies for early intervention. *Revista Brasileira Psiquiatria.* (2015) 37:343–9. doi: 10.1590/1516-4446-2014-1620
9. Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. *J Affective Disord.* (2010) 126:1–13. doi: 10.1016/j.jad.2009.10.003
10. Correll CU, Penzner JB, Frederickson AM, Richter JJ, Auther AM, Smith CW, et al. Differentiation in the preonset phases of schizophrenia and mood disorders: evidence in support of a bipolar mania prodrome. *Schizophrenia Bull.* (2007) 33:703–14. doi: 10.1093/schbul/sbm028
11. Conroy SK, Francis MM, Hulvershorn LA. Identifying and treating the prodromal phases of bipolar disorder and schizophrenia. *Curr Treat Options Psychiatry.* (2018) 5:113–28. doi: 10.1007/s40501-018-0138-0
12. Lee P, Anttila V, Won H, Yen-Chen F, Rosenthal J, Zhu Z, et al. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell.* (2019) 179:1469–82. doi: 10.1016/j.cell.2019.11.020
13. Leopold K, Ritter P, Correll CU, Marx C, Özgürdal S, Juckel G, et al. Risk constellations prior to the development of bipolar disorders: rationale of a new risk assessment tool. *J Affective Disord.* (2012) 136:1000–10. doi: 10.1016/j.jad.2011.06.043
14. Rydén E, Thase ME, Stråht D, Åberg-Wistedt A, Bejerot S, Landén M. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. *Acta Psychiatr Scand.* (2009) 120:239–46. doi: 10.1111/j.1600-0447.2009.01399.x
15. Torres I, Gómez N, Colom F, Jiménez E, Bosch R, Bonnín CM, et al. Bipolar disorder with comorbid attention-deficit and hyperactivity disorder. *Acta Psychiatr Scand.* (2015) 132:389–99. doi: 10.1111/acps.12426
16. Wingo AP, Ghaemi SN. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. *J Clin Psychiatry.* (2007) 68:1776–84. doi: 10.4088/JCP.v68n1118
17. Meier SM, Pavlova B, Dalsgaard S, Nordentoft M, Mors O, Mortensen PB, et al. Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood. *Br J Psychiatry.* (2018) 213:555–60. doi: 10.1192/bjp.2018.111
18. O'Connell KS, Shadrin A, Bahrami S, Smeland OB, Bettella F, Frei O, et al. Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. *Mol Psychiatry.* (2019). doi: 10.1038/s41380-019-0613-z
19. Mistry S, Escott-Price V, Florio AD, Smith DJ, Zammit S. Genetic risk for bipolar disorder and psychopathology from childhood to early adulthood. *J Affective Disord.* (2019) 246:633–9. doi: 10.1016/j.jad.2018.12.091
20. Hulzen KJE, Van Scholz CJ, Franke B, Ripke S, Mcquillin A, Sonuga-barke EJ, et al. 120th anniversary of the kraepelinian dichotomy of psychiatric disorders. *HHS Public Access.* (2017) 82:634–41. doi: 10.1016/j.biopsych.2016.08.040
21. Fritz K, Russell AMT, Allwang C, Kuiper S, Lampe L, Malhi GS. Is a delay in the diagnosis of bipolar disorder inevitable? *Bipolar Disord.* (2017) 19:396–400. doi: 10.1111/bdi.12499
22. Gilman SE, Dupuy JM, Perlis RH. Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on alcohol and related conditions. *J Clin Psychiatry.* (2012) 73:829–36. doi: 10.4088/JCP.11m06912
23. Propper L, Ortiz A, Slaney C, Garnham J, Ruzickova M, Calkin CV, et al. Early-onset and very-early-onset bipolar disorder: distinct or similar clinical conditions? *Bipolar Disord.* (2015) 17:814–20. doi: 10.1111/bdi.12346
24. Kim H, Kim Y, Baek JH, Fava M, Mischoulon D, Nierenberg AA, et al. Predictive factors of diagnostic conversion from major depressive

disorder to bipolar disorder in young adults ages 19–34: a nationwide population study in South Korea. *J Affective Disord.* (2020) 265:52–8. doi: 10.1016/j.jad.2020.01.009
25. Østergaard SD, Straszek S, Petrides G, Skadhede S, Jensen SOW, Munk-Jørgensen P, et al. Risk factors for conversion from unipolar psychotic depression to bipolar disorder. *Bipolar Disord.* (2014) 16:180–9. doi: 10.1111/bdi.12152
26. Ratheesh A, Davey C, Hetrick S, Alvarez-Jimenez M, Voutier C, Bechdolf A, et al. A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. *Acta Psychiatr Scand.* (2017) 135:273–84. doi: 10.1111/acps.12686
27. Pedrotti Moreira F, Cardoso TC, Mondin TC, Wiener CD, de Mattos Souza LD, Oses JP, et al. Serum level of nerve growth factor is a potential biomarker of conversion to bipolar disorder in women with major depressive disorder. *Psychiatry Clin Neurosci.* (2019) 73:590–3. doi: 10.1111/pcn.12896
28. ter Meulen WG, Draisma S, Beekman ATF, Penninx BWJH, Kupka RW. The predictive performance of the bipolarity index in a Dutch epidemiological sample manuscript. *J Affective Disord.* (2020) 262:373–80. doi: 10.1016/j.jad.2019.10.055
29. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genetics.* (2013) 45:984–94. doi: 10.1038/ng.2711
30. Musliner KL, Østergaard SD. Patterns and predictors of conversion to bipolar disorder in 91 587 individuals diagnosed with unipolar depression. *Acta Psychiatr Scand.* (2018) 137:422–32. doi: 10.1111/acps.12869
31. Stahl E, Bipolar Working Group of the Psychiatric Genomics Consortium. Genome-wide association study identifies twenty new loci associated with bipolar disorder. *Eur Neuropsychopharmacol.* (2019) 29:S816. doi: 10.1016/j.euroneuro.2017.08.061
32. Ikeda M, Saito T, Kondo K, Iwata N. Genome-wide association studies of bipolar disorder: a systematic review of recent findings and their clinical implications. *Psychiatry Clin Neurosci.* (2018) 72:52–63. doi: 10.1111/pcn.12611
33. Ruderfer DM, Ripke S, McQuillin A, Boocock J, Stahl EA, Pavlides JMW, et al. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell.* (2018) 173:1705–15.e16. doi: 10.1016/j.cell.2018.05.046
34. Sklar P, Purcell SM, Ripke S, Daly M, Ferreira MA, O'Dushlaine C, et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genetics.* (2011) 43:977–85. doi: 10.1038/ng.943
35. Witt SH, Streit F, Jungkunz M, Frank J, Awasthi S, Reinbold CS, et al. Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. *Transl Psychiatry.* (2017) 7:e1155. doi: 10.1038/tp.2017.115
36. Choi SW, Heng Mak TS, O'Reilly PF. A guide to performing Polygenic Risk Score analyses. *bioRxiv* (2018) 416545. doi: 10.1101/416545
37. So HC, Sham PC, Valencia A. Exploring the predictive power of polygenic scores derived from genome-wide association studies: a study of 10 complex traits. *Bioinformatics.* (2017) 33:886–92. doi: 10.1093/bioinformatics/btw745
38. Dudbridge F. Correction: power and predictive accuracy of polygenic risk scores. *PLOS Genet.* (2013) 9. doi: 10.1371/annotation/b91ba224-10be-409d-93f4-7423d502cba0
39. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, et al. Psychiatric genomics: an update and an agenda. *Am J Psychiatry.* (2018) 175:15–27. doi: 10.1176/appi.ajp.2017.17030283
40. Ritter PS, Bermpohl F, Gruber O, Hautzinger M, Jansen A, Juckel G, et al. Aims and structure of the German Research Consortium BipoLife for the study of bipolar disorder. *Int J Bipolar Disord.* (2016) 4:26. doi: 10.1186/s40345-016-0066-0
41. Pfennig A, Leopold K, Martini J, Boehme A, Lambert M, Stamm T, Bermpohl F, et al. Improving early recognition and intervention in people at increased risk for the development of bipolar disorder-Study protocol of a prospective-longitudinal, naturalistic cohort study (Early-BipoLife). *Int J Bipolar Disord.* (2020) 8:22. doi: 10.1186/s40345-020-00183-4
42. Mayer JS, Hees K, Medda J, Grimm O, Asherson P, Bellina M, et al. Bright light therapy versus physical exercise to prevent co-morbid depression and obesity in adolescents and young adults with attention-deficit / hyperactivity disorder: study protocol for a randomized controlled trial. *Trials.* (2018) 19:1. doi: 10.1186/s13063-017-2426-1
43. Chmitorz A, Neumann RJ, Kollmann, B. Ahrens KF, Öhlschläger S, Goldbach N, et al. Longitudinal determination of resilience in humans to identify mechanisms of resilience to modern-life stressors: the longitudinal resilience assessment (LORA) study. *Eur Arch Psychiatry Clin Neurosci.* (2020). doi: 10.1007/s00406-020-01159-2
44. Gorgens KA. Structured clinical interview for DSM-IV (SCID-I/SCID-II). *Encyclop Clin Neuropsychol.* (2011) 2410–7. doi: 10.1007/978-0-387-79948-3_2011
45. Kooij JJS. Diagnostic interview for ADHD in adults 2.0 (DIVA 2.0). In: *Adult ADHD. Diagnostic Assessment and Treatment*. Amsterdam: Pearson Assessment & Information BV (2010).
46. Rösler M, Retz W, Retz-Junginger P, Thome J, Supprian T, Nissen T, et al. Instrumente zur diagnostik der aufmerksamkeitsdefizit-/hyperaktivitätsstörung (ADHS) im erwachsenenalter. *Nervenarzt.* (2004) 75:888–95. doi: 10.1007/s00115-003-1622-2
47. Retz-Junginger P, Retz W, Blocher D, Stieglitz RD, Georg T, Supprian T, et al. Reliabilität und validität der Wender-Utah-Rating-Scale-Kurzform: Retrospektive erfassung von symptomen aus dem spektrum der aufmerksamkeitsdefizit/hyperaktivitätsstörung. *Nervenarzt.* (2003) 74:987–93. doi: 10.1007/s00115-002-1447-4
48. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. (1998) 59(Suppl 20):22–33; quiz 34–57.
49. Chang CC, Chow CC, Tellier LCAM, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience.* (2015) 4:8. doi: 10.1186/s13742-015-0047-8
50. Choi SW, O'Reilly PF. PRSice-2: polygenic Risk Score software for biobank-scale data. *GigaScience.* (2019) 8:giz082. doi: 10.1093/gigascience/giz082
51. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* (2019) 51:63–75. doi: 10.1038/s41588-018-0269-7
52. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* (2018) 50:668–81. doi: 10.1038/s41588-018-0090-3
53. Erdfelder E, Faul F, Buchner A. GPOWER: a general power analysis program. *Behav Res Method Instr Comp.* (1996) 28:1–11. doi: 10.3758/BF03203630
54. Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: a systematic review. *J Affective Disord.* (2018) 234:148–55. doi: 10.1016/j.jad.2018.02.005
55. Gordovez FJA, McMahon FJ. The genetics of bipolar disorder. *Mol Psychiatry.* (2020) 25:544–59. doi: 10.1038/s41380-019-0634-7
56. Coleman JRI, Gaspar HA, Bryois J, Byrne EM, Forstner AJ, Holmans PA, et al. The genetics of the mood disorder spectrum: genome-wide association analyses of more than 185,000 cases and 439,000 controls. *Biol Psychiatry.* (2020) 88:169–84. doi: 10.1016/j.biopsych.2019.10.015
57. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1,000 STEP-BD participants. *Biol Psychiatry.* (2005) 57:1467–73. doi: 10.1016/j.biopsych.2005.01.036
58. Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. *Am J Psychiatry.* (2012) 169:1247–55. doi: 10.1176/appi.ajp.2012.11111725
59. Hamshere ML, Stergiakouli E, Langley K, Martin J, Holmans P, Kent L, et al. Shared polygenic contribution between childhood attention-deficit hyperactivity disorder and adult schizophrenia. *Br J Psychiatry.* (2013) 203:107–11. doi: 10.1192/bjp.bp.112.117432
60. Burkhardt E, Pfennig A, Breitling G, Pfeiffer S, Sauer C, Bechdolf A, et al. Creativity in persons at-risk for bipolar disorder-A pilot study. *Early Interv Psychiatry*. (2019) 13:1165–72. doi: 10.1111/eip.12748
61. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* (2020) 12:44. doi: 10.1186/s13073-020-00742-5

62. Ge T, Chen C, Ni Y, Anne Feng Y-C, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun.* (2019) 10:1776. doi: 10.1038/s41467-019-09718-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 23 November 2020
doi: 10.3389/fpsyt.2020.530026

Predictors of Functional Outcome in Patients With Bipolar Disorder: Effects of Cognitive Psychoeducational Group Therapy After 12 Months

Gabriele Sachs[1]*, *Andrea Berg*[1], *Reinhold Jagsch*[2], *Gerhard Lenz*[1] and *Andreas Erfurth*[1,3]

[1] Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria, [2] Department for Clinical and Health Psychology, University of Vienna, Vienna, Austria, [3] First Department of Psychiatry and Psychotherapeutic Medicine, Klinik Hietzing, Vienna, Austria

Background: Cognitive deficits are known as a core feature in bipolar disorder. Persisting neurocognitive impairment is associated with low psychosocial functioning. The aim of this study was to identify potential cognitive, clinical and treatment-dependent predictors for functional impairment, symptom severity and early recurrence in bipolar patients, as well as to analyze neurocognitive performance compared to healthy controls.

Methods: Forty three remitted bipolar patients and 40 healthy controls were assessed with a neurocognitive battery testing specifically attention, memory, verbal fluency and executive functions. In a randomized controlled trial, remitted patients were assigned to two treatment conditions as add-on to state-of-the-art pharmacotherapy: cognitive psychoeducational group therapy over 14 weeks or treatment-as-usual. At 12 months after therapy, functional impairment and severity of symptoms were assessed.

Results: Compared to healthy controls, bipolar patients showed lower performance in executive function (perseverative errors $p < 0.01$, categories correct $p < 0.001$), sustained attention (total hits $p < 0.001$), verbal learning (delayed recall $p < 0.001$) and verbal fluency (p-words $p < 0.002$). Cognitive psychoeducational group therapy and attention predicted occupational functioning with a hit ratio of 87.5%. Verbal memory recall was found to be a predictor for symptom severity (hit ratio 86.8%). Recurrence in the follow-up period was predicted by premorbid IQ and by years of education (hit ratio 77.8%).

Limitations: Limitations of the present study result mainly from a small sample size. The extent of cognitive impairment appears to impact occupational disability, clinical outcome as well as recurrence rate. This result must be interpreted with caution because statistical analysis failed to show higher significance.

Conclusions: Bipolar patients benefit from cognitive psychoeducational group therapy in the domain of occupational life. Deficits in sustained attention have an impact on occupational impairment. Implications for treatment strategies are discussed. Further evaluation in larger studies is needed.

Keywords: bipolar disorder, cognitive function, psychosocial functioning, occupational impairment, symptom severity, recurrence, cognitive psychoeducational group therapy

OPEN ACCESS

Edited by:
Andreas Reif,
University Hospital Frankfurt, Germany

Reviewed by:
Martin Schäfer,
Kliniken Essen-Mitte, Germany
Harald Scherk,
Vitos Klinikum Riedstadt, Germany

***Correspondence:**
Gabriele Sachs
gabriele.sachs@meduniwien.ac.at

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *27 January 2020*
Accepted: *29 October 2020*
Published: *23 November 2020*

Citation:
Sachs G, Berg A, Jagsch R, Lenz G and Erfurth A (2020) Predictors of Functional Outcome in Patients With Bipolar Disorder: Effects of Cognitive Psychoeducational Group Therapy After 12 Months. Front. Psychiatry 11:530026. doi: 10.3389/fpsyt.2020.530026

INTRODUCTION

Growing evidence suggests a considerable gap between syndromal and functional recovery among bipolar patients (1). Bipolar disorder (BD) is a severe mental illness; the course of the disease and the clinical outcome can be quite diverse. Treatment of BD often requires long-term medication and subsequently treatment adherence. There is a close relationship between treatment adherence and neurocognitive impairment (2). Neurocognitive deficits are known as a core feature in BD (3), including euthymic BD (4–6), subgroups (7) and are present during all stages (8) with a heterogeneous profile (4). Bipolar patients show poor performance in most cognitive domains, in processing speed, attention, verbal memory and executive functioning; in particular, context processing performance and associative learning are impaired (9, 10). Cognitive deficits are similar in bipolar I and bipolar II patients (11). Bipolar patients with psychosis exhibited more poorly on memory and executive function and had lower psychosocial functioning predicting limited recovery (12). There is not enough evidence so far for cognitive deficits being progressive in BD. A meta-analytic study did not support the hypothesis of a progressive decline of cognitive deficits (13). Cognitive dysfunction seems to be stable over time, only dysfunction in verbal recall was found to show a progressive course in a 5-year follow-up study (14). Medial temporal dysfunction (15) and reduced white matter integrity (16) have been suggested to be involved with verbal memory impairment early in the course of bipolar I disorder.

Psychosocial dysfunction may differ when patients with first- and multiple-episode BD are compared. Repeated episodes may contribute to higher impairment in multiple areas of psychosocial functioning. Clinical factors such as depressive symptoms seem to have a negative impact on functioning (17). Persisting neurocognitive impairments are also found to be associated with low psychosocial functioning (18–20), specifically with significant impairment in work, family and social life, beyond the acute phases of the illness and depending on the patient's own evaluations of their subjective functioning (21).

There is a need for further knowledge regarding predictors of the course of the disorder. Previous number of mixed episodes, subdepressive symptomatology, number of hospitalizations and older age were found to predict functional outcome. Bonnín et al. (22) demonstrated that subdepressive symptomatology together with neurocognitive impairments related to verbal memory and executive functions are predictor variables of long-term functional outcome in BD. The number of hospitalizations for depressive episodes and illness duration were associated with a reduction in occupational functioning in patients suffering from BD (23). Ryan et al. (24) examined impact of cognition on work status and underemployment in euthymic BD patients. Patients with BD who have better cognitive functioning are more likely to be employed. After accounting for number of mood episodes patients with BD who are unemployed/unable to work have greater difficulties processing emotional information and on executive tasks comprising a shifting or interference resolution component compared to BD patients who are employed. Bonnín et al. (25) examined predictors of functional outcome after a manic episode and showed that number of past depressive episodes, psychotic symptoms at index episode, and Body Mass Index (BMI) predict worse outcome after 6 months follow-up.

There is evidence that maintenance pharmacotherapy in conjunction with psychological interventions can improve the outcome (26). Adjunctive psychosocial interventions (27–36), including web-based and mobile approaches have been suggested to enhance symptomatic and functional outcome (37–43) in patients with BD -comprising adolescents (44)-, as well as in patients with subthreshold manifestations such as cyclothymic disorder (45). Presence of mixed episodes, full medication adherence and therapeutic blood levels of mood stabilizers were found predictive to attend a psychoeducation program (46). In a study with 55 patients with BD I and II in remission, 16-session psychoeducation seemed to be ineffective to prevent mood episodes or improve functioning (47). Functional remediation, a novel group intervention, showed efficacy in improving the functional outcome of a sample of euthymic bipolar patients as compared with treatment as usual (48, 49). Improvement in psychosocial functioning after functional remediation has been shown to be maintained after 1-year follow-up (50).

Clinical features and cognition related to functional outcome may have important effects on the overall therapeutic outcome. There is little evidence which clinical and neurocognitive variables would best predict the functional outcome in BD patients.

Aim of the present study was to identify potential cognitive, clinical and treatment-dependent predictors on functional impairment, symptom severity and early recurrence in patients with BD. As an additional predictor, the impact of cognitive psychoeducational group therapy [CPEGT, (51)] on psychosocial function was explored. Furthermore, it was assessed whether bipolar patients and healthy controls differ regarding neurocognitive performance in executive functions and sustained attention.

METHODS

Participants

Remitted bipolar patients were recruited consecutively from psychiatric outpatient and inpatient units at the Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria ($N = 43$) with the following inclusion criteria: age between 18 and 65 years, diagnosis of bipolar I or II disorder according to DSM-IV TR criteria using the Structured Clinical Interview for DSM-IV (SCID) (52) and the MINI [Neuropsychiatric Interview, (53)], at least two episodes in the last 3 years or three episodes in the last 5 years, ongoing medication with mood stabilizers and remission. Remission was defined by the following scores: Beck Depression Rating Scale <18 [BDI, (54)], Manie-Selbstbeurteilungsskala <14 [MSS: German version of the Self-Report Manic Inventory, SRMI, (55)], Bech Rafaelsen Mania Scale <9, [BRMAS, (56)], Bech Rafaelsen Melancholia Scale <26 [BRMES, (57)].

Exclusion criteria were intellectual disability, history of substance abuse, neurological disease, as well as any medical condition that could affect neuropsychological performance.

Patients were also excluded if they had participated in any structured psychological intervention, such as psychoeducation or cognitive remediation, within the past 2 years.

To assess neurocognitive performance in bipolar patients in comparison to healthy volunteers, 40 controls matched by age, gender and years of education were included into the study. Using the MINI it was ensured that the controls had no antecedent of neurological disease, no current diagnosis or history of psychiatric illness, current or previous alcohol/substance dependence or abuse, and that they were not taking psychotropic medication.

All participants, patients and controls, were fluent in German. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Vienna University Hospital Ethics Committee. All subjects received extensive information about the study and gave written informed consent for their participation before they were enrolled in the study.

Assessments

Demographical and clinical assessment: In addition to the SCID and MINI, all patients were evaluated with BDI, MSS, BRMES, and BRMAS.

Demographical and clinical information were obtained from clinical charts and patient interviews (age, gender, years of education, duration of illness, bipolar subtype, number of manic, hypomanic and depressive episodes, history of psychosis, current medication). The severity of symptoms was assessed using the Clinical Global Impression scale [CGI, (58)].

Functional impairment in areas of vocational, social and family was rated applying the Sheehan Disability Scale [SDS, (59)].

Neuropsychological assessment: At baseline bipolar patients completed a neurocognitive test battery including different tasks divided into cognitive domains: estimated premorbid IQ, using a German multiple choice vocabulary test, the Mehrfachwahl-Wortschatz-Test [MWT, (60)]; attention/vigilance, which was evaluated by the Continuous Performance Test, Identical Pairs [CPT-IP, (61)]; executive function (set shifting, planning and response inhibition) using the Computerized Wisconsin Card Sorting Test [WCST, (62)]; verbal learning and memory which were assessed by the Verbal Learning and Memory Test [VLMT, (63)] and verbal fluency using the Regensburger Word Fluency Test [RWT, (64)].

Reassessment: Patients underwent clinical and functional reassessment after completion of the intervention (14 weeks after baseline evaluation). Furthermore, a follow-up assessment was performed after 12 months.

At 12 months functional impairment in areas of vocational, social and family life was assessed applying the SDS, severity of symptoms was rated using the CGI. The recurrence rate was established. Recurrence was diagnosed when full DSM-IV TR criteria for a new affective episode were met; adherence toward psychopharmacology was measured using the Medication Compliance Questionnaire [MCQ, (65)].

Interventions

Of the 43 bipolar patients, 19 (12 female) were randomly assigned to the intervention group and 24 to the treatment as usual (14 female). There were no significant differences between the groups with regard to age, gender, BD I/BD II, rapid cycling, duration of illness, number of episodes, education, being in a job or current medication (choice of mood stabilizer, taking an antipsychotic). All 43 patients received state-of-the-art pharmacotherapy and completed the study.

Patients were randomized to either cognitive psychoeducational group therapy (CPEGT) (51, 66) over 14 weeks or to treatment as usual (TAU information group).

CPEGT consisted of 14 sessions; the duration of each session was 90 min. The contents of CPEGT were distributed in the following way: session 1–introduction and overview, session 2–explanatory models of bipolar disorders, session 3–pharmacotherapy, session 4–side effects of medications, session 5–depression I–symptoms and coping strategies, session 6–depression II—increase of pleasant activities, session 7–depression III—modification of depressive cognitive patterns, session 8–depression IV–relapse prevention, session 9–mania I–symptoms and coping strategies, session 10–mania II–relapse prevention, session 11–healthy lifestyle I–regular rhythm of life without alcohol and drugs, session 12–healthy lifestyle II—the "Life Chart Method," session 13–healthy lifestyle III–goal attainment and communication strategies, session 14–review.

Additionally, between two and four sessions were performed with relatives.

Patients in the control group also had regular group sessions. The thematic focus was on reading a book about BD ["Sturzfliegen" by Vasak and Katschnig, (67)]. In addition, three questions and answers sessions were provided. Booster sessions were offered after 6 and 9 months for both treatment and control group.

Statistical Analysis

Data were analyzed using the Statistical Package of Social Sciences (SPSS Inc. 19th Version, Chicago, IL, USA). Differences in demographic characteristics and neurocognitive measures between patients with bipolar disorder and controls were studied using independent *t*-test for continuous variables. Chi–square was used to examine categorial data. Pearson correlations were calculated to identify which demographic, clinical and neurocognitive variables were linked to functional impairment (three domains assessed by the SDS), symptom severity (CGI) and recurrence rate (number of episodes in the follow-up period of 12 months). The demographic variables were age, gender, years of education. The clinical variables were CPEGT, duration of illness, BDI, MSS, number of affective episodes in the 12 months prior to the start of the study, history of psychosis, current medication. The neuropsychological variables were premorbid IQ (MWT), attention/vigilance (CPT-IP, CPT –IP total hits, total false), WCST categories (categories correct, perseverative errors, verbal learning and memory (VLMT, immediate recall, delayed recall) and verbal fluency (RWT, *p*-words, *s*-words).

All significant variables (demographic, clinical and neurocognitive) that were found to correlate with functioning,

CGI and recurrence rate were introduced in a five backwards stepwise logistic regression analyses. Additional variables from the literature, including correlations between clinical, neurocognitive measures and functional outcome, were considered (23). Backward (Wald) logistic regressions were used to predict functioning, CGI and recurrence rate and estimate percentage variance accounted for by variables of interest.

Level of significance was set at ≤ 0.05.

RESULTS

Demographic and Clinical Characteristics

Thirty three patients with bipolar I disorder and 10 patients with bipolar II disorder were included; of the 43 bipolar patients seven were rapid cyclers. The age (mean ± SD) was 42.2 ± 10.9 years, the years of education 16.0 ± 4.0. The average duration of illness was 15.3 ± 10.3 years; the number of affective episodes in the 12 months prior to the start of the study was 3.4 ± 2.4 [0–8]. Fifteen patients (34.9%) had a history of psychotic symptoms, 26 (60.5%) were female. All 43 patients received at least one mood stabilizer (lamotrigine 17, sodium valproate/valproic acid 16, lithium carbonate 11, carbamazepine 3); additional medications were atypical antipsychotics (22 patients), antidepressants (10) and hypnotic drugs (benzodiazepines/zolpidem: 5). For an overview of all demographic, clinical and neurocognitive characteristics see **Table 1**.

TABLE 1 | Demographic, clinical and neurocognitive characteristics of patients with BD at baseline ($n = 43$).

Variables	Mean	SD
Age, years	42.2	10.9
Education, years	16.0	4.0
Duration of illness, years	15.3	10.3
Number of affective episodes in the 12 months prior to the start of the study	3.4	2.4
	N	**%**
Female	26	60.5
Male	17	39.5
History of psychotic symptoms	15	34.9
Medication		
Lithium carbonate	11	25.6
Sodium valproate/valproic acid	16	37.2
Lamotrigine	17	39.5
Carbamazepine	3	7.0
Atypical antipsychotics	22	51.1
Antidepressants (SSRI)	10	23.3
Hypnotic drugs (benzodiazepines/zolpidem)	5	11.6
Neurocognition	**Mean**	**SD**
MWT	30.5	4.2
WCST total correct	68.3	13.9
WCST perseverative errors	19.2	18.7
CPT-IP Total hits	0.47	0.2
CPT-IP Total false	0.16	0.1
VMLT immediate recall	9.95	2.8
VMLT delayed recall	7.04	2.0
RWT *p*-words	12.60	4.8
RWT *s*-words	21.11	3.8

MWT, Mehrfach-Wortschatz-Test: assessment of premorbid intelligence; WCST, Wisconsin Card sorting test; CPT-IP, Continuous Performance Test, identical pairs; VMLT, Verbal Learning and Memory Test; RWT, Regensburger Word Fluency Test.

Neurocognitive Performance in Bipolar Patients

Comparison With Healthy Controls

Neurocognitive performance was compared to 40 healthy controls matched by age, sex and years of education. Compared to healthy controls, patients with BD showed lower performance in executive functions as measured by the WCST (perseverative errors $p \leq 0.01$, categories correct $p \leq 0.001$), in sustained attention (CPT-IP total hits $p \leq 0.001$), in verbal learning (VLMT delayed recall $p \leq 0.001$) and verbal fluency (RWT *p*-words $p \leq 0.002$).

Pearson Correlations of Demographic, Clinical, and Neurocognitive Characteristics of Patients With BD (Table 2)

CPT-IP false hits ($r = 0.36$, $p = 0.023$) and WCST total correct ($r = 0.41$; $p = 0.009$) correlated with number of affective episodes in the 12 months prior to the start of the study.

Effects of Therapy

Effects of Therapy on Number of Episodes

As previously communicated (68, 69), after 14 weeks of therapy an improvement in illness concepts and adherence was observed in both the CPEGT group and the TAU group; after further 12 months the number of manic episodes was significantly decreased in both groups as compared to the 12 months before the intervention. A significant reduction of the number of depressive episodes was observed after CPEGT; after TAU the number of depressive episodes remained unchanged.

Functional Impairment, Severity of Symptoms, and Early Recurrence: Pearson Correlations

SDS score impairment in areas of vocational functioning correlated with CPEGT ($r = 0.381$; $p = 012$) and CPT-IP (false $r = -0.411$; $p = 0.006$). Scores in CGI correlated with verbal learning immediate recall ($r = 0.338$, $p = 0.038$) and verbal learning delayed recall ($r = 0.336$, $p = 0.039$). Finally, recurrence was found to correlate with verbal learning immediate recall ($r = 0.381$, $p = 0.018$) and verbal learning delayed recall ($r = 0.397$, $p = 0.014$).

Regression Analyses

As shown in **Table 3**, CPEGT and CPT-IP (total false) predicted the amount of occupational impairment (hit ratio of 87.5%). VLMT delayed recall was found to be a predictor for symptom severity as measured by CGI (hit ratio 86.8%). Recurrence in the follow-up period of 12 months was predicted by MWT and years of education (hit ratio 77.8%).

Of these predictors reaching the previously defined significance level of $p \leq 0.05$, CPEGT (with regard to

TABLE 2 | Pearson correlations of demographic, clinical and neurocognitive characteristics of patients with BD at baseline ($n = 43$).

	MWT	CPT-IP hits	CPT-IP false	WCST total	WCST persev.	VMLT immediate	VMLT delay	RWT *p*-words	RWT *s*-words
Gender	−0.12	−0.01	0.06	0.08	0.15	0.22	0.11	0.22	−0.10
Age	0.30*	−0.17*	−0.07	−0.00	0.20*	−0.23	−0.33*	0.18	0.10
Years of education	0.24*	−0.01	−0.14	0.01	−0.13	0.01	−0.18	0.16	0.22
Illness duration	0.25	−0.12	0.09	0.10	0.12	−0.13	−0.04	0.26	−0.10
Number of episodes	0.00	0.14	0.36*	0.41**	−0.17	−0.11	−0.04	0.01	−0.21
Psychosis	−0.34*	0.15	−0.10	0.15	−0.11	−0.02	0.11	−0.01	0.09
Atypical antipsychotics	−0.26	−0.17	−0.08	0.01	−0.04	−0.01	0.14	−0.05	0.03

*$p \leq 0.05$, **$p \leq 0.01$.

MWT, Mehrfach-Wortschatz-Test: assessment of premorbid intelligence; CPT-IP hits, continuous performance test total hits; CPT-IP false, continuous performance test total false; WCST total, Wisconsin Card sorting test, total correct; WCST persev., Wisconsin Card sorting test, perseverative errors; VMLT immediate, Verbal Learning and Memory Test, immediate recall; VMLT delay, Verbal Learning and Memory Test, delayed recall; RWT pwords, Regensburger Word Fluency Test p-words; RWT s-words, Regensburger Word Fluency Test s-words; Number of episodes, number of affective episodes in the 12 months prior to the start of the study.

TABLE 3 | Functional impairment, severity of symptoms and early recurrence: results of regression analyses.

	Regression coefficient B	Wald	Exp(B)	*p*
Occupational impairment (SDS)				
Cognitive psychoeducational group therapy (CPEGT)	−2.30	6.68	0.10	0.010**
CPT-IP total false	−11.73	5.45	0.00	0.020*
CGI				
Atypical antipsychotics	−1.82	3.03	0.16	0.082
VLMT delayed recall	0.48	4.24	1.62	0.039*
Early recurrence				
VLMT delayed recall	0.34	3.64	1.41	0.056
MWT	0.36	4.93	1.43	0.026*
Years of education	−0.38	5.68	0.69	0.017*

*Significance level was set at *$p \leq 0.05$, **$p \leq 0.01$.

SDS, Sheehan Disability Scale at 12-month follow-up; CPT-IP total false, Continuous Performance Test total false at baseline; CGI, Clinical Global Impression scale at 12-month follow-up; early recurrence, occurrence of an affective episode within the 12-month followup period; VLMT delayed recall, Verbal Learning and Memory Test, delayed recall at baseline; MWT, Mehrfach-Wortschatz-Test: assessment of premorbid intelligence at baseline.

occupational impairment) was the only predictor reaching a significance level of $p \leq 0.01$.

No significant predictors were found for social disability and family-life impairment.

DISCUSSION

Patients with BD are impaired in the domains of attention, verbal memory and executive functions (4). The results of our study confirm these findings showing specific deficits in sustained attention, executive function, verbal memory and also in verbal fluency. Remitted bipolar patients had clinically significant cognitive deficits compared to healthy controls. The patients in this study were characterized by a particularly long duration of illness (average of 15.3 years). Looking at the association between number of affective episodes in the 12 months prior to the start of the study and cognitive function a significant correlation was found between number of affective episodes and impairment in the domain of sustained attention (continuous performance test: total false). Unfortunately, due to the small sample size ($N = 43$), it was not possible to assess which type of past episodes (depressive, manic or mixed) led to the reduction of sustained attention in these remitted patients. Clearly, further research on neurocognitive dysfunction in rapid cycling bipolar disorder (70) is suggested by our finding. Data on cognitive impairment in bipolar patients might have important clinical and therapeutic implications and provide support for the necessity to use neurocognitive assessments in routine clinical examination in patients with BD (2–4, 71).

Cognitive deficits might be also an important factor for the success or failure of therapeutic interventions, both pharmacological and non-pharmacological. As cognitive deficits are a core feature in BD, recommendation should be given for specific cognitive interventions in subgroups of patients with clinically significant cognitive impairments. The effectiveness of different psychosocial interventions might be influenced by cognitive function: so far this has not been thoroughly studied to our knowledge. In this study bipolar patients were offered a cognitive psychoeducational group therapy program [CPEGT, (51)]. This study reports data from a logistic regression analysis looking at the impact of this training on functional outcome and recurrence rate. The sample in this study was characteristic in that patients showed a long duration of illness and a corresponding cognitive impairment.

Our study shows a significant impact of CPEGT on functional outcome in patients with BD; to a lesser degree also CPT-IP (false hits) predicted occupational impairment. These findings are clearly preliminary due to the small sample size, but CPEGT seems to be a useful additional therapy to medication to treat patients with long duration of illness. All patients completed the 14-week intervention group, which is consistent with a high acceptability of the treatment strategy. Our study on CPEGT

supports the concept that specific psychosocial interventions targeting specific aspects of BD can be beneficial (72, 73).

Very little is known about the longitudinal course of cognitive deficits and the neuropsychological underpinnings of the dynamics of BD (74). Improving the knowledge on the development in time of cognitive dysfunction in BD [role of depressive episodes, role of manic episodes, role of mixed episodes, role of specific medications for better or for worse, role of cognitive remediation programs, role of inflammatory mediators (75), role of genetic factors (76, 77)] would contribute to identify targets for treatment, to determine possible subtypes of the disorder, and to develop better therapeutic strategies (78, 79). The metaanalytic study by Samamé et al. (13) showed that cognitive deficits remain stable after a follow-up period of 4.62 years. In a study of Demant et al. (80) no significant effect of shortterm cognitive remediation on cognitive dysfunction was found. In our study verbal learning memory deficits at baseline showed correlation with severity of symptoms after 12 months; we therefore suggest that specific intensive and individualized cognitive training may be indicated for this chronic subgroup of patients with BD.

LIMITATIONS

Limitations of the present study clearly result from the small sample size. While the number of affective episodes in the 12 months prior to the start of the study was correlated to disturbances in sustained attention, it was not possible to assess which polarity of episodes was responsible for this effect.

CONCLUSION

Compared to healthy controls bipolar patients show cognitive impairment.

The extent of cognitive impairment appears to impact occupational disability and clinical outcome.

Occupational impairment was reduced by cognitive psychoeducational group therapy (CPEGT).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical University of Vienna, Austria. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GS wrote the manuscript, performed the statistics, coordinated, and performed the clinical study. AB contributed to the realization of group therapy and cognitive tests. RJ performed the statistics. GL planned, coordinated, and performed the clinical study. AE wrote the manuscript, reviewed the existing literature, and contributed to the recruitment of patients. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Tohen M, Zarate CA Jr., Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry*. (2003) 160:2099–107. doi: 10.1176/appi.ajp.160.12.2099
2. Martinez-Aran A, Scott J, Colom F, Torrent C, Tabares-Seisdedos R, Daban C, et al. Treatment nonadherence and neurocognitive impairment in bipolar disorder. *J Clin Psychiatry*. (2009) 70:1017–23. doi: 10.4088/JCP.08m04408
3. Sachs G, Schaffer M, Winklbaur B. Cognitive deficits in bipolar disorder. *Neuropsychiatr*. (2007) 21:93–101. doi: 10.5414/NEPBand21093
4. Martino DJ, Strejilevich SA, Marengo E, Ibanez A, Scapola M, Igoa A. Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder. *J Affect Disord*. (2014) 167:118–24. doi: 10.1016/j.jad.2014.05.059
5. Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JT, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand*. (2013) 128:149–62. doi: 10.1111/acps.12133
6. Baş TÖ, Poyraz CA, Baş A, Poyraz BÇ, Tosun M. The impact of cognitive impairment, neurological soft signs and subdepressive symptoms on functional outcome in bipolar disorder. *J Affect Disord*. (2015) 174:336–41. doi: 10.1016/j.jad.2014.12.026
7. Aminoff SR, Hellvin T, Lagerberg TV, Berg AO, Andreassen OA, Melle I. Neurocognitive features in subgroups of bipolar disorder. *Bipolar Disord*. (2013) 15:272283. doi: 10.1111/bdi.12061
8. Torres IJ, Kozicky J, Popuri S, Bond DJ, Honer WG, Lam RW, et al. 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar Disord*. (2014) 16:159–71. doi: 10.1111/bdi.12184
9. Brambilla P, Macdonald AW III, Sassi RB, Johnson MK, Mallinger AG, Carter CS, et al. Context processing performance in bipolar disorder patients. *Bipolar Disord*. (2007) 9:230–7. doi: 10.1111/j.1399-5618.2007.00398.x
10. Brambilla P, Cerruti S, Bellani M, Perlini C, Ferro A, Marinelli V, et al. Shared impairment in associative learning in schizophrenia and bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. (2011) 35:1093–9. doi: 10.1016/j.pnpbp.2011.03.007
11. Palsson E, Figueras C, Johansson GM, Ekman CJ, Hultman B, Östlind J, et al. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. *BMC Psychiatry*. (2013) 13:1–9. doi: 10.1186/1471-244X-13-165
12. Levy B, Medina AM, Weiss RD. Cognitive and psychosocial functioning in bipolar disorder with and without psychosis during early remission from an acute mood episode: a comparative longitudinal study. *Compr Psychiatry*. (2013) 54:618–26. doi: 10.1016/j.comppsych.2012.12.018
13. Samamé C, Martino DJ, Strejilevich SA. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. *J Affect Disord*. (2014) 164:130–8. doi: 10.1016/j.jad.2014.04.028
14. Santos JL, Aparicio A, Bagney A, Sanchez-Morla EM, Rodriguez-Jimenez R, Mateo J, et al. A five-year follow-up study of neurocognitive functioning in bipolar disorder. *Bipolar Disord*. (2014) 170:334–41. doi: 10.1111/bdi.12215
15. Chakrabarty T, Kozicky JM, Torres IJ, Lam RW, Yatham LN. Verbal memory impairment in new onset bipolar disorder: relationship with frontal and medial temporal morphology. *World J Biol Psychiatry*. (2015) 16:249–60. doi: 10.3109/15622975.2014.1000373
16. Bauer IE, Ouyang A, Mwangi B, Sanches M, Zunta-Soares GB, Keefe RS, et al. Reduced white matter integrity and verbal fluency impairment in young adults with bipolar disorder: a diffusion tensor imaging study. *J Psychiatr Res*. (2015) 62:115–22. doi: 10.1016/j.jpsychires.2015.01.008

17. Rosa AR, González-Ortega I, González-Pinto A, Echeburúa E, Comes M, Martínez-Àran A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. *Acta Psychiatr Scand*. (2012) 125:335–41. doi: 10.1111/j.1600-0447.2011.01830.x
18. Wingo AP, Harvey PD, Baldessarini RJ. Neurocognitive impairment in bipolar disorder patients: functional implications. *Bipolar Disord*. (2009) 11:113–25. doi: 10.1111/j.1399-5618.2009.00665.x
19. Sanchez-Moreno J, Martinez-Aran A, Tabarés-Seisdedos R, Torrent C, Vieta E, AyusoMateos JL. Functioning and disability in bipolar disorder: an extensive review. *Psychother Psychosom*. (2009) 78:285–97. doi: 10.1159/000228249
20. Vlad M, Raucher-Chéné D, Henry A, Kaladjian A. Functional outcome and social cognition in bipolar disorder: is there a connection? *Eur Psychiatry*. (2018) 52:116–25. doi: 10.1016/j.eurpsy.2018.05.002
21. Van Rheenen TE, Rossell SL. Objective and subjective psychosocial functioning in bipolar disorder: an investigation of the relative importance of neurocognition, social cognition and emotion regulation. *J Affect Disord*. (2014) 162:134–41. doi: 10.1016/j.jad.2014.03.043
22. Bonnín CM, González-Pinto A, Solé B, Reinares M, González-Ortega I, Alberich S, et al. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. *J Affect Disord*. (2014) 160:50–4. doi: 10.1016/j.jad.2014.02.034
23. Schoeyen HK, Melle I, Sundet K, Aminoff SR, Hellvin T, Auestad BH, et al. Occupational outcome in bipolar disorder is not predicted by premorbid functioning and intelligence. *Bipolar Disord*. (2013) 15:294–305. doi: 10.1111/bdi.12056
24. Ryan KA, Vederman AC, Kamali M, Marshall D, Weldon AL, McInnis MG, et al. Emotion perception and executive functioning predict work status in euthymic bipolar disorder. *Psychiatry Res*. (2013) 210:472–8. doi: 10.1016/j.psychres.2013.06.031
25. Bonnín CM, Reinares M, Hidalgo-Mazzei D, Undurraga J, Mur M, Sáez C, et al. Predictors of functional outcome after a manic episode. *J Affect Disord*. (2015) 182:121–5. doi: 10.1016/j.jad.2015.04.043
26. Solé B, Jiménez E, Torrent C, Reinares M, Bonnín CDM, Torres I, et al. Cognitive impairment in bipolar disorder: treatment and prevention strategies. *Int J Neuropsychopharmacol*. (2017) 20:670–80. doi: 10.1093/ijnp/pyx032
27. Panhorst H, Ramacher P, Wagener R, Erfurth A. Psychoedukation bei bipolaren Störungen. *Nervenheilkunde*. (2001) 20(Suppl. 2):34–8.
28. Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry*. (2003) 60:402–7. doi: 10.1001/archpsyc.60.4.402
29. Erfurth A, Dobmeier G, Zechendorff M. *Kurzpsychoedukation für bipolare Patienten*. Stuttgart: Thieme Verlag (2005).
30. Michalak EE, Yatham LN, Wan DD, Lam RW. Perceived quality of life in patients with bipolar disorder. Does group psychoeducation have an impact? *Can J Psychiatry*. (2005) 50:95–100. doi: 10.1177/070674370505000204
31. Fiorillo A, Del Vecchio V, Luciano M, Sampogna G, De Rosa C, Malangone C, et al. Efficacy of psychoeducational family intervention for bipolar I disorder: a controlled, multicentric, real-world study. *J Affect Disord*. (2014) 172C:291–9. doi: 10.1016/j.jad.2014.10.021
32. Barnes CW, Hadzi-Pavlovic D, Wilhelm K, Mitchell PB. A web-based preventive intervention program for bipolar disorder: outcome of a 12-months randomized controlled trial. *J Affect Disord*. (2015) 174:485–92. doi: 10.1016/j.jad.2014.11.038
33. Bond K, Anderson IM. Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. *Bipolar Disord*. (2015) 17:349–62. doi: 10.1111/bdi.12287
34. Depp CA, Ceglowski J, Wang VC, Yaghouti F, Mausbach BT, Thompson WK, et al. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. *J Affect Disord*. (2015) 174:23–30. doi: 10.1016/j.jad.2014.10.053
35. Tsapekos D, Seccomandi B, Mantingh T, Cella M, Wykes T, Young AH. Cognitive enhancement interventions for people with bipolar disorder: a systematic review of methodological quality, treatment approaches, and outcomes. *Bipolar Disord*. (2019) 22:216–30. doi: 10.1111/bdi.12848
36. Tsapekos D, Strawbridge R, Cella M, Wykes T, Young AH. Do we really need a "new" cognitive therapy for bipolar disorder? Paradigm refinements and treatment mechanisms for cognitive remediation. *Bipolar Disord*. (2020) 22:213–5. doi: 10.1111/bdi.12890
37. Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. *Am J Psychiatry*. (2008) 165:1408–19. doi: 10.1176/appi.ajp.2008.08040488
38. Dijk SV, Jeffrey J, Katz MR. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. *J Affect Disord*. (2013) 145:386–93. doi: 10.1016/j.jad.2012.05.054
39. Lauder S, Chester A, Castle D, Dodd S, Gliddon E, Berk L, et al. A randomized head to head trial of MoodSwings.net.au: an Internet based self-help program for bipolar disorder. *J Affect Disord*. (2015) 171:13. doi: 10.1016/j.jad.2014.08.008
40. van der Voort TY, van Meijel B, Goossens PJ, Hoogendoorn AW, Draisma S, Beekman A, et al. Collaborative care for patients with bipolar disorder: randomised controlled trial. *Br J Psychiatry*. (2015) 206:393–400. doi: 10.1192/bjp.bp.114.152520
41. Zyto S, Jabben N, Schulte PF, Regeer BJ, Kupka RW. A pilot study of a combined group and individual functional remediation program for patients with bipolar I disorder. *J Affect Disord*. (2016) 194:9–15. doi: 10.1016/j.jad.2016.01.029
42. Haffner P, Quinlivan E, Fiebig J, Sondergeld LM, Strasser ES, Adli M, et al. Improving functional outcome in bipolar disorder: a pilot study on metacognitive training. *Clin Psychol Psychother*. (2018) 25:50–8. doi: 10.1002/cpp.2124
43. Zhang Y, Ma X, Liang S, Yu W, He Q, Zhang J, et al. Social cognition and interaction training (SCIT) for partially remitted patients with bipolar disorder in China. *Psychiatry Res*. (2019) 274:377–82. doi: 10.1016/j.psychres.2019.03.002
44. Weintraub MJ, Axelson DA, Kowatch RA, Schneck CD, Miklowitz DJ. Comorbid disorders as moderators of response to family interventions among adolescents with bipolar disorder. *J Affect Disord*. (2019) 246:754–62. doi: 10.1016/j.jad.2018.12.125
45. Perugi G, Hantouche E, Vannucchi G, Pinto O. Cyclothymia reloaded: a reappraisal of the most misconceived affective disorder. *J Affect Disord*. (2015) 183:119–33. doi: 10.1016/j.jad.2015.05.004
46. Cakir S, Bensusan R, Akca ZK, Yazici O. Does a psychoeducational approach reach targeted patients with bipolar disorder? *J Affect Disord*. (2009) 119:190–3. doi: 10.1016/j.jad.2009.08.016
47. de Barros Pellegrinelli K, de O Costa LF, Silval KI, Dias VV, Roso MC, Bandeira M, et al. Efficacy of psychoeducation on symptomatic and functional recovery in bipolar disorder. *Acta Psychiatr Scand*. (2013) 127:153–8. doi: 10.1111/acps.12007
48. Torrent C, Bonnín CM, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am J Psychiatry*. (2013) 170:852–9. doi: 10.1176/appi.ajp.2012.12070971
49. Solé B, Bonnín CM, Mayoral M, Amann BL, Torres I, González-Pinto A, et al. Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. *Eur Neuropsychopharmacol*. (2015) 25:257–64. doi: 10.1016/j.euroneuro.2014.05.010
50. Bonnín CM, Torrent C, Arango C, Amann BL, Solé B, González-Pinto A, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *Br J Psychiatry*. (2016) 208:87–93. doi: 10.1192/bjp.bp.114.162123
51. Schaub A, Bernhard B, Gauck L. *Kognitiv-psychoedukative Therapie bei bipolaren Erkrankungen. Ein Therapiemanual*. Göttingen: Hogrefe Verlag (2004).
52. First MG, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Patient Edition (SCID-P)*. New York, NY: Biometrics Research Department, State Psychiatric Institute (1995). doi: 10.1037/t07827-000
53. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, et al. The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview. *J Clin Psychiatry*. (1998) 59(Suppl. 20):22–33. doi: 10.1037/t18597-000

54. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. (1961) 4:561–71. doi: 10.1001/archpsyc.1961.01710120031004
55. Krüger S, Bräunig P, Shugar G. *Manie-Selbstbeurteilungsskala (MSS)*. Göttingen: Beltz (1997).
56. Bech P, Rafaelsen OJ, Kramp P, Bolwig TG. The mania rating scale: scale construct and inter-observer agreement. *Neuropharmacology*. (1978) 17:430–1. doi: 10.1016/0028-3908(78)90022-9
57. Licht RW, Qvitzau S, Allerup P, Bech P. Validation of the Bech–Rafaelsen Melancholia Scale and the Hamilton Depression Scale in patients with major depression: is the total score a valid measure of illness severity? *Acta Psychiatr Scand*. (2005) 111:144–9. doi: 10.1111/j.1600-0447.2004.00440.x
58. Guy W. *ECDEU Assessment Manual for Psychopharmacology-Revised (DHEW Publ No ADM 76-338)*. Rockville, MD: Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs (1976). p. 218–22.
59. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. (1996) 11(Suppl. 3):89–95. doi: 10.1097/00004850-199606003-00015
60. Lehrl S. *Manual MWT-B*. Erlangen: Straube (1977).
61. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Res*. (1988) 26:223–38. doi: 10.1016/0165-1781(88)90076-5
62. Heaton RK. *Wisconsin Card Sorting Test Manual*. Odessa, FL: Psychological Assessment Resources (1981).
63. Helmstaedter C, Lendt M, Lux S. *Verbaler Lern- und Merkfähigkeitstest (VLMT)*. Göttingen: Beltz (2001).
64. Aschenbrenner S, Rucha O, Lange KW. *Regensburger Wortflüssigkeitstest (RWT)*. Göttingen: Hogrefe Testzentrale (2001).
65. Lam DH, Bright J, Jones S, Hayward P, Schuck N, Chisholm D, et al. Cognitive therapy for bipolar illness - A pilot study of relapse prevention. *Cognit Ther Res*. (2000) 24:503–20. doi: 10.1023/A:1005557911051
66. Schaub A, Neubauer N, Bernhard B, Born C, Möller HJ, Grunze H. Cognitive psychoeducational group programme for bipolar disorder: pilot study with two-year follow up. *Fortschr Neurol Psychiatr*. (2013) 81(Suppl. 1):30–4. doi: 10.1055/s-0033-1335242
67. Vasak G, Katschnig H. *Sturzfliegen: Leben in Depressionen und Manien*. Zürich: Rüffer & Rub (2001).
68. Breit-Gabauer B, Berg A, Demelbauer S, Schrott A, Stampfer I, Lenz G. Prodromes and coping strategies in patients with bipolar disorder. *Verhaltenstherapie*. (2010) 20:183191. doi: 10.1159/000319447
69. Lenz, G. Cognitive-psychoeducative group-therapy vs. TAU with additional information group: a randomized controlled study. *Eur Psychiatry*. (2010) 25(Suppl. 1):19. doi: 10.1016/S0924-9338(10)70019-5
70. Erfurth A, Perugi G. Rapid cycling. In: Kasper S, Hirschfeld RMA, editors. *Handbook of Bipolar Disorder*. New York, London: Taylor & Francis (2005). p. 201–12.
71. Bauer IE, Keefe RS, Sanches M, Suchting R, Green CE, Soares JC. Evaluation of cognitive function in bipolar disorder using the Brief Assessment of Cognition in Affective Disorders (BAC-A). *J Psychiatr Res*. (2015) 60:81–6. doi: 10.1016/j.jpsychires.2014.10.002
72. Miziou S, Tsitsipa E, Moysidou S, Karavelas V, Dimelis D, Polyzoidou V, et al. Psychosocial treatment and interventions for bipolar disorder: a systematic review. *Ann Gen Psychiatry*. (2015) 14:19. doi: 10.1186/s12991-015-0057-z
73. Kim Y, Kwon A, Min D, Kim S, Jin MJ, Lee SH. Neurophysiological and psychological predictors of social functioning in patients with schizophrenia and bipolar disorder. *Psychiatry Investig*. (2019) 16:718–27. doi: 10.30773/pi.2019.07.28
74. Wessa M, Perlini C, Brambilla P. Neuropsychological underpinnings of the dynamics of bipolar disorder. *Epidemiol Psychiatr Sci*. (2015) 9:1–5. doi: 10.1017/S2045796015000098
75. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. *J Psychiatr Res*. (2014) 56:18–27. doi: 10.1016/j.jpsychires.2014.04.017
76. Frazier TW, Youngstrom EA, Frankel BA, Zunta-Soares GB, Sanches M, Escamilla M, et al. Candidate gene associations with mood disorder, cognitive vulnerability, and fronto-limbic volumes. *Brain Behav*. (2014) 4:418–30. doi: 10.1002/brb3.226
77. Budde M, Friedrichs S, Alliey-Rodriguez N, Ament S, Badner JA, Berrettini WH, et al. Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder. *Eur Neuropsychopharmacol*. (2019) 29:156–70. doi: 10.1016/j.euroneuro.2018.10.005
78. Breitborde NJ, Dawson SC, Woolverton C, Dawley D, Bell EK, Norman K, et al. A randomized controlled trial of cognitive remediation and dcycloserine for individuals with bipolar disorder. *BMC Psychol*. (2014) 2:41. doi: 10.1186/s40359-014-0041-4
79. Lahera G, Bayón C, Fe Bravo-Ortiz M, Rodríguez-Vega B, Barbeito S, Sáenz M, et al. Mindfulness-based cognitive therapy versus psychoeducational intervention in bipolar outpatients with sub-threshold depressive symptoms: a randomized controlled trial. *BMC Psychiatry*. (2014) 14:215. doi: 10.1186/s12888-014-0215-x
80. Demant KM, Vinberg M, Kessing LV, Miskowiak KW. Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: results of a randomised controlled trial. *PLoS ONE*. (2015) 10:e0127955. doi: 10.1371/journal.pone.0127955

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 11 January 2021
doi: 10.3389/fpsyt.2020.560138

Comorbid Bipolar Disorder and Migraine: From Mechanisms to Treatment

Jinfeng Duan[1], Rongmei Yang[2], Wenwen Lu[3], Lingfei Zhao[4], Shaohua Hu[1] and Chenxia Hu[5]**

[1] Key Laboratory of Mental Disorder's Management of Zhejiang Province, Department of Psychiatry, School of Medicine, First Affiliated Hospital, Zhejiang University, Hangzhou, China, [2] Department of Psychogeriatrics, Hangzhou Seventh People's Hospital, Hangzhou, China, [3] Department of Traditional Chinese Medicine, School of Medicine, First Affiliated Hospital, Zhejiang University, Hangzhou, China, [4] Key Laboratory of Kidney Disease Prevention and Control Technology, School of Medicine, First Affiliated Hospital, Zhejiang University, Hangzhou, China, [5] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, School of Medicine, First Affiliated Hospital, Zhejiang University, Hangzhou, China

OPEN ACCESS

Edited by:
Andreas Reif,
University Hospital Frankfurt, Germany

Reviewed by:
Mirko Manchia,
University of Cagliari, Italy
Christian Simhandl,
Sigmund Freud University
Vienna, Austria

***Correspondence:**
Shaohua Hu
dorhushaohua@zju.edu.cn
Chenxia Hu
11318093@zju.edu.cn

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 08 May 2020
Accepted: 02 December 2020
Published: 11 January 2021

Citation:
Duan J, Yang R, Lu W, Zhao L, Hu S and Hu C (2021) Comorbid Bipolar Disorder and Migraine: From Mechanisms to Treatment. Front. Psychiatry 11:560138. doi: 10.3389/fpsyt.2020.560138

Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of manic/hypomanic or depressive symptoms and euthymic periods, with some patients suffering a gradual deterioration of illness and consequent cognitive deficits during the late stage. Migraine is a disease generally without abnormal medical examinations, neurological examinations or laboratory studies, and the diagnosis is made based on the retrospective demonstration of headache features and groupings of disease-associated symptoms. The epidemiology of comorbid BD and migraine is high and it is obligatory to find effective treatments to improve the prognosis. Recent investigations demonstrated that the close relationship between BD and migraine significantly increased the rapid cycling rates of both BD and migraine in patients. Although the detailed mechanism is complex and largely unclear in comorbid BD and migrain, genetic factors, neurotransmitters, altered signaling pathways, disturbances of inflammatory cytokines, and mitochondrial dysfunction are risk factors of BD and migraine. Particularly these two diseases share some overlapping mechanisms according to previous studies. To this end, we call for further investigations of the potential mechanisms, and more efforts are underway to improve the treatment of people with comorbid BD and migraine. In this review, we provide an overview of the potential mechanisms in patients with BD or migraine and we further discuss the treatment strategies for comorbid BD and migraine and it is obligatory to find effective treatments to improve the prognosis. This work will provide insights for us to know more about the mechanisms of comorbid BD and migraine, provides new therapeutic targets for the treatment and give clinicians some guidance for more appropriate and beneficial treatment.

Keywords: bipolar disorder, migraine, mechanism, treatment, genetics, inflammation, neurotransmitter, mitochondrial dysfunction

INTRODUCTION

Bipolar disorder (BD) is a severe psychiatric disorder and characterized by recurrent episodes of manic/hypomanic (namely BD-I/BD-II, respectively) or depressive symptoms and euthymic periods, and some patients experience a gradual deterioration of illness and consequent cognitive deficits (1). Therefore, these 2 types of BD was distinguished according to the severity of manic symptoms. Furthermore, BD-II is not severe enough to cause social or occupational functional impairment or hospitalization; in contrast, manic and even psychotic symptoms are more severe in BD-I, and patients often require hospitalization. The incidence rate of symptomatic depression in patients with BD (BD-I or BD-II) are 3 times more than the incidence rate of mania or hypomania (2). The onset of BD occurs predominantly in adolescence or early adulthood. The lifetime prevalence of BD is appropriately 2.1% globally, and the prevalence of subthreshold forms is ∼2.4% (3). With a diagnosis of BD, life expectancy decreases by 9 years on average (4), and the completed suicide rates of men and women with BD are 7.8 and 4.9%, respectively (4, 5). After the development of complications related to BD, such as metabolic and cardiovascular diseases, patients with BD will consequently experience poor quality of life, impaired cognitive function, functional impairments and social impairments.

Migraine is a disease without abnormal medical examinations, neurological examinations or laboratory findings, and the diagnosis is made based on retrospective demonstration of headache features and groupings of disease-associated symptoms. Patients with migraine frequently experience episodic attacks, including recurrent headache, gastrointestinal symptoms, and autonomic nervous system symptoms (6). Migraine can also results in decreased quality of life, impaired cognitive function, disturbed brain function and social impairments (7). The prevalence rate of migraine in healthy individuals was 14% with the lifetime prevalence in men was 6%, and 17.6% in women in the United States (8, 9). Psychiatric disorders are common in multiple neurological disorders, migraine is one of the disorders with a high prevalence, and there is a heritable link between BD and migraine (10, 11). Even migraine is not caused by psychiatric illness, and a large proportion of people with migraine are not diagnosed with any comorbid psychiatric disorder. Parental migraine was associated with increased likelihood and a risk factor for offspring BD even in the absence of parental BD, the prevalence of migraine in the BD population may be as high as 39% and rapid cycling as a feature of bipolar disorder and comorbid migraine (10, 12, 13). BD and migraine share multiple similar risk factors, including genetic factors, environmental risk factors, oxidative stress and disturbances of inflammatory cytokines. Both diseases lead to decreased quality of life and multiple dysfunctions in humans (**Figure 1**). Patients with comorbid BD and migraine have poorer treatment outcomes and increased disability (14). In this review, we provide an overview of the potential mechanisms in patients with BD or migraine and we further discuss the overlapping mechanisms and treatment strategies for comorbid BD and migraine, the potential treatments for patients with comorbid BD and migraine, with the purpose of giving clinicians some guidance for more appropriate and beneficial treatment to the comorbidity.

Abbreviations: BD, bipolar disorder; GABA, gamma-amino butyric acid; GDNF, glial cell-derived neurotrophic factor; NT-3, neurotrophin-3; BDNF, brain-derived neurotrophic factor; IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; NO, nitric oxide; NF-κβ, nuclear factor-kappa β subunits; sTNFR1, soluble TNF-α receptor-1; sIL-6R, soluble IL-6 receptor; IL-1RA, IL-1 receptor antagonist; sIL-2R, soluble IL-2 receptor; TBARS, thiobarbituric acid reactive substances; GST, glutathione S-transferase; PET, positron emission tomography; FHM, familial hemiplegic migraine; PLA_2, phospholipase A_2; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; AA, arachidonic acid; TMS,transcranial magnetic stimulation; DLPFC, left dorsolateral prefrontal cortex.

METHODS

We conducted a systematic search of two major databases: PubMed and Embase from January 1991 to July 2020. The search terms used were "bipolar disorder/s, manic depressive, manic depression, comorbidity, and migraine." The terms were cross-referenced to yield a comprehensive search. We also conducted manual searches of bibliographies of reviewed articles. We included in this review original research articles of descriptive, controlled and animal studies and several review articles. The search was limited to English language journals.

Potential Mechanisms of BD

Multiple pathophysiological processes, such as genetic abnormalities, abnormal regulation of neurotransmitters, altered signaling pathways, reduced neurotrophic factors, inflammatory disturbances, mitochondrial dysfunction, cell apoptosis and impaired cell resilience, may be involved in the development of BD. The interaction of these processes leads to abnormal neuronal function which may result in mood instability, disturbed energy metabolism, abnormal biological rhythms and cognition defects (**Table 1**). Patients with BD present an increased rate of DNA damage compared to that of controls, which is closely related to the severity of BD symptoms (32). The gray matter volume showed by the positron emission tomography (PET) was significantly decreased in the subgenual prefrontal cortex sections from BD patients, which was closely related to a reduced glial cell number and neuronal cell number or size (33, 34). Calcium signaling, particularly through voltage-gated calcium channels, was thought to play vital roles in the pathogenesis and treatment of BD, the expression of the calcium channel Cav1.2 subunit, which is encoded by *CACNA1C* (the most likely BD gene), was also abnormally regulated in the pathogenesis of BD (15, 35). Combined data from genome-wide association studies (GWASs) and gene expression experiments revealed that hormone regulation, second messenger pathways, glutamatergic transmission and histone expression, even the immune system were all involved in the pathogenesis of BD (36, 37). Monoamines and gamma-amino butyric acid (GABA) are important in the pathophysiology of BD (16). In addition, serum brain-derived neurotrophic factor (BDNF) is decreased (17), while neurotrophin-3 (NT-3) (18) is upregulated in patients with BD who are experiencing a manic state or a depressive state.

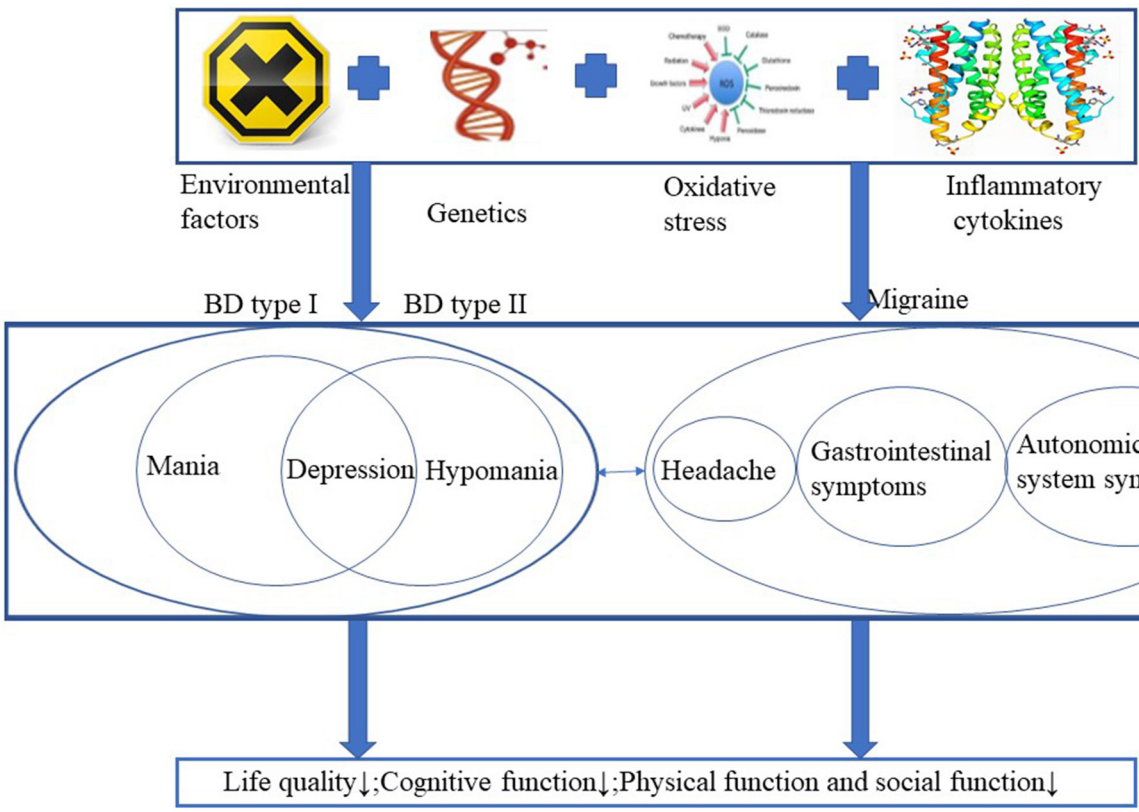


FIGURE 1 | BD and migraine share multiple similar risk factors, including genetic factors, environmental risk factors, oxidative stress and disturbances of inflammatory cytokines. Both diseases lead to decreased quality of life and multiple dysfunctions in humans.

Furthermore, controlling the release of BDNF contributes to the effective treatment of BD, and BDNF has been reported to regulate the cell survival rate in individuals with BD (38).

Patients with BD always exhibit a disturbed balance between pro-inflammatory factors and anti-inflammatory factors. The peripheral levels of inflammatory factors, including the interleukin (IL) family, IFN-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), are upregulated in the manic episode of BD patients compared to those in healthy controls, while the level of IL-4 is downregulated in BD patients compared to that in healthy controls (19). Modabbernia et al. demonstrated significantly elevated levels of TNF-α and its receptor, IL-6 and its receptor, IL-2 receptor, IL-4, IL-10, and IL-1 receptor antagonist (IL-1RA) in patients with BD compared to those in healthy individuals (21, 22). In addition, individuals with BD who are experiencing mania have been shown to express higher levels of TNF-α, sTNF-R1, and sIL-2R than healthy controls, and the levels of sTNF-R1 and TNF-α in manic BD patients are higher than those in patients experiencing euthymia. Furthermore, the expression level of sTNF-R1 is significantly upregulated in patients experiencing euthymia compared to that in healthy controls (23). The expression level of the TNF receptor was more significantly decreased in BD patients experiencing a depressive state than in those experiencing a manic/hypomanic state or euthymic state, and this expression level was also downregulated in BDII patients compared to that in BD I patients (24). Adiponectin is decreased in bipolar depression, and might interfere with the pathophysiological mechanisms of BD and its somatic comorbidities via involvement in metabolic and inflammatory processes (39). Glial inflammatory factors, including glial fibrillary acidic protein, nitric oxide (NO) synthase, c-fos and CD11b, and astroglial inflammatory factors, including myeloid differentiation factor 88, nuclear factor-kappa β (NF-κβ), cyclooxygenase, prostaglandin-E synthase, IL-1β and IL-1 receptor, were significantly upregulated in the postmortem frontal cortex of BD patients compared to those in healthy controls, thus indicating that microglial and astroglial activation are promoted during the pathogenetic process of BD (20). However, another study showed that the levels of the N-methyl-D-aspartate (NMDA)receptors NR-1 and NR-3A were downregulated in BD patients compared to those in healthy controls, and the levels of TNF-α and Neural Nitric Oxide Synthase(nNOS) were not altered in these patients (20).

On the other hand, mitochondrial dysfunction results in the impairment of cell resilience and participates in the initiation and progression of BD (40). BD has also been demonstrated to be associated with impaired respiratory complex function and the induction of cellular degeneration (41). Oxidative stress

TABLE 1 | Multiple pathophysiological processes participate in the development of BD.

Author, Date	Type	Potential mechanism	Regulation	Result	References
S. Bhat, 2012	Genetics	*CACNA1C*	Abnormally regulated	More robust associations in BD patients than in depression or schizophrenia patients	(15)
Y. Oda, 2012	Neurotransmitters	GABA-inhibitory interneuronal activity	Dysfunction	Deficits in gamma band oscillations in BD patients	(16)
K. Hashimoto, 2004	Neurotrophic factor	Serum brain-derived neurotrophic factor (BDNF)	Downregulated	Stress-induced neuronal damage; impaired neurogenesis in the hippocampus	(17)
J. C. Walz, 2007	Neurotrophic factor	Neurotrophin-3 (NT-3)	Upregulated	Higher in manic and depressed BD patients than in euthymic patients and healthy controls	(18)
Y. K. Kim, 2007	Inflammatory factors	IL-6/IL-4,TNF-α/IL-4, IL-2/IL-4, and IFN-γ/IL-4 ratios	Upregulated	Higher in manic BD patients than in healthy controls	(19)
Y. K. Kim, 2007	Inflammatory factors	IL-4	Downregulated	Lower in BD patients than in healthy controls	(19)
J. S. Rao, 2010	Inflammatory factors	NMDA receptors NR-1 and NR-3A	Downregulated	Lower in BD patients than in healthy controls	(20)
J. S. Rao, 2010	Inflammatory factors	IL-1β, IL-1 receptor, myeloid differentiation factor 88 (MyD88), nuclear factor-kappa B subunits, glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS), c-fos and CD11b	Upregulated	Higher in BD patients than in healthy controls	(20)
J. S. Rao, 2010	Inflammatory factors	Tumor necrosis factor-alpha (TNF-α) and nNOS	Not altered	Equivalent in BD patients and healthy controls	(20)
Modabbernia, 2013	Inflammatory factors	TNF-α and its receptor, IL-6 and its receptor, IL-2 receptor, IL-4, IL-10, and IL-1 receptor antagonist (IL-1RA)	Upregulated	Higher in BD patients than in healthy controls	(21)
K. Munkholm, 2013	Inflammatory factors	soluble IL-2 receptor (sIL-2R), TNF-α, soluble tumor necrosis factor receptor type 1 (sTNFR1), sIL-6R and IL-4	Upregulated	Higher in BD patients than in healthy controls	(22)
K. Munkholm, 2013	Inflammatory factors	TNF-α, sTNF-R1, sIL-2R	Upregulated	Higher in manic BD patients than in healthy controls	(23)
K. Munkholm, 2013	Inflammatory factors	sTNF-R1 and TNF-α	Upregulated	Higher in manic BD patients than in euthymic BD patients	(23)
K. Munkholm, 2013	Inflammatory factors	sTNF-R1	Upregulated	Higher in euthymic BD patients than in healthy controls	(23)
Y. M. Bai, 2014	Inflammatory factors	sTNF-R1	Downregulated	Lower in bipolar II patients than in bipolar I patients; lower in depressive BD patients than in manic/hypomanic/euthymic BD patients	(24)
T. Kato, 1993	Mitochondrial dysfunction	pH	Upregulated	Higher in manic BD patients than in euthymic BD patients	(25)
T. Kato, 1993	Mitochondrial dysfunction	pH	Downregulated	Lower in euthymic BD patients than in healthy controls	(25)
X. Sun, 2006	Mitochondrial dysfunction	Complex I, complex IV and complex V	Downregulated	Lower in BD patients than in healthy controls	(26)
N. Buttner, 2007	Mitochondrial dysfunction	DNA fragmentation	Upregulated	Higher in BD patients than in schizophrenic patients or healthy controls	(27)
R. E. Riegel, 2009	Mitochondrial dysfunction	TBARS and superoxide generation	Upregulated	Higher in rats with a mania-like state than in normal rats	(28)
J. F. Wang, 2009	Mitochondrial dysfunction	4-hydroxynonenal	Upregulated	Higher in BD patients than in healthy controls; 4-HNE levels significantly correlated with pH values only in BD patients	(29)

(Continued)

TABLE 1 | Continued

Author, Date	Type	Potential mechanism	Regulation	Result	References
M. Kunz, 2008	Mitochondrial dysfunction	SOD activity	Upregulated	Higher in manic and depressed BD patients than in healthy controls/euthymic BD patients	(30)
M. Kunz, 2008	Mitochondrial dysfunction	TBARS	Upregulated	Higher in euthymic/manic/depressed BD patients than in healthy controls	(30)
M. Yumru, 2009	Mitochondrial dysfunction	The total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI)	Upregulated	Higher in BD patients than in healthy controls	(31)
M. Yumru, 2009	Mitochondrial dysfunction	TOS	Upregulated	Higher in BD I patients than in BD II patients	(31)

occurs after an imbalance of redox homeostasis is initiated, accompanied by overexpression of free radicals or deficiencies in the antioxidant response. The pH was increased in cerebral tissue from manic patients compared to that in cerebral tissue from euthymic BD patients, but was decreased in cerebral tissue from euthymic BD patients compared to that in cerebral tissue from healthy controls (25). Moreover, expression of mitochondrial electron transport chain-related genes, such as complex I, complex IV and complex V, were downregulated in the frontal cortex of BD patients compared to that in healthy controls (26). In another postmortem study, Buttner et al. showed that oxidative stress-induced DNA fragmentation was enhanced in non-GABAergic neurons in the anterior cingulate cortex of BD patients compared to that of schizophrenic patients or healthy controls (27). Ouabain significantly increased superoxide generation, lipid peroxidation and thiobarbituric acid reactive substances (TBARS) to induce the generation of rats in a mania-like state (28). Moreover, Wang et al. found that the level of 4-hydroxynonenal (4-HNE, a major product of lipid peroxidation) was significantly increased in postmortem anterior cingulate brain sections from BD patients compared to the healthy controls, and 4-HNE levels were significantly correlated with pH values in BD patients (29). However, superoxide dismutase (SOD) activity was found to be upregulated only in patients experiencing acute phases of BD, such as manic episode or depressive episode, but not altered in patients experiencing an euthymic state of BD or healthy controls. In addition, the TBARS level was upregulated in BD patients at all stages compared to that in healthy controls (30). The expression level of 3-nitrotyrosine is upregulated during the early and late stages of BD; in contrast, the expression levels of glutathione reductase and glutathione S-transferase (GST) are significantly upregulated in patients during the late stage of BD compared to those in patients during the early stage of BD. Consequently, cumulative oxidative stress promoted the release of these antioxidant enzymes to reduce further oxidative stress-induced damage during the progression of BD. The total antioxidant status, total oxidant status and oxidative stress index are significantly upregulated in BD patients compared to those in healthy controls. Furthermore, the fact that BD-I is more severe than BD-II may be attributed to the higher total oxidant status in BD-I patients than in BD-II patients (31).

Potential Mechanisms of Migraine

Patients with migraine are more susceptible to headaches and associated clinical symptoms when they are experiencing a hyperexcitable brain state, and they perceive painful emotions and experiences. However, the potential mechanisms underlying the pathophysiology of migraine should be further investigated to shed light on the treatment of this complicated disease (**Table 2**). The dysfunction of descending pain modulatory circuits, which leads to a loss of pain inhibition and hyperexcitability in nociceptive areas of the brain (53). Dopamine receptors are involved in the determination of migraine trait, and migraine patients with dopaminergic symptoms are characterized by a full-blown, more disabling migraine (54). After scanning five patients who did not receive any migraine prophylaxis by PET, Afridi et al. found that there was a significant activation of the dorsolateral pons during spontaneous migraine attacks and concluded that migraine was a kind of subcortical disorder (55). More recently, other imaging studies have shown that there is also a significant activation of posterior/dorsal thalamic sections in patients with spontaneous migraine (56). Pain signals in the brain are transferred centrally to the trigeminal nucleus caudalis and the trigeminocervical complex, which then sends fibers to the thalamus and the autonomic nuclei, and finally, the thalamic neurons project to the somatosensory cortex and parts of the limbic system. This progress of neural communication is mediated by a number of neuropeptides and neurotransmitters, including monoamines (57). Altered perception of stimuli that is not painful promotes the reflection of pain and activates the feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve. After stimulation with functional 5-hydroxy tryptamine in the trigeminal nerve endings, the release of calcitonin gene-related peptide was decreased, and a mild level of vasoconstriction could be triggered by stimulating receptors on meningeal blood vessels and the trigeminal nucleus caudalis, thus resulting in decreased central neuronal signaling (57). Monoclonal antibodies to Calcitonin Gene-related Peptide (CGRP) or its receptors, have proven efficacy on migraine prevention, in both episodic and chronic migraine. Kainate and NMDA receptor antagonists, pituitary adenylate cyclase-activating polypeptide(PACAP) type 1 receptor (PAC1) agonists and Kynurenic Acid(KYNA) analogs are still in preclinical phase for the treatment of migraine (58).

TABLE 2 | The potential underlying mechanism during the pathophysiological process of migraine.

Author, Date	Type	Potential mechanism	Regulation	Result	References
R. A. Ophoff, 1996	Genetics	CACNA1A	Polymorphic variations (a (CA)n-repeat (D19S1150), a (CAG)n-repeat in the 3'-UTR) and different types of deleterious mutations	FHM	(42)
E. Garza-Lopez, 2012	Genetics	G protein-dependent modulation of mutations W1684R and V1696I	Affects the apparent dissociation and reassociation rates of the Gβγ dimer	G protein-Ca(2+) channel affinity may be altered in FHM type I	(43)
M. De Fusco, 2003	Genetics	ATP1A2	Loss of function of a single allele of ATP1A2	FHM type II	(44)
M. Dichgans, 2005	Genetics	SCN1A	A heterozygous missense mutation (Gln1489Lys) in the neuronal voltage-gated sodium channel gene	FHM type III	(45)
R. Burstein, 2010	Inflammatory factors	Blood oxygenation level-dependent (BOLD) signals	Stronger BOLD responses	Migraine attack with extracephalic allodynia compared to the corresponding responses	(46)
F. Perini, 2005	Inflammatory factors	IL-10, TNF-α, and IL-1β	Upregulated	Higher in patients during attacks than outside of attacks	(47)
F. Perini, 2005	Inflammatory factors	Serum levels of IL-10 and TNF-α	Upregulated/downregulated	Higher in migraine patients soon after headache onset and lower over time	(47)
P. P. Bruno, 2007	Inflammatory factors	Chemokines	Upregulated	Stimulate the activation of trigeminal nerves	(48)
P. P. Bruno, 2007	Mitochondrial dysfunction	Nitric oxide (NO)	Upregulated	Induces inflammation in migraine patients	(48)
J. Olesen, 2010	Mitochondrial dysfunction	NO	Upregulated	Causes headache in normal volunteers and a delayed headache in migraine patients	(49)
C. Bernecker, 2011	Mitochondrial dysfunction	4-hydroxy-2-nonenal (HNE)	Upregulated	Higher in female migraine patients than in healthy controls; HNE is significantly correlated with the nitric oxide pathway and with insulin and lipid metabolism	(50)
M. Neri, 2015	Mitochondrial dysfunction	NO	Upregulated	Higher in migraine patients with aura during attacks	(51)
M. Neri, 2015	Mitochondrial dysfunction	Thiobarbituric acid reactive substances (TBARS)	Upregulated	Higher in migraine patients than in healthy controls	(51)
I. Ciancarelli, 2004	Mitochondrial dysfunction	Urinary levels of NO and TBARS	Upregulated	Higher in migraine patients than in healthy controls	(52)

Migraine may also be induced by brainstem dysfunction, which initiates perimeningeal vasodilatation and neurogenic inflammation. As the potential mechanisms of migraine are extraordinarily complex, inflammation is a salient factor in the pathophysiology of migraine. The levels of blood oxygenation level-dependent (BOLD) signals are significantly elevated in migraine attacks with extracephalic allodynia compared to those in the corresponding responses (46). In addition, levels of the well-known pro-inflammatory cytokines, including IL-10, TNF-α, and IL-1β were significantly upregulated during acute migraine attacks compared to those outside of acute attacks, while the levels of IL-10 and TNF-α were increased in migraine patients soon after headache onset but decreased over time (47). The release of chemokines was increased in migraine patients and stimulated the activation of trigeminal nerves (48). Oxidative stress, such as NO, serves as a critical factor in the pathophysiology of migraine, and an elevated level of NO-induced inflammation has been reported in migraine patients (48). Moreover, increased expression of NO induced headache in normal volunteers and delayed headache in migraine patients (49). 4-Hydroxy-2-nonenal levels are upregulated in female migraine patients compared to those in healthy controls and have been shown to be significantly correlated with the NO pathway, insulin metabolism and lipid metabolism (50). NO and TBARS levels were upregulated in patients with migraine compared to those in healthy individuals (51, 52). In recent years, studies have shown that imbalances between oxidative stress and the antioxidative response participate in the pathophysiology

of migraine, as the levels of oxidative stress-related genes and enzymes are elevated, whereas the levels of antioxidant genes and enzymes are diminished during the progression of migraine.

The Overlapping Mechanisms of BD and Migraine

In recent years, the potential mechanisms of comorbid BD and migraine have been widely investigated, and future research focused on genetic factors, brain imaging, mitochondrial dysfunction and inflammatory factors may further elucidate the underlying mechanisms. Epidemiological and clinical studies have showed a high degree of comorbidity between BD and migraine, they two may have multifactorial polygenic etiology and share common pathophysiology (59). Since there is a strong bidirectional association between migraine and BD, revealing the potential overlapping neurobiological mechanisms of these two diseases could promote the development of novel treatments. Parental migraine has been demonstrated to serve as a risk factor for offspring BD, even in patients without parental BD, and there seems to be a common genetic factor between BD and migraine. However, BD is more closely related to comorbid migraine than parental migraine, and this elevated comorbidity may be attributed to nongenetic factors (60). Both of BD and migraine are closely associated with abnormalities in serotonergic pathways, dopaminergic pathways, and glutaminergic systems. Central serotonergic activity is reduced during the depressive and euthymic phases of BD (61), while the serotonin level is low in migraine patients between attacks and is upregulated after the initiation of a migraine attack (62). As dopamine is a well-recognized factor in migraine pathophysiology, dopamine receptor antagonists, as prochlorperazine, chlorpromazine, metoclopramide, and promethazine are first-line agents in the emergency room setting for migraine (63). The levels of glutamate were significantly upregulated in the anterior cingulate cortex and downregulated in the hippocampus in BD patients compared to those in controls (64). Glutamate from platelets was released and amino acids was increased in migraine patients with aura and without aura, although this increase was more significant in migraine patients with aura. Platelet glutamate uptake, assessed by 3H-glutamate intake, was increased in migraine patients with aura, but it was reduced in migraine patients without aura compared to that in healthy controls (65). The blood levels of leptin and adiponectin of the migraineurs are associated with disease pathogenesis of migraine (66).

Calcium channels Cav1, Cav2, and Cav3 are the targets of mutations and polymorphisms that alter their function and regulation can lead to neuropsychiatric diseases, including migraine and BD (67). Genome-wide linkage studies in BD and migraine patients proved that there were overlapping areas of linkage on chromosomes. *CACNA1A* and *CACNA1C,* which are voltage-dependent calcium channels, have recently been proven to play critical roles in FHM and BD. Furthermore, there is a locus on chromosome 20p11 with overlapping elevated logarithm of odds scores for both migraine and BD, and the locus harbors a well-known gene, namely, *SLC24A3,* which encodes a potassium-dependent sodium/calcium exchanger for maintaining calcium homeostasis in nervous tissue (68). Although another study found that there was no relationship between rs10994336 in *ANK3* during the progression of BD and rs1006737 in *CACNA1C* during the progression of migraine, this result may be attributed to the small sample size (69). Oedegaard et al. used GWAS to compare BD patients without headache and BD patients with migraine and found that there were nine single nucleotide polymorphism (SNP) (Chr13:41192397-41388566) values in chromosome 13q14.1 in BD patients with migraine, and genetic variants of the *KIAA0564* gene region may predispose to migraine headaches in patients with BD. The strongest relationship was reported for several single nucleotide polymorphisms in a 317-kb region, whereas rs9566845 and rs9566867 remained the most prominent genetic variants in this study (70). Dopamine pathway genes, including LIM homeobox transcription factor 1, alpha (LMX1A) and neuregulin 1 (NRG1), are associated with cognitive performance in BD patients, the rs35753505 SNP was associated with increased performance, while the rs11809911 SNP in LMX1A was associated with reduced IQ and memory (71).

Furthermore, it has been reported that the pathophysiologic mechanisms of BD and migraine can be attributed to chronic inflammation, a disturbance of the balance between oxidative stress and the antioxidative stress response, and the regulation of nitrosative stress (72, 73). Panx1 channels and Connexins 43 hemichannels appears to be involved in inflammation and has been documented in migraine and BD (74). Furthermore, targeting the inflammatory pathways may decrease the cooccurrence of BD and migraine; thus, the elucidation of the related inflammatory pathways may offer new pharmacological strategies (75, 76). In addition, these inflammatory cytokines may serve as biomarkers for the prediction of outcomes. These pathological mechanisms may induce cross-sensitization between BD and migraine, thus shifting the illnesses to a more severe form, and patients with both diseases respond poorly to pharmacotherapies, with relapsing acute mood episodes, cognitive dysfunction and functional deficiency, and decreased life expectancy.

Current Treatments of BD and Migraine

Current Treatments of BD

Patients with BD theoretically experience interspersed euthymia and relapsing mood episodes of depressive and manic status (77), while actual BD symptoms are more complex, and the patients experience mixed mood states and potential cognitive impairments (78). As BD is termed as a dynamic and fluctuating disease, the control of this lifelong disease is challenging. During the early stages, patients with BD respond favorably to psychiatric and psychosocial therapy and exhibit less cognitive dysfunction and fewer functional impairments, but they exhibit accelerated rapid cycling of episodes, severe brain structural abnormalities, a higher prevalence of other comorbid diseases, and many more abnormal peripheral biomarkers after the illness progresses (79).

Mood stabilizers, including the univalent ion lithium, valproate, lamotrigine, and carbamazepine, serve as the cornerstones of therapy, and individual atypical antipsychotic medications are emerged as common choices to control acute

manic/hypomanic and acute depression in order to maintain the treatment during the remission phase (80). Although patients with BD sometimes experience a normal mood state, they may also experience persistent mood instability during this period (81). Moreover, the relapse rate is high even in patients receiving combination treatment. Depression or mania will recur in 37% of patients within 1 year and in 60% of patients within 2 years (82). Mood episodes, especially mania, have been demonstrated to be related to cell death of neuronal cells and glial cells, which is induced by apoptotic inflammatory cytokines (83). Thus, it is urgent for investigators to develop new drugs to eliminate these inflammatory factors targeting at these disorders; lithium and valproate exert protective effects through their immunomodulatory properties in BD patients (75). Traditional mood stabilizers for BD significantly downregulate the levels of phospholipase A_2 (PLA_2) and cyclooxygenase (COX), which directly participate in the regulation of immunity and inflammatory cytokine release (84), and other drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, also exert anti-inflammatory activity to ameliorate BD symptoms (85). In addition to anti-inflammatory function, mood stabilizers (lithium and valproate) upregulate SOD activity and glutathione activity and downregulate the generation of oxidative stress and mitochondrial dysfunction in BD (86). Long-term oral administration of lamotrigine or olanzapine significantly upregulated GST-M1 expression levels and GST activity in rat cerebral cortical cells, which suggested that GST-M1 may serve as an important drug target for the treatment of BD (87). Patients receiving behavioral and cognitive-behavioral therapies are free from the adverse effects of chemical drugs; in addition, such therapies make it easier for the patients to control their own disease by modifying distorted thinking, increasing their motivation to participate in pleasurable activities and improving their problem-solving abilities, and these therapies can be easily added to integrated therapy. The combination of pharmacotherapy, behavioral and cognitive-behavioral therapies improves medication adherence, delaying disease recurrence and improving the maintenance of treatment gains in patients with BD (88).

Current Treatments of Migraine

The symptoms of patients with migraine can be influenced by environmental triggers, including bad eating habits, sleep disorders, stressful stimulation, emotional status, hormone fluctuations in women, and weather changes (57). The current main treatment for moderate-to-severe migraine is serotonin receptor agonists, namely, triptans (89). After treatment with a triptan and another serotonergic agent, migraine patients may experience serotonin syndrome (90), and clinicians must pay attention to control the side effects of these agents. Several preventive medications, including anti-depressive drugs, antiepileptic drugs, hypotensive drugs, dietary supplements, herbal medicines, and botulinum toxin, are widely used as effective preventive treatments for clinical migraine symptoms (91). The comorbidity of migraine with evening chronotype BD patients is higher than compared with non-evening types of BD, and exogenous melatonin supplementation plays the potential prophylactic role in patients with episodic migraine, even there is no conclusive evidence comparing the efficacy of exogenous melatonin supplementation for migraine prophylaxis to the other FDA-approved pharmacotherapy (92, 93). Doctors can choose a targeted medication according to the patient's general health state, current comorbidities, additional drugs and personal preferences. In addition to medications, other strategies, including lifestyle changes, self-management techniques, and relaxation, can be used to control the symptoms of migraine in patients (94).

Potential Treatments for Patients With Comorbid BD and Migraine

There are still no optimal alternative treatments for patients suffering from comorbid BD and migraine, but several pharmacological treatments, such as valproate, lithium, lamotrigine, quetiapine and topiramate, are widely used to prevent the onset of both migraine attacks and acute manic or depressive episodes in patients with BD (95, 96). Patients with comorbid BD and migraine were younger and more educated and had a family history of either disease, but they had fewer hospitalizations for psychiatric disorders. The initial symptom for such patients is depression rather than hypomania or mania, and they are prescribed fewer mood stabilizers but more atypical antidepressants by their doctors. Improper antidepressant treatment used and analgesic drug abuse in cormobid patients is not rare, which leads to the reduction threshold of pain in cormobid BD with migraine patients, and then, may further interfer the patients' clinical medication (97). BD patients with migraine experience missed diagnosis and a lack of effective treatments; 27.9% of these patients receive antimigraine medications (triptans) (98). A study demonstrated that 1.8% of the total study population received specific treatments for migraine, and 0.45% of the population received a mood-stabilizing agent for BD; among these patients, only 843 in 4,640,219 individuals received both types of medications. Moreover, there was a strong positive association between treatment with migraine medications and treatment with mood-stabilizing agents (99). In recent years, comorbidity with BD has garnered increased attention, particularly in the psychiatric literature. Some treatments may exert adverse effects on the comorbid condition of BD and migraine, and that a tricyclic antidepressant may induce mania and aggravate the progression of disease (100). For patients with comorbid BD and migraine, mood stabilizer maybe the useful treatment, include lithium, anticonvulsant drugs and atypical antipsychotics. In the presence of mixed features of mood episodes, patients with comorbid BD and migraine should be better prescribed with sodium valproate, lamotrigine priority rather than lithium (101). Some specific psychoactive medications such as cognitive behavioral therapy and social rhythm therapy also have effects on the treatment of both BD and migraine (102).To this end, additional clinical and preclinical experimental studies should expand the investigation of new therapies for treating both BD and migraine.Deep transcranial magnetic stimulation (dTMS) (one of the new physical stimulation techniques used for the treatment of different neuropathologies) was also

explored as a possible treatment for BD and migraine and may have beneficial neurocognitive effects by targeting on the left dorsolateral prefrontal cortex (DLPFC) (103). Electrical neuromodulation approaches as vagus nerve stimulation (VNS) is one of the treatment to migraine and may cause changes in leptin and associated mediators of immunometabolic signaling, with higher at baseline level of IL-10 and elevated IL-1b (104, 105). Improving the clinicians' recognition and diagnosis of comorbid BD with migraine accurately is of great importance.

CONCLUSIONS

There are several limitations in this review. Firstly, included studies in this review are not systematic and may be intrinsically susceptible to bias, we cannot guarantee the quality and pertinence of these studies. Secondly, animal models of BD and migraine are scarce for further investigation of the mechanisms and treatments. Thirdly, we are not able to get a conclusion about the treatments between BD and migraine since the diagnosis varies according to different researches. Lastly, although the overlapping biological mechanisms seem to be genetic factors, abnormal neurotransmitters, inflammation, and mitochondrial dysfunction, and these factors cooperate to initiate and accelerate the progression of BD and migraine. It is hard to find a specific strategy to improve the therapeutic effects of the comorbidity according to current studies since the underling mechanisms are very complex and migraine symptoms may exacerbate BD symptoms and interfere with BD management. In recent years, inflammation and mitochondrial dysfunction have attracted interest from multiple investigators, and they have been shown to exert important effects on the pathogenesis of BD and migraine. By this way, an improved understanding of the overlapping mechanisms during the pathogenesis of comorbid BD and migraine will significantly improve the diagnosis and treatment then improve the therapeutic effects for patients with comorbid BD and migraine. In our opinion, although preventive medications, including mood-stabilizing agents and serotonergic agents, are widely used in patients with BD and migraine, respectively, additional effort is needed. To improve the prognosis of patients with comorbid BD and migraine, the identification of more effective and less toxic drugs and the improvement of poor compliance are essential. Safe and efficacious neuromodulatory approaches offer the prospect of treatment on comorbid BD with migraine in the future, as clinical researches on TMS or VNS to treat comorbid BD and migraine are expected to show effective therapeutic and cognitive improvement, as well as long-term follow-up studies about the changes in inflammatory factors, leptin and adipokines before and after treatment. Also experiments exploring the mechanisms of comorbid BD and migraine are necessary. In the near future, we are looking forward to find an effective treatment targeting on the intersectional mechanism for alleviating illness of patients with comorbid BD and migraine.

AUTHOR CONTRIBUTIONS

CH conceived the original idea. JD, RY, WL, and LZ wrote the article. SH revised this manuscript, which all authors reviewed and approved for publication.

FUNDING

Support for this work was provided by the grants from Administration of Traditional Chinese Medicine of Zhejiang Province (2017ZB060) awarded to JD, the National Natural Science Foundation of China (No. 81700553) awarded to CH, the China Postdoctoral Science Foundation (No. 2017M183789) awarded to CH.

REFERENCES

1. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, et al. Clinical implications of a staging model for bipolar disorders. *Expert Rev Neurother.* (2009) 9:957–66. doi: 10.1586/ern.09.31
2. Joffe RT, MacQueen GM, Marriott M, Trevor Young L. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disord.* (2004) 6:62–6. doi: 10.1046/j.1399-5618.2003.00091.x
3. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry.* (2007) 64:543–52. doi: 10.1001/archpsyc.64.5.543
4. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry.* (2013) 70:931–9. doi: 10.1001/jamapsychiatry.2013.1394
5. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry.* (2011) 68:1058–64. doi: 10.1001/archgenpsychiatry.2011.113
6. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol.* (2006) 5:148–57. doi: 10.1016/S1474-4422(06)70348-9
7. Lofland JH, Frick KD. Workplace absenteeism and aspects of access to health care for individuals with migraine headache. *Headache.* (2006) 46:563–76. doi: 10.1111/j.1526-4610.2006.00404.x
8. Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal KK, Akiskal HS. Migraine headache in affectively ill latino adults of mexican american origin is associated with bipolarity. *Prim Care Comp J Clin Psychiatry.* (2009) 11:302–6. doi: 10.4088/PCC.08m00728
9. Lipton RB, Stewart WF, Simon D. Medical consultation for migraine: results from the American Migraine Study. *Headache.* (1998) 38:87–96. doi: 10.1046/j.1526-4610.1998.3802087.x
10. Sinha A, Shariq A, Said K, Sharma A, Jeffrey Newport D, Salloum IM. Medical comorbidities in bipolar disorder. *Curr Psychiatry Rep.* (2018) 20:36. doi: 10.1007/s11920-018-0897-8
11. Hesdorffer DC. Comorbidity between neurological illness and psychiatric disorders. *CNS Spectr.* (2016) 21:230–8. doi: 10.1017/S1092852915000929
12. McIntyre RS, Konarski JZ, Wilkins K, Bouffard B, Soczynska JK, Kennedy SH. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. *Headache.* (2006) 46:973–82. doi: 10.1111/j.1526-4610.2006.00469.x
13. Gordon-Smith K, Forty L, Chan C, Knott S, Jones I, Craddock N, et al. Rapid cycling as a feature of bipolar disorder and comorbid migraine. *J Affect Disord.* (2015) 175:320–4. doi: 10.1016/j.jad.2015.01.024

14. Jeyagurunathan A, Abdin E, Vaingankar JA, Chua BY, Shafie S, Chang SHS, et al. Prevalence and comorbidity of migraine headache: results from the Singapore Mental Health Study 2016. *Soc Psychiatry Psychiatr Epidemiol.* (2020) 55:33–43. doi: 10.1007/s00127-019-01755-1
15. Bhat S, Dao DT, Terrillion CE, Arad M, Smith RJ, Soldatov NM, et al. CACNA1C (Cav1.2) in the pathophysiology of psychiatric disease. *Prog Neurobiol.* (2012) 99:1–14. doi: 10.1016/j.pneurobio.2012.06.001
16. Oda Y, Onitsuka T, Tsuchimoto R, Hirano S, Oribe N, Ueno T, et al. Gamma band neural synchronization deficits for auditory steady state responses in bipolar disorder patients. *PLoS ONE.* (2012) 7:e39955. doi: 10.1371/journal.pone.0039955
17. Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Res Brain Res Rev.* (2004) 45:104–14. doi: 10.1016/j.brainresrev.2004.02.003
18. Walz JC, Andreazza AC, Frey BN, Cacilhas AA, Cereser KM, Cunha AB, et al. Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. *Neurosci Lett.* (2007) 415:87–9. doi: 10.1016/j.neulet.2007.01.002
19. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord.* (2007) 104:91–5. doi: 10.1016/j.jad.2007.02.018
20. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol Psychiatry.* (2010) 15:384–92. doi: 10.1038/mp.2009.47
21. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry.* (2013) 74:15–25. doi: 10.1016/j.biopsych.2013.01.007
22. Munkholm K, Brauner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. *J Psychiatr Res.* (2013) 47:1119–33. doi: 10.1016/j.jpsychires.2013.05.018
23. Munkholm K, Vinberg M, Vedel Kessing L. Cytokines in bipolar disorder: a systematic review and meta-analysis. *J Affect Disord.* (2013) 144:16–27. doi: 10.1016/j.jad.2012.06.010
24. Bai YM, Su TP, Tsai SJ, Wen-Fei C, Li CT, Pei-Chi T, et al. Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. *J Affect Disord.* (2014) 166:187–92. doi: 10.1016/j.jad.2014.05.009
25. Kato T, Takahashi S, Shioiri T, Inubushi T. Alterations in brain phosphorous metabolism in bipolar disorder detected by *in vivo* 31P and 7Li magnetic resonance spectroscopy. *J Affect Disord.* (1993) 27:53–9. doi: 10.1016/0165-0327(93)90097-4
26. Sun X, Wang JF, Tseng M, Young LT. Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. *J Psychiatry Neurosci.* (2006) 31:189–96.
27. Buttner N, Bhattacharyya S, Walsh J, Benes FM. DNA fragmentation is increased in non-GABAergic neurons in bipolar disorder but not in schizophrenia. *Schizophr Res.* (2007) 93:33–41. doi: 10.1016/j.schres.2007.01.030
28. Riegel RE, Valvassori SS, Elias G, Reus GZ, Steckert AV, de Souza B, et al. Animal model of mania induced by ouabain: evidence of oxidative stress in submitochondrial particles of the rat brain. *Neurochem Int.* (2009) 55:491–5. doi: 10.1016/j.neuint.2009.05.003
29. Wang JF, Shao L, Sun X, Young LT. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. *Bipolar Disord.* (2009) 11:523–9. doi: 10.1111/j.1399-5618.2009.00717.x
30. Kunz M, Gama CS, Andreazza AC, Salvador M, Cereser KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* (2008) 32:1677–81. doi: 10.1016/j.pnpbp.2008.07.001
31. Yumru M, Savas HA, Kalenderoglu A, Bulut M, Celik H, Erel O. Oxidative imbalance in bipolar disorder subtypes: a comparative study. *Prog Neuropsychopharmacol Biol Psychiatry.* (2009) 33:1070–4. doi: 10.1016/j.pnpbp.2009.06.005
32. Andreazza AC, Frey BN, Erdtmann B, Salvador M, Rombaldi F, Santin A, et al. DNA damage in bipolar disorder. *Psychiatry Res.* (2007) 153:27–32. doi: 10.1016/j.psychres.2006.03.025
33. Drevets WC, Price JL, Simpson JR, Jr., Todd RD, Reich T, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature.* (1997) 386:824–7. doi: 10.1038/386824a0
34. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA.* (1998) 95:13290–5. doi: 10.1073/pnas.95.22.13290
35. Berridge MJ. Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia. *Cell Tissue Res.* (2014) 357:477–92. doi: 10.1007/s00441-014-1806-z
36. Nurnberger JI Jr, Koller DL, Jung J, Edenberg HJ, Foroud T, Guella I, et al. Identification of pathways for bipolar disorder: a meta-analysis. *JAMA Psychiatry.* (2014) 71:657–64. doi: 10.1001/jamapsychiatry.2014.176
37. Network T, O'Dushlaine C, Rossin L, Lee PH, Duncan L, Parikshak NN, et al. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci.* (2015) 18:199–209. doi: 10.1038/nn.3922
38. Kapczinski F, Frey BN, Kauer-Sant'Anna M, Grassi-Oliveira R. Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder. *Expert Rev Neurother.* (2008) 8:1101–13. doi: 10.1586/14737175.8.7.1101
39. Platzer M, Fellendorf FT, Bengesser SA, Birner A, Dalkner N, Hamm C, et al. Adiponectin is decreased in bipolar depression. *World J Biol Psychiatry.* (2019) 20:813–20. doi: 10.1080/15622975.2018.1500033
40. Kato T, Kato N. Mitochondrial dysfunction in bipolar disorder. *Bipolar Disord.* (2000) 2:180–90. doi: 10.1034/j.1399-5618.2000.020305.x
41. Calabrese V, Scapagnini G, Giuffrida Stella AM, Bates TE, Clark JB. Mitochondrial involvement in brain function and dysfunction: relevance to aging, neurodegenerative disorders and longevity. *Neurochem Res.* (2001) 26:739–64. doi: 10.1023/A:1010955807739
42. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell.* (1996) 87:543–52. doi: 10.1016/S0092-8674(00)81373-2
43. Garza-Lopez E, Sandoval A, Gonzalez-Ramirez R, Gandini MA, Van den Maagdenberg A, De Waard M, et al. Familial hemiplegic migraine type 1 mutations W1684R and V1696I alter G protein-mediated regulation of Ca(V)2.1 voltage-gated calcium channels. *Biochim Biophys Acta.* (2012) 1822:1238–46. doi: 10.1016/j.bbadis.2012.04.008
44. De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet.* (2003) 33:192–6. doi: 10.1038/ng1081
45. Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet.* (2005) 366:371–7. doi: 10.1016/S0140-6736(05)66786-4
46. Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z, Hargreaves R, et al. Thalamic sensitization transforms localized pain into widespread allodynia. *Ann Neurol.* (2010) 68:81–91. doi: 10.1002/ana.21994
47. Perini F, D'Andrea G, Galloni E, Pignatelli F, Billo G, Alba S, et al. Plasma cytokine levels in migraineurs and controls. *Headache.* (2005) 45:926–31. doi: 10.1111/j.1526-4610.2005.05135.x
48. Bruno PP, Carpino F, Carpino G, Zicari A. An overview on immune system and migraine. *Eur Rev Med Pharmacol Sci.* (2007) 11:245–8.
49. Olesen J. Nitric oxide-related drug targets in headache. *Neurotherapeutics.* (2010) 7:183–90. doi: 10.1016/j.nurt.2010.03.006
50. Bernecker C, Ragginer C, Fauler G, Horejsi R, Moller R, Zelzer S, et al. Oxidative stress is associated with migraine and migraine-related metabolic risk in females. *Eur J Neurol.* (2011) 18:1233–9. doi: 10.1111/j.1468-1331.2011.03414.x
51. Neri M, Frustaci A, Milic M, Valdiglesias V, Fini M, Bonassi S, et al. A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. *Cephalalgia.* (2015) 35:931–7. doi: 10.1177/0333102414564888
52. Ciancarelli I, Tozzi-Ciancarelli MG, Di Massimo C, Marini C, Carolei A. Flunarizine effects on oxidative stress in migraine patients. *Cephalalgia.* (2004) 24:528–32. doi: 10.1111/j.1468-2982.2003.00705.x
53. Burch R. Headache currents commentary. *Headache.* (2013) 53:E1. doi: 10.1111/head.12021

54. Barbanti P, Aurilia C, Egeo G, Fofi L, Guadagni F, Ferroni P. Dopaminergic symptoms in migraine: a cross-sectional study on 1148 consecutive headache center-based patients. *Cephalalgia.* (2020) 40:1168–76. doi: 10.1177/0333102420929023
55. Afridi SK, Giffin NJ, Kaube H, Friston KJ, Ward NS, Frackowiak RS, et al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol.* (2005) 62:1270–5. doi: 10.1001/archneur.62.8.1270
56. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain.* (2013) 154:44–53 (Suppl. 1). doi: 10.1016/j.pain.2013.07.021
57. Ward TN. Migraine diagnosis and pathophysiology. *Continuum.* (2012) 18:753–63. doi: 10.1212/01.CON.0000418640.07405.31
58. Ferroni P, Barbanti P. Biomarkers in migraine headache: prognostic and therapeutic implications. *Curr Med Chem.* (2019) 26:6188–90. doi: 10.2174/0929867326341911121424 48
59. Di Marco O, Di Mauro S. Bipolar disorder and chronic migraine: an open problem. *Neurol Sci.* (2018) 39:85–6. doi: 10.1007/s10072-018-3356-8
60. Sucksdorff D, Brown AS, Chudal R, Heinimaa M, Suominen A, Sourander A. Parental and comorbid migraine in individuals with bipolar disorder: a nationwide register study. *J Affect Disord.* (2016) 206:109–14. doi: 10.1016/j.jad.2016.07.034
61. Mahmood T, Silverstone T. Serotonin and bipolar disorder. *J Affect Disord.* (2001) 66:1–11. doi: 10.1016/S0165-0327(00)00226-3
62. Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M. Serotonergic mechanisms in the migraine brain - a systematic review. *Cephalalgia.* (2017) 37:251–64. doi: 10.1177/0333102416640501
63. Ong JJY, De Felice M. Correction to: migraine treatment: current acute medications and their potential mechanisms of action. *Neurotherapeutics.* (2018) 15:525–6. doi: 10.1007/s13311-017-0599-7
64. Ehrlich A, Schubert F, Pehrs C, Gallinat J. Alterations of cerebral glutamate in the euthymic state of patients with bipolar disorder. *Psychiatry Res.* (2015) 233:73–80. doi: 10.1016/j.pscychresns.2015.05.010
65. Vaccaro M, Riva C, Tremolizzo L, Longoni M, Aliprandi A, Agostoni E, et al. Platelet glutamate uptake and release in migraine with and without aura. *Cephalalgia.* (2007) 27:35–40. doi: 10.1111/j.1468-2982.2006.01234.x
66. Abbasi M, Noori-Zadeh A, Seidkhani-Nahal A, Kaffashian M, Bakhtiyari S, Panahi S. Leptin, adiponectin, and resistin blood adipokine levels in migraineurs: systematic reviews and meta-analyses. *Cephalalgia.* (2019) 39:1010–21. doi: 10.1177/0333102418807182
67. Nanou E, Catterall WA. Calcium channels, synaptic plasticity, neuropsychiatric disease. *Neuron.* (2018) 98:466–81. doi: 10.1016/j.neuron.2018.03.017
68. Oedegaard KJ, Greenwood TA, Lunde A, Fasmer OB, Akiskal HS, Kelsoe JR. A genome-wide linkage study of bipolar disorder and co-morbid migraine: replication of migraine linkage on chromosome 4q24, and suggestion of an overlapping susceptibility region for both disorders on chromosome 20p11. *J Affect Disord.* (2010) 122:14–26. doi: 10.1016/j.jad.2009.06.014
69. Wober-Bingol C, Tropeano M, Karwautz A, Wagner G, Campos-de-Sousa S, Zesch HE, et al. No association between bipolar disorder risk polymorphisms in ANK3 and CACNA1C and common migraine. *Headache.* (2011) 51:796–803. doi: 10.1111/j.1526-4610.2011.01858.x
70. Oedegaard KJ, Greenwood TA, Johansson S, Jacobsen KK, Halmoy A, Fasmer OB, et al. A genome-wide association study of bipolar disorder and comorbid migraine. *Genes Brain Behav.* (2010) 9:673–80. doi: 10.1111/j.1601-183X.2010.00601.x
71. Rolstad S, Palsson E, Ekman CJ, Eriksson E, Sellgren C, Landen M. Polymorphisms of dopamine pathway genes NRG1 and LMX1A are associated with cognitive performance in bipolar disorder. *Bipolar Disord.* (2015) 17:859–68. doi: 10.1111/bdi.12347
72. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res.* (2014) 218:61–8. doi: 10.1016/j.psychres.2014.04.005
73. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev.* (2011) 35:804–17. doi: 10.1016/j.neubiorev.2010.10.001
74. Sarrouilhe D, Dejean C, Mesnil M. Connexin43- and pannexin-based channels in neuroinflammation and cerebral neuropathies. *Front Mol Neurosci.* (2017) 10:320. doi: 10.3389/fnmol.2017.00320
75. Knijff EM, Breunis MN, Kupka RW, de Wit HJ, Ruwhof C, Akkerhuis GW, et al. An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. *Bipolar Disord.* (2007) 9:743–53. doi: 10.1111/j.1399-5618.2007.00444.x
76. Durham P, Papapetropoulos S. Biomarkers associated with migraine and their potential role in migraine management. *Headache.* (2013) 53:1262–77. doi: 10.1111/head.12174
77. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet.* (2013) 381:1663–71. doi: 10.1016/S0140-6736(13)60989-7
78. Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JT, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand.* (2013) 128:149–62. doi: 10.1111/acps.12133
79. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vazquez GH, Vieta E, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* (2009) 33:1366–71. doi: 10.1016/j.pnpbp.2009.07.027
80. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet.* (2013) 381:1672–82. doi: 10.1016/S0140-6736(13)60857-0
81. Broome MR, Saunders KE, Harrison PJ, Marwaha S. Mood instability: significance, definition and measurement. *Br J Psychiatry.* (2015) 207:283–5. doi: 10.1192/bjp.bp.114.158543
82. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. *Am J Psychiatry.* (1995) 152:1635–40. doi: 10.1176/ajp.152.11.1635
83. McAfoose J, Koerner H, Baune BT. The effects of TNF deficiency on age-related cognitive performance. *Psychoneuroendocrinology.* (2009) 34:615–9. doi: 10.1016/j.psyneuen.2008.10.006
84. Rao JS, Rapoport SI. Mood-stabilizers target the brain arachidonic acid cascade. *Curr Mol Pharmacol.* (2009) 2:207–14. doi: 10.2174/1874467210902020207
85. Stolk P, Souverein PC, Wilting I, Leufkens HG, Klein DF, Rapoport SI, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. *Prostaglandins Leukot Essent Fatty Acids.* (2010) 82:9–14. doi: 10.1016/j.plefa.2009.10.007
86. de Sousa RT, Zarate Jr CA, Zanetti MV, Costa AC, Talib LL, Gattaz WF, et al. Oxidative stress in early stage bipolar disorder and the association with response to lithium. *J Psychiatr Res.* (2014) 50:36–41. doi: 10.1016/j.jpsychires.2013.11.011
87. Bakare A, Shao L, Cui J, Young LT, Wang JF. Mood stabilizing drugs lamotrigine and olanzapine increase expression and activity of glutathione S-transferase in primary cultured rat cerebral cortical cells. *Neurosci Lett.* (2009) 455:70–3. doi: 10.1016/j.neulet.2009.03.022
88. Lipchik GL, Smitherman TA, Penzien DB, Holroyd KA. Basic principles and techniques of cognitive-behavioral therapies for comorbid psychiatric symptoms among headache patients. *Headache.* (2006) 46:S119–32. doi: 10.1111/j.1526-4610.2006.00563.x
89. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E, et al. Canadian Headache Society Guideline: acute drug therapy for migraine headache. *Can J Neurol Sci.* (2013) 40:S1–80. doi: 10.1017/S0317167100017819
90. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug-drug interactions. *Headache.* (2007) 47:266–9. doi: 10.1111/j.1526-4610.2006.00691.x
91. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* (2012) 39:S1−59. doi: 10.1017/S0317167100015109
92. Tseng PT, Yang CP, Su KP, Chen TY, Wu YC, Tu YK, et al. The association between melatonin and episodic migraine: a pilot network meta-analysis of randomized controlled trials to compare the prophylactic effects with exogenous melatonin supplementation and pharmacotherapy. *J Pineal Res.* (2020) 69:e12663. doi: 10.1111/jpi.12663
93. Romo-Nava F, Blom TJ, Cuellar-Barboza AB, Winham SJ, Colby CL, Nunez NA, et al. Evening chronotype as a discrete clinical subphenotype in bipolar disorder. *J Affect Disord.* (2020) 266:556–62. doi: 10.1016/j.jad.2020.01.151

94. Sorbi MJ, Balk Y, Kleiboer AM, Couturier EG. Follow-up over 20 months confirms gains of online behavioural training in frequent episodic migraine. *Cephalalgia.* (2017) 37:236–50. doi: 10.1177/0333102416657145
95. Karimi N, Tavakoli M, Charati JY, Shamsizade M. Single-dose intravenous sodium valproate (Depakine) vs. dexamethasone for the treatment of acute migraine headache: a double-blind randomized clinical trial. *Clin Exp Emerg Med.* (2017) 4:138–45. doi: 10.15441/ceem.16.199
96. Rej S, Yu C, Shulman K, Herrmann N, Fischer HD, Fung K, et al. Medical comorbidity, acute medical care use in late-life bipolar disorder: a comparison of lithium, valproate, other pharmacotherapies. *Gen Hosp Psychiatry.* (2015) 37:528–32. doi: 10.1016/j.genhosppsych.2015.07.001
97. Oedegaard KJ, Riise T, Dilsaver SC, Lund A, Akiskal HS, Fasmer OB, et al. A pharmaco-epidemiological study of migraine and antidepressant medications: complete one year data from the Norwegian population. *J Affect Disord.* (2011) 129:198–204. doi: 10.1016/j.jad.2010.09.009
98. Low NC, Du Fort GG, Cervantes P. Prevalence, clinical correlates, and treatment of migraine in bipolar disorder. *Headache.* (2003) 43:940–9. doi: 10.1046/j.1526-4610.2003.03184.x
99. Oedegaard KJ, Dilsaver SC, Hundal O, Riise T, Lund A, Akiskal HS, et al. Are migraine and bipolar disorders comorbid phenomena?: findings from a pharmacoepidemiological study using the Norwegian Prescription Database. *J Clin Psychopharmacol.* (2011) 31:734–9. doi: 10.1097/JCP.0b013e318235f4e9
100. Belmaker RH. Bipolar disorder. *N Engl J Med.* (2004) 351:476–86. doi: 10.1056/NEJMra035354
101. Chiossi L, Negro A, Capi M, Lionetto L, Martelletti P. Sodium channel antagonists for the treatment of migraine. *Exp Opin Pharmacother.* (2014) 15:1697–706. doi: 10.1517/14656566.2014.929665
102. Leo RJ, Singh J. Migraine headache and bipolar disorder comorbidity: a systematic review of the literature and clinical implications. *Scand J Pain.* (2016) 11:136–45. doi: 10.1016/j.sjpain.2015.12.002
103. Tendler A, Roth Y, Barnea-Ygael N, Zangen A. How to use the H1 deep transcranial magnetic stimulation coil for conditions other than depression. *J Vis Exp.* (2017) 119:e55100. doi: 10.3791/55100
104. Kinfe TM, Buchfelder M, Chaudhry SR, Chakravarthy KV, Deer TR, Russo M, et al. Leptin and associated mediators of immunometabolic signaling: novel molecular outcome measures for neurostimulation to treat chronic pain. *Int J Mol Sci.* (2019) 20:4737. doi: 10.3390/ijms20194737
105. Chaudhry SR, Lendvai IS, Muhammad S, Westhofen P, Kruppenbacher J, Scheef L, et al. Inter-ictal assay of peripheral circulating inflammatory mediators in migraine patients under adjunctive cervical non-invasive vagus nerve stimulation (nVNS): a proof-of-concept study. *Brain Stimul.* (2019) 12:643–51. doi: 10.1016/j.brs.2019.01.008

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 22 June 2021
doi: 10.3389/fpsyt.2021.518722

Comparing Screening Abilities of the 33-Item Hypomania Checklist (HCL-33) and the 33-Item Hypomania Checklist External Assessment (HCL-33-EA) for the Detection of Bipolar Disorder

Yuan-Yuan Wang[1†], Yuan Feng[2†], Meng Fang[2†], Chengwei Guo[2†], Gabor S. Ungvari[3,4], Brian J. Hall[5,6], Gang Wang[2] and Yu-Tao Xiang[7,8,9]*

[1] Division of Psychology, Faculty of Health and Life Sciences, De Montfort University, Leicester, United Kingdom, [2] The National Clinical Research Center for Mental Disorders, Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital and the Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China, [3] University of Notre Dame Australia, Fremantle, WA, Australia, [4] Division of Psychiatry, School of Medicine, University of Western Australia/Graylands Hospital, Perth, WA, Australia, [5] New York University Shanghai, Shanghai, China, [6] School of Global Public Health, New York University, New York, NY, United States, [7] Unit of Psychiatry, Department of Public Health and Medicinal Administration, Institute of Translational Medicine, Faculty of Health Sciences, University of Macau, Macao, China, [8] Centre for Cognitive and Brain Sciences, University of Macau, Macao, China, [9] Institute of Advanced Studies in Humanities and Social Sciences, University of Macau, Macao, China

OPEN ACCESS

Edited by:
Dina Popovic,
Sheba Medical Center, Israel

Reviewed by:
Jules Angst,
Psychiatric University Hospital Zurich, Switzerland
Michele Fornaro,
New York State Psychiatric Institute (NYSPI), United States

***Correspondence:**
Gang Wang
gangwangdoc@gmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 09 December 2019
Accepted: 20 May 2021
Published: 22 June 2021

Citation:
Wang Y-Y, Feng Y, Fang M, Guo C, Ungvari GS, Hall BJ, Wang G and Xiang Y-T (2021) Comparing Screening Abilities of the 33-Item Hypomania Checklist (HCL-33) and the 33-Item Hypomania Checklist External Assessment (HCL-33-EA) for the Detection of Bipolar Disorder. Front. Psychiatry 12:518722. doi: 10.3389/fpsyt.2021.518722

Background: Bipolar disorder (BD) is a severe psychiatric disorder that is often misdiagnosed and under-diagnosed in clinical settings. The 33-item Hypomania Checklist (HCL-33) is a newly developed self-administered scale for BD detection, while the 33-item Hypomania Checklist-external assessment (HCL-33-EA) is a version of the HCL-33 for external rating used by patient's carer (e.g., family member or friend). We aimed to compare the screening abilities between the HCL-33 and the HCL-33-EA, and evaluate the screening consistency between the two scales.

Methods: The data were collected from 269 patients with diagnosed BD ($n = 84$) or major depressive disorder (MDD) ($n = 185$). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) between the HCL-33 and the HCL-33-EA for BD were compared against clinician diagnosis as the gold standard.

Results: Using Youden's index, the optimal cut-off value of the HCL-33 is 20, while the corresponding figure for HCL-33-EA is 11. Using Youden's index, the HCL-33-EA showed a better performance than the HCL-33 (0.51 vs.0.41). The HCL-33-EA was more sensitive in correctly identifying BD patients from MDD patients than the HCL-33 (0.83 vs. 0.59), while the HCL-33 presented better specificity than the HCL-33-EA (0.82 vs. 0.68). There was significant screening consistency between the two scales ($p < 0.001$).

Conclusions: Both scales have acceptable psychometric properties in detection BD from MDD. Use of the two scales should be considered based on the assessment purpose in clinical research or daily practice (i.e., prefer sensitivity or specificity). Noticeably, the current sample size is insufficient and future studies are recommended to further evaluate the scales.

Keywords: bipolar disorder, sensitivity, specificity, HCL-33-EA, HCL-33

BACKGROUND

Bipolar disorder (BD) is a chronic and severe mood disorder comprising depressive and manic/hypomanic episodes (1). BD is frequently under-recognized, partly because patients are misdiagnosed as having major depressive disorder (MDD) during depressive episodes of BD (1–3). Moreover, BD patients usually do not report hypomanic episodes to clinicians, since patients may not experience impairment, and therefore do not consider hypomania as BD symptoms (2). Due to the commonly neglected hypomania, it is difficult to estimate the prevalence of misdiagnosed and underdiagnosed BD among those treated as MDD. Studies found that an average of 10 years was needed before accurate diagnoses of BD were established; in addition, around one-third of BD patients experienced at least once misdiagnosis (4, 5). The misdiagnosis of BD may have serious consequences, including high suicide risk (6) and low antidepressant treatment efficacy (7). Thus, it is crucial to distinguish BD accurately from other disorders, particularly MDD.

The Hypomania Checklists (HCL) are a series of widely used scales in detecting hypomanic symptoms and identifying BD, such as the 32-item Hypomania Checklist (HCL-32) (8), the 33-item Hypomania Checklist (HCL-33) (9), the 33-item Hypomania Checklist-external assessment (HCL-33-EA) (10), and their short versions (11, 12). The HCL-32 is a widely used patient-rated screening instrument for hypomanic symptoms with good psychometric properties in differentiating BD from MDD (8) and has been widely used in different countries (13–18). The HCL-33 is a recently developed questionnaire based on the extension of the HCL-32, which provides a more detailed assessment of hypomanic symptoms (9). The HCL-33-EA is the external assessment version of the HCL-33, which was designed to assess hypomanic symptoms by carers (such as spouses, parents, and friends) (10).

Several studies on the screening ability of the HCL-33 and the HCL-33-EA found satisfactory BD screening abilities of the two scales (9, 19). The consistency between the HCL-33 and the HCL-33-EA has been evaluated in a sample of Polish adults, which showed sufficient consistency between them (10). However, comparison between the HCL-33 and the HCL-33-EA for the detection of BD in patients with MDD and BD has not been conducted in China. The optimal cut-off value of the HCL-33 for distinguish BD from MDD is 15 in China (9), while the corresponding values of HCL-33-EA were not reported (10, 19). This is a critical gap in the literature, since there are an estimated 1.54 million people in China with BD (20). We aimed to compare the psychometric properties of the HCL-33 and the HCL-33-EA, including scale reliability, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). In addition, we also measured the consistency between the HCL-33 and the HCL-33-EA, and aimed to provide optimal cut-off values of the HCL-33 and HCL-33-EA for distinguishing of BD from MDD in Chinese patients.

Abbreviations: HCL-33, 33-item Hypomania Checklist (HCL-33); HCL-33-EA, the 33-item Hypomania Checklist External Assessment.

METHOD

Participants and Site

Following previous studies on psychometric properties of the HCL scales (11, 21–23), 269 inpatients and the same number of their carers were consecutively recruited between October, 2016 and January, 2019 in a major tertiary psychiatric hospital in Beijing, China. The patients were included if they were (1) adult patients diagnosed as MDD or BD depressive episode by two psychiatrists using the Mini-International Neuropsychiatric Interview Version 5.0 (24, 25) according to the International Classification of Diseases (ICD-10) (26), which was confirmed by a review of medical records; (2) could understand the contents of the interview. Patients with MDD or BD secondary to major medical conditions were excluded. All patients and their carer provided written consent and the Ethics Committee of Beijing Anding Hospital approved the study protocol.

Assessments

Basic demographic characteristics of patients and their carers were collected. The Chinese version of the HCL-33 was used with patients, and the HCL-33-EA was used with their carers. The HCL-33 (9) and HCL-33-EA (10) are self-rated questionnaires on patients' hypomanic symptoms. The total scores of the two scales are calculated by adding up all the positive answers and the total score ranges from 0 to 33 (9, 10). The Chinese versions of the two scales have been validated previously (9, 19).

Statistical Analyses

The sample size was calculated using G*power (27). Using reported screening abilities of HCL scales (9, 12) and the allocation ratio of MDD and BD patients as reported previously (4, 5) and given the alpha error probability of 0.05, and a conservative medium effect size of 0.5, at least 294 participants, with 68 BD and 226 MDD patients, would be needed.

TABLE 1 | Characteristics of patients with mood disorders and their carers.

	Carers ($n = 269$)		Patients ($n = 269$)			
			MDD ($n = 185$)		BD ($n = 84$)	
	N	**%**	***N***	**%**	***N***	**%**
Men	149	55.4	42	22.7	22	26.2
Married	236	87.7	113	61.1	37	44.0
Employed	266	98.9	164	88.6	73	86.9
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	42.7	11.7	35.9	12.8	32.9	12.4
Education (years)	13.1	2.9	13.9	3.1	14.1	2.8

BD, bipolar disorder; MDD, major depressive disorder.

TABLE 2 | Comparison between the HCL-33 and the HCL-33-EA in terms of sensitivity, specificity, PPV, NPV, and Area Under the Curve (AUC) for the detection of bipolar disorder from major depressive disorder.

Scales	AUC	95% CI	Cut-off value	Sensitivity (SE)	Specificity (SP)	Youden's *J*	PPV	NPV
HCL-33	0.73	0.66–0.81	18	0.66	0.71	0.37	0.52	0.84
			19	0.62	0.78	0.39	0.57	0.83
			20[a]	0.59	0.82	0.41	0.60	0.82
			21	0.47	0.87	0.34	0.63	0.79
HCL-33-EA	0.82	0.77–0.88	9	0.89	0.55	0.43	0.45	0.91
			10	0.86	0.61	0.46	0.47	0.89
			11[a]	0.83	0.68	0.51	0.50	0.89
			12	0.75	0.74	0.49	0.53	0.86

[a] *Optimal cutoff in current sample; PPV, Positive Predictive Value; NPV, Negative Predictive Value; AUC, Area under the curve; CI, 95% confidence interval for AUC; HCL-33, Hypomania Checklist-33; HCL-33-EA, Hypomania Checklist-33-externl assessment.*

SPSS 25 (IBM Corp, Armonk) was used for all analyses. The HCL-33 and the HCL-33-EA were compared by sensitivity, specificity, PPV and NPV. The Receiver Operating Characteristic (ROC) curve was plotted to represent the ability of the instrument to distinguish between BD and MDD. The internal consistency was measured by the Cronbach's alpha, in which excellent α coefficient was defined as ≥0.90, good was defined as 0.80–0.89, and adequate was defined as 0.70–0.79 (28). Following previous studies (12, 29), the optimal cut-off was calculated using the maximum sum score of sensitivity + specificity – 1, according to Youden's index (30). Cohen's kappa was used to determine the consistency between HCL-33 and the HCL-33-EA, with below 0.40 as poor agreement, 0.40–0.75 as fair to good agreement, and above 0.75 as excellent agreement (31). Statistical significance was set at was set at <0.05 (two-tailed).

RESULTS

A total number of 269 patients (MDD: $n = 185$ and BD: $n = 84$), and 269 carers who met the study criteria were included during the study period for analyses. Their basic characteristics are shown in **Table 1**.

The Cronbach's alpha of the HCL-33 was 0.867 and that the HCL-33-EA was 0.872, which suggests that the two scales had good reliability, while the HCL-33-EA had slightly higher reliability than the HCL-33. The mean sum score of the HCL-33 and the HCL-33-EA were 15.3 (SD = 6.5) and 11.0 (SD = 6.2), respectively. Using the optimal cut-offs calculated in the current sample, there was a significant, but poor agreement between the HCL-33 and the HCL-33-EA ($k = 0.36$, $p < 0.001$). The proportion of BD was relatively higher in the current sample than the calculated proportion, thus the chance agreement should be adjusted according to the influence of prevalence and bias (32). The Prevalence and Bias Adjusted Kappa (PBAK) was also calculated ($k = 0.37$, prevalence index = −0.22, bias index = −0.17). As shown in **Table 2**, the HCL-33 and HCL-33-EA was compared in terms of sensitivity, specificity, Youden's *J,* PPV, NPV, and AUC, using the optimal cut-offs of the two scales.

Using Youden's index, the optimal cut-off value of the HCL-33 is 20, while the optimal cut-off value for HCL-33-EA is 11. The HCL-33-EA showed a better performance than the HCL-33 in discriminating BD from MDD (the maximum of sensitivity + specificity – 1: 0.51 vs. 0.41; **Table 2**). **Figure 1** shows the ROC curves of the HCL-33 and the HCL-33-EA. The HCL-33-EA demonstrated better sensitivity than the HCL-33 (0.83 vs. 0.59) to correctly identify patients with BD from patients with MDD, while the HCL-33 presented better specificity than the HCL-33-EA (0.82 vs. 0.68).

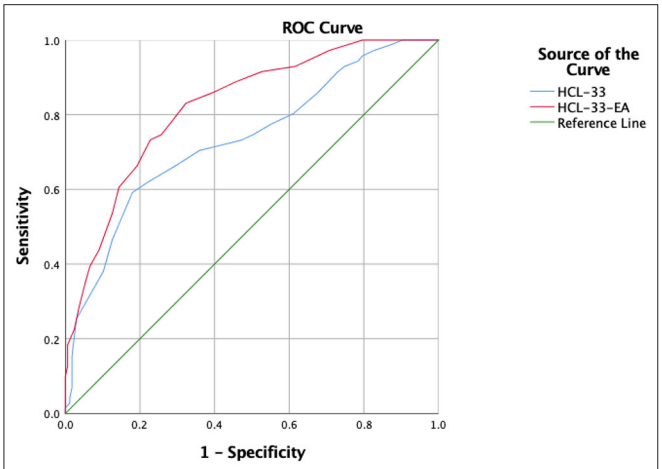


FIGURE 1 | ROC curves for the HCL-33 and the HCL-33-EA. HCL-33, Hypomania Checklist-33; HCL-33-EA, Hypomania Checklist-33-external assessment.

DISCUSSION

This was the first study to compare the screening abilities of the Chinese version of the HCL-33 and the HCL-33-EA and their consistency in identifying BD from MDD. In terms of AUC, the HCL-33-EA showed better performance than the HCL-33, although the difference did not reach significance. The HCL-33-EA had higher sensitivity and the HCL-33 had higher specificity. There is no significant difference between the two scales in terms of detection BD from MDD, and thus we recommended the joint use of the two scales. Moreover, the relatively low Youden's *J* suggests that positive screenings should be confirmed in formal diagnostic interviews with a mental health professional. While a high sensitivity is the key property of a screening instrument, the relatively lower specificity indicates that false positives will likely be included in positive screenings.

Consistent with previous findings (10), this study found the HCL-33-EA was useful in assessing hypomanic symptoms. Similar to other studies (19), we found that the HCL-33-EA had higher reliability and the HCL-33-EA total score was lower than the HCL-33. This is also the first study that calculated an optimal cut-off for the HCL-33-EA. For discriminating BD from MDD, the optimal cut-off for the HCL-33-EA was 11 in the Chinese population, which is lower than the optimal cut-off of 20 for the HCL-33 in this study and 15 in a previous study (9) as expected. The discrepancy in cut-off values could be due to the different reflection and observation on hypomanic symptoms between patient's and their carer's assessments.

The HCL-33-EA had higher sensitivity than the HCL-33, which suggests that the HCL-33-EA, and carers more generally, could have better ability to correctly identify patients with hypomanic symptoms. The HCL-33 had higher specificity than the HCL-33-EA, which suggests that the HCL-33, and patients themselves, could have better ability in correctly identifying patients without hypomanic symptoms. Although the HCL-33 and the HCL-33-EA could be used according to different clinical purposes, joint use of the two scales is associated with more reliable assessment for BD patients.

The results showed a large difference in the optimal cut-off values between the HCL-33 and the HCL-33-EA, which could be partly due to the different perspective of the interviewers. For instance, a recent study found different feelings about clinical features of anxiety between patients and their carers using the pediatric short form (completed by patients) and proxy form (completed by carers) of the National Institutes of Health's Patient Reported Outcomes Measurement Information System scale. Carers tended to identify the existence of anxiety more than the patients themselves (33). In addition, recall bias may partly account for the discrepancy between mood disorder patients' and their carers' assessments (34). Compared to patients, their carers were less likely to have recall bias; therefore, the HCL-33-EA version is more prone to identify BD than the HCL-33. The results showed there were significant, but poor agreement between the HCL-33 and the HCL-33-EA assessments ($k = 0.36$, $p < 0.001$). The gap between the subjective and the external assessments indicates the importance of the combined use of the HCL-33 and the HCL-33-EA in identifying BD patients in clinical practice. Furthermore, the HCL-33-EA had a higher sensitivity, while the HCL-33 had a higher specificity in identifying BD patients from MDD patients in this study, which suggests that patients' carers were more likely to detect BD, while patients themselves were more likely to recognize the absence of BD. Hence, use of the two scales should be considered based on the assessment purpose in clinical research or daily practice (i.e., prefer sensitivity or specificity).

This study had several limitations. First, all participants were consecutively recruited in one major psychiatric hospital, and a relatively higher proportion of BD patients, therefore the findings cannot be generalized to patients in other clinical settings, which may bias the results to uncertain extent. However, the higher proportion of BD patients in the study sample reflects the real situation in daily practice in this major tertiary psychiatric hospital in China. Second, the ICD-10 is used in clinical practice in China, therefore, the diagnosis of BD-I and BD-II cannot be established. As such, we did not examine screening capacities for BD subtypes. In addition, the Mini-International Neuropsychiatric Interview Version 5.0 cannot generate DSM-5 diagnoses. Therefore, certain specifiers related to BD, such as mixed depression, could not be assessed. Third, we were unable to explore the differences in screening abilities between different carers who provided data on the HCL-33-EA (e.g., parents, spouses, or friends). Variation in the sources of self-reports should be examined in future studies. Fourth, the psychometric properties of the HCL-33-EA need to be tested with additional measures, such as the MDQ, as reference tools. Fifth, the possibility of recall bias could not be excluded, particularly in the HCL-33 assessment (34). Finally, diagnostic properties of screening instruments (e.g., sensitivity, specificity, PPV, and NPV) are associated with disease prevalence, study design, sampling method, and sample size (35). Similar to previous studies on the psychometric properties of the HCL scales (11, 21–23), the sample size of this study was relatively small; therefore,

our findings are tentative, and will need to be replicated in future studies with a larger sample size and a multicentre design.

CONCLUSIONS

In conclusion, both the HCL-33 and the HCL-33-EA appeared to have acceptable psychometric properties and screening abilities in accurately detecting and differentiating between BD and MDD. The two scales could facilitate identification of people with BD in clinical practice, and use of the two scales should be considered based on the assessment purpose in clinical research or daily practice (i.e., prefer sensitivity or specificity).

DATA AVAILABILITY STATEMENT

The Ethics Committee of Beijing Anding Hospital that approved the study prohibits the authors from making the research data set publicly available. Readers and all interested researchers may contact Dr. Gang Wang (Email address: gangwangdoc@gmail.com) for details. Dr. Wang could apply to the Ethics Committee of Beijing Anding Hospital for the release of the data.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Beijing Anding Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent for publication was obtained.

AUTHOR CONTRIBUTIONS

Y-YW, GW, and Y-TX: study design. MF, CG, Y-YW, and YF: analysis and interpretation of data. Y-YW, GW, and Y-TX: drafting of the manuscript. BH and GU: critical revision of the manuscript. All authors approval of the final version for publication.

FUNDING

The study was supported by the University of Macau (MYRG2015-00230-FHS; MYRG2016-00005-FHS), the National Key Research & Development Program of China (Grant No. 2016YFC1307200), the Beijing Municipal Science & Technology Commission (Grant No. Z181100001718124), and the Beijing Talents Foundation (Grant No. 2017000021469G222).

REFERENCES

1. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet.* (2013) 381:1663–71. doi: 10.1016/S0140-6736(13)60989-7
2. Chou CC, Lee IH, Yeh TL, Chen KC, Chen PS, Chen WT, et al. Comparison of the validity of the Chinese versions of the Hypomania Symptom Checklist-32 (HCL-32) and Mood Disorder Questionnaire (MDQ) for the detection of bipolar disorder in medicated patients with major depressive disorder. *Int J Psychiatr Clin Pract.* (2012) 16:132–7. doi: 10.3109/13651501.2011644563
3. Culpepper L. Misdiagnosis of bipolar depression in primary care practices. *J Clin Psychiatry.* (2014) 75:e05. doi: 10.4088/JCP13019tx1c
4. Lish JD, Dimemeenan S, Whybrow PC, Price RA, Hirschfeld RMA. The National Depressive and Manic-Depressive Association (Dmda) survey of bipolar members. *J Affect Disord.* (1994) 31:281–94. doi: 10.1016/0165-0327(94)90104-X
5. Drancourt N, Etain B, Lajnef M, Henry C, Raust A, Cochet B, et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatr Scand.* (2013) 127:136–44. doi: 10.1111/j.1600-0447.2012.01917x
6. Mccombs JS, Ahn J, Tencer T, Shi L. The impact of unrecognized bipolar disorders among patients treated for depression with antidepressants in the fee-for-services California Medicaid (Medi-Cal) program: a 6-year retrospective analysis. *J Affect Disord.* (2007) 97:171–9. doi: 10.1016/j.jad.2006.06018
7. Smith D, Ghaemi S, Craddock N. The broad clinical spectrum of bipolar disorder: implications for research and practice. *J Psychopharmacol.* (2008) 22:397–400. doi: 10.1177/0269881108089585
8. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord.* (2005) 88:217–33. doi: 10.1016/j.jad.2005.05011
9. Feng Y, Xiang YT, Huang W, Wang G, Feng L, Tian TF, et al. The 33-item Hypomania Checklist (HCL-33): a new self-completed screening instrument for bipolar disorder. *J Affect Disord.* (2016) 190:214–20. doi: 10.1016/j.jad.2015.09057
10. Lojko D, Dudek D, Angst J, Siwek M, Michalak M, Rybakowski JK. The 33-item Hypomania Checklist (HCL-33) - a study of the consistency between self - and external assessments in Polish bipolar patients. *Psychiatr Pol.* (2016) 50:1085–92. doi: 10.12740/PP/66358
11. Bech P, Christensen EM, Vinberg M, Bech-Andersen G, Kessing LV. From items to syndromes in the Hypomania Checklist (HCL-32): psychometric validation and clinical validity analysis. *J Affect Disord.* (2011) 132:48–54. doi: 10.1016/j.jad.2011.01017
12. Wang YY, Feng Y, Xu DD, Huang W, Chow IHI, Ng CH, et al. The development and validation of a short version of the 33-item Hypomania Checklist (HCL-33). *J Affect Disord.* (2018) 235:206–10. doi: 10.1016/j.jad.2018.04019
13. Meyer TD, Hammelstein P, Nilsson LG, Skeppar P, Adolfsson R, Angst J. The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. *Compr Psychiatry.* (2007) 48:79–87. doi: 10.1016/j.comppsych.2006.07001
14. Yang HC, Yuan CM, Liu TB, Li LJ, Peng HJ, Liao CP, et al. Validity of the 32-item Hypomania Checklist (HCL-32) in a clinical sample with mood disorders in China. *BMC Psychiatry.* (2011) 11:84. doi: 10.1186/1471-244X-11-84
15. Poon Y, Chung KF, Tso KC, Chang CL, Tang D. The use of Mood Disorder Questionnaire, Hypomania Checklist-32 and clinical predictors for screening previously unrecognised bipolar disorder in a general psychiatric setting. *Psychiatry Res.* (2012) 195:111–7. doi: 10.1016/j.psychres.2011.07014
16. Yang HC, Xiang YT, Liu TB, Han R, Wang G, Hu C, et al. Hypomanic symptoms assessed by the HCL-32 in patients with major depressive disorder: a multicenter trial across China. *J Affect Disord.* (2012) 143:203–7. doi: 10.1016/j.jad.2012.06002
17. Gamma A, Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, et al. Transcultural validity of the Hypomania Checklist-32 (HCL-32) in patients with major depressive episodes. *Bipolar Disord.* (2013) 15:701–12. doi: 10.1111/bdi12101
18. Mosolov SN, Ushkalova AV, Kostukova EG, Shafarenko AA, Alfimov PV, Kostyukova AB, et al. Validation of the Russian version of the Hypomania Checklist (HCL-32) for the detection of Bipolar II disorder in patients with a current diagnosis of recurrent depression. *J Affect Disord.* (2014) 155:90–5. doi: 10.1016/j.jad.2013.10029
19. Fang M, Wang YY, Feng Y, Ungvari GS, Ng CH, Wang G, et al. Exploration of the psychometric properties of the 33-item Hypomania Checklist -

external assessment (HCL-33-EA). *J Affect Disord.* (2019) 245:987–90. doi: 10.1016/j.jad.2018.11023
20. Zhang L, Cao XL, Wang SB, Zheng W, Ungvari GS, Ng CH, et al. The prevalence of bipolar disorder in China: a meta-analysis. *J Affect Disord.* (2017) 207:413–21. doi: 10.1016/j.jad.2016.08062
21. Vieta E, Sanchez-Moreno J, Bulbena A, Chamorro L, Ramos JL, Artal J, et al. Cross validation with the mood disorder questionnaire (MDQ) of an instrument for the detection of hypomania in Spanish: the 32 item hypomania symptom check list (HCL-32). *J Affect Disord.* (2007) 101:43–55. doi: 10.1016/j.jad.2006.09040
22. Wu YS, Angst J, Ou CS, Chen HC, Lu RB. Validation of the Chinese version of the hypomania checklist (HCL-32) as an instrument for detecting hypo (mania) in patients with mood disorders. *J Affect Disord.* (2008) 106:133–43. doi: 10.1016/j.jad.2007.06004
23. Mosolov S, Yaltonskaya P, Senko O, Angst J. Validation of the Russian version of the hypomania checklist (HCL-33) for the detection of bipolar disorder in patients with a current diagnosis of recurrent depression. *J Affect Disord Rep.* (2021) 4:100086. doi: 10.1016/j.jadr.2021100086
24. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* (1998) 59:22–33;quiz 34–57.
25. Si TM, Shu L, Dang WM, Su YA, Chen JX, Dong WT, et al. Evaluation of the reliability and validity of Chinese version of the mini international neuropsychiatric interview in patients with mental disorders (in Chinese). *Chin Ment Health J.* (2009) 23:493–503. doi: 10.3969/j.issn.1000-6729.2009.07.011
26. World Health Organization (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.
27. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, biomedical sciences. *Behav Res Methods.* (2007) 39:175–91. doi: 10.3758/BF03193146
28. Hunsley J, Mash EJ. *A Guide to Assessments that Work*. Oxford: Oxford University Press (2008). doi: 10.1093/med:psych/9780195310641.0010001
29. Lee K, Oh H, Lee EH, Kim JH, Kim JH, Hong KS. Investigation of the clinical utility of the hypomania checklist 32 (HCL-32) for the screening of bipolar disorders in the non-clinical adult population. *BMC Psychiatry.* (2016) 16:124. doi: 10.1186/s12888-016-0831-8
30. Youden WJ. Index for rating diagnostic tests. *Cancer.* (1950) 3:32–5. doi: 10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0CO;2-3
31. Fleiss JL. *Statistical Methods for Rates and Proportions*. New York: Wiley (1981).
32. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol.* (1993) 46:423–9. doi: 10.1016/0895-4356(93)90018-V
33. Gibson DJ, Glazier JJ, Olson KR. Evaluation of anxiety and depression in a community sample of transgender youth. *JAMA Netw Open.* (2021) 4:e214739. doi: 10.1001/jamanetworkopen.202 14739
34. Boschloo L, Nolen WA, Spijker AT, Hoencamp E, Kupka R, Penninx BW, et al. The Mood Disorder Questionnaire (MDQ) for detecting (hypo)manic episodes: its validity and impact of recall bias. *J Affect Disord.* (2013) 151:203–8. doi: 10.1016/j.jad.2013.05078
35. Steinberg DM, Fine J, Chappell R. Sample size for positive and negative predictive value in diagnostic research using case–control designs. *Biostatistics.* (2009) 10:94–105. doi: 10.1093/biostatistics/kxn018

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

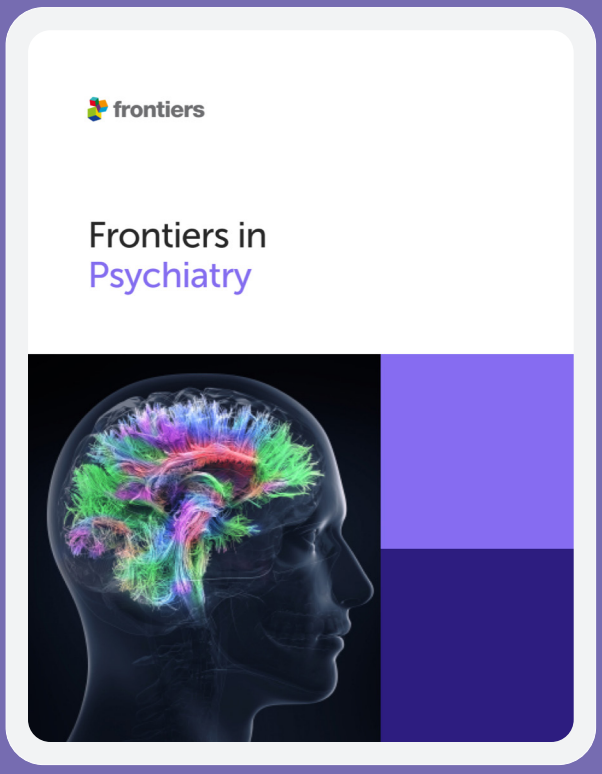
Frontiers in Psychiatry

Explores and communicates innovation in the field of psychiatry to improve patient outcomes

The third most-cited journal in its field, using translational approaches to improve therapeutic options for mental illness, communicate progress to clinicians and researchers, and consequently to improve patient treatment outcomes.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact