EARLY INTERVENTION IN MOOD DISORDERS

EDITED BY: Steven Marwaha, June S. L. Brown and Christopher G. Davey
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EARLY INTERVENTION IN MOOD DISORDERS

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EDITORIAL
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Editorial: Early Intervention in Mood Disorders

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Keywords: early intervention, mood disorder, depression, bipolar (affective/mood) disorders, school

Editorial on the Research Topic

Early Intervention in Mood Disorders

Mood disorders such as depression and bipolar disorder are a major global mental health challenge. Both are common, with the prevalence of depression being 4.4% (1) and bipolar disorder 2.4% (2). They are highly recurrent disorders, with depression causing the greatest burden of disease in young people aged 10–24, and bipolar disorder the fourth greatest (3). The peak incidence for these conditions is in the 10–24 year age group. Mood disorders damage education, relationships and personal development, and are associated prospectively with physical health problems, and with early death (4, 5). Their financial costs are very large indeed (6) and closely linked to work days lost, presenteeism, and absenteeism (7, 8).

Early intervention, meaning action in prevention and treatment of young people at elevated risk or after first onset of mood disorders is critical to reducing the major morbidity and harms of the conditions. It is desirable and important that the interventions are interdisciplinary in nature as the scale of the challenge means that multi-level approaches are needed. This includes interventions at the population level, schools, community, or in mental health or primary care clinics. These hold the promise of changing trajectory and life course of the large population of people who are impacted by mood disorders.

The collection of papers brought together in this Research Topic series offer an important glimpse into early intervention both now and for the future. Using innovative smart-phone technology to assist in monitoring of mood symptoms and rest-activity data appears critically important to the field. The work of Melbye et al. offers insight into how automatically generated smart-phone data could be linked to symptoms in 40 newly diagnosed patients with BD. Similarly, a review of 30 studies on online interventions that focussed on indicated prevention of mood disorders in people with subthreshold symptoms appears to show promise in clinical outcomes, though engagement rates may be fairly modest, suggesting that human support remains important van Doorn et al. A key task in early intervention is being able to stratify treatment. This relies on staging young people correctly when they seek help from youth mental health services so that needs, and help are matched. Work is underway in how this could be done at a service scale and in an automated fashion, with help from mental health staff as needed Iorfino et al..

New or re-purposed treatments are badly needed for people with mood disorders. Therapies are being developed and specialized for young people with at-risk features of bipolar disorder and Scott and Meyer describe the development and initial piloting of treatment on 14 young people at risk of developing bipolar disorder, focussing on problem-solving, reducing sleep-wake cycle disturbances,

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and self-management of rumination Scott and Meyer. It is also important to recognize that not all adolescents respond to medication or psychological treatment. There is emerging evidence for a different approach in repetitive transcranial magnetic stimulation (rTMS) in adolescent depression (9). Oberman et al. provide an erudite review in this area Oberman et al..

School based interventions are an important area of early intervention for young people (10). De Jonge-Heesen et al. report that providing a CBT depression prevention program for 130 adolescents with elevated depressive symptoms can lead to reduction in comorbid anxiety, leading to better outcomes in this population De Jonge-Heesen et al. Pile et al. describe a highly innovative approach to a school based intervention for the prevention of depression by reviewing the literature and describing the co-development of an imagery rescripting protocol for 37 young people with depression symptoms Pile et al..

Finally, Lagerberg et al. provide data in a much needed area; that of comorbid substance misuse in people in the early phases of bipolar disorder. They report data from 112 individuals which shows substance abuse decreased in the early phases of bipolar disorder and that stopping alcohol misuse may lead to substantial benefits in the clinical course of the condition.

This collection of research papers indicates that the field of early intervention in mood disorders is beginning to thrive, but there is much work to do, in order to meet the challenge of these disabling conditions.

AUTHOR CONTRIBUTIONS

SM wrote the initial draft of the manuscript. JB and CD contributed to content, text, and style iteratively. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Brief Research Report: A Pilot Study of Cognitive Behavioral Regulation Therapy (CBT-REG) for Young People at High Risk of Early Transition to Bipolar Disorders

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Attempts to increase early identification of individuals in the early stages of bipolar disorders (i.e., individuals at high risk of bipolar disorders and/or experiencing a subthreshold syndrome with bipolar symptoms) have highlighted the need to develop high benefit-low risk interventions. We suggest that any new psychological therapy should (i) be acceptable to young people seeking help for the first time, (ii) be applicable to "at risk" conditions and sub-syndromal states and (iii) consider pluripotent factors that may be linked to illness progression not only for bipolar disorders specifically but also for other potential disease trajectories. However, evidence indicates that current interventions for youth with emerging mood disorders mainly represent approaches abbreviated from "disorder-specific" therapies used with older adults and are primarily offered to first episode cases of bipolar disorders who are also receiving psychotropic medication. This brief report discusses empirical findings used to construct core targets for therapeutic interventions that might reduce or delay transition to full-threshold bipolar disorders. We describe an intervention that includes strategies for problem-solving, reducing sleep-wake cycle disturbances, self-management of rumination and that addresses the needs of individuals with "sub-threshold" presentations who are probably at risk of developing a bipolar or other major mental disorders. Outcome data from a case series of 14 youth indicates that the intervention appears to demonstrate a relatively high benefit-to-risk ratio, promising levels of engagement with the therapy modules, and the therapy appears to be acceptable to a wide range of help-seeking youth with early expressions of bipolar psychopathology.

Keywords: psychological interventions, early stage, bipolar disorders, adolescent, at risk

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INTRODUCTION

In young people aged <25 years, three of the four most burdensome health problems worldwide are depression, schizophrenia, and bipolar disorders (BD) (1). Given this scenario, early intervention strategies are increasingly advocated for help-seeking adolescents and young adults. To date, most interventions have been "disorder-specific" aiming to reduce or delay onsets of full-threshold

episodes of a particular diagnosis. However, it is debatable whether a pure "disorder-specific" strategy is the best option as longitudinal and concurrent comorbidity among psychotic and mood disorders is the rule rather than the exception in youth (2) and those with onsets by age 20 have the greatest risk of developing other mental disorders over the following 15 years (3, 4). Furthermore, subthreshold psychotic, depressive or bipolar syndromes show both homotypic continuity (continuity to the full-threshold disorder most similar to the subthreshold condition) and heterotypic continuity (transition to a different full-threshold disorder) (5).

The complexity and heterogeneity of the evolution of mental disorders presenting during adolescence and early adulthood (i.e., the peak age range for onset of adult-pattern illnesses) has exposed significant concerns regarding the reliability, validity and of traditional diagnoses and the applicability of "disorder-specific" interventions (6). Many experts suggest employing trans-diagnostic models as a more constructive approach for research, prevention, and clinical treatments (6, 7). Whilst this view may not be so critical to individuals with a clearly defined full-threshold first episode or with an established mental disorder, there is increasing support for this approach for individuals deemed "at high risk" of developing major mental disorders in the near future (so-called early transition). The notion of targeting earlier expressions of psychopathology or subthreshold conditions is compatible with the philosophy of clinical staging, which suggests that the evolution of severe mental disorders parallels that of chronic medical disorders (such as cancer, diabetes, etc.), and as such warrant similar approaches to clinical management (6, 7).

Clinical staging models attempt to identify where an individual is located on a "disease continuum" from an asymptomatic state in an individual with enhanced vulnerability for a specific disorder (stage 0) through to end stage disease (stage 4). The application of staging in general medicine has led to the development of interventions for individuals at the earliest clinical stages (usually designated as stages 0 and 1) with the aim of preventing progression to the later stages of illness. For example, risk factors for ischaemic heart disease, that contribute to the early stage presentations (family history of heart disease; obesity; sedentary lifestyle; high cholesterol; borderline increase in blood pressure) are often treated with behavioral or non-pharmacological interventions, with the gradual introduction of stage-specific medications and more complex treatments when the condition become more pronounced (hypertension, angina, etc.).

In psychiatry, the term "early stages" is usually used to describe asymptomatic but at-risk states (stage 0), with early expressions of psychopathology (e.g., mixed presentations with symptoms such as anxiety and depression, etc.) and more discrete subthreshold conditions (stage 1) preceding the first full threshold episode of a disorder (stage 2) (6, 7). For example, in BD, stage 0 can be represented by asymptomatic offspring of a parent with BD (OSBD). Stage 1 cases can be recognized by e.g., the presence of distress or non-specific symptoms in OSBD, or persistent sub-threshold manic symptoms, etc (6, 8). Individuals in stage 1 do not always seek help for their symptoms, but they may come to the attention of clinical services because of distress and/or reduced functioning (8).

The application of staging models to BD is still in its infancy, but the use of "staging frameworks" has led to discussions about the types of treatment modalities that can be targeted at young people in stage 1, i.e., interventions for individuals who do not have a full-threshold mental disorder and traditionally have been excluded from mental health services (8). This is an interesting problem, as it is inappropriate to simply prescribe medications that are used for stage 2 onwards because (a) there is no evidence that the medications used for later stage BD will be helpful in the early stages and (b) only about 20–30% individuals with a condition that meets criteria for Stage 1 will ultimately develop BD (i.e., the disorder for which the medication is recommended) (8). Furthermore, whilst progression to BD is a common transition pathway, the frequency of heterotypic continuity and/or of comorbid psychotic, substance misuse and other disorders has the potential to confound the choice of psychological therapy. So far, this issue is not been considered in detail in the interventions applied to stage 2 BD (i.e., first full-threshold episodes), and approaches for stage 0–1 do not appear to have addressed this problem (8, 9). The therapies for early stage BD described in the literature are potentially low-risk/high benefit, but most are abbreviated, age-appropriate versions of existing BD-specific interventions, and some add peer-groups or family meetings (8, 9). Reviews highlight that these interventions appear to target key issues in BD (such as mood instability) and that family psychoeducation (PED) may be helpful in those who are already receiving treatment (8, 9). However, outcomes of published clinical trials are inconsistent, with lack of evidence of additional benefits compared with support or control interventions (10, 11). Given these findings, and awareness that formal family PED may be unfeasible or unwanted by some adolescents and young adults, we decided to pilot an intervention that could be delivered to individuals, with an option of family sessions if appropriate. We tried to target risk factors for transition to the first full-threshold episode of BD, whilst considering the potential for heterotypic transition and aiming to improve social functioning and/or reduce other sub-threshold problems in those who did not show transition to stage 2. To do this, we examined pluripotent risk factors that may be (a) more prominent in adolescents such as changes in sleep-wake cycle regulation and cognitive-emotional regulation, (b) show associations to impaired functioning and/or the evolution of a range of adult-pattern mental disorders, and (c) may especially be linked to recurrent episodes of mood disorder and/or the onset of BD.

In this brief research article, we provide preliminary data from a pilot study that examined feasibility and acceptability of the therapy (which we describe as CBT-REG i.e., cognitive behavior therapy- regulation model), changes in presenting problems and symptoms, and estimates of changes in core target variables (such as mood, sleep, rumination). Also, we extracted information from clinical records to give an indication of individual outcomes up to 3 years post-intervention where available.

METHODS

We briefly begin by describing the intervention then briefly outline the study protocol (further information is provided in **Appendix 1**).

Intervention

We developed a new therapy model, called CBT-REG (cognitive behavior therapy- regulation model) which particularly considered the role of developmental trajectories, comorbidities, and heterotypic outcomes [for details see (12) and (13)]. While first targeting whatever problems led the individual to seeking help, our intervention then focuses on engaging the person into how to manage risk for a mood/mental disorder, alongside potential triggers for mood, activity or sleep variations that occur in the age group. Some sessions specifically focus on two robust developmental characteristics, namely disturbed sleep-wake cycle, and ruminative thinking style. To date, no interventions for young adults have been adapted explicitly to target these mechanisms simultaneously. Given their central importance to CBT-REG and the fact that they may represent underlying pathophysiological mechanisms, we briefly describe these phenomena in **Table 1**.

The rationale for selecting sleep-wake cycle (circadian regulation) and cognitive-emotional processes is because they are known to undergo predictable, developmental changes (in association with frontal lobe maturation) during adolescence and early adulthood (14). Furthermore, there is consistent evidence of inter-relationships between rumination, sleep, behavior, cognition, and mood (see **Figure 1**). Our model hypothesizes that dysregulation of these rest-activity patterns and cognitive-emotional developmental processes will exacerbate or perpetuate current mood symptoms and increase the risk of early transition from stage 1 to stage 2 or will be associated with persistent academic and social impairments and/or the evolution of other psychopathology (e.g., rumination is also increased in individuals with substance misuse) (14, 15).

The therapy comprises of four modules delivered over about 24 sessions. There is some flexibility in the course, as the duration of the first module (problem-solving and engagement) depends on the nature of the presenting problems and how readily the client engages with therapy. Also, this module offers the possibility of some family sessions if the individuals wants this option (8). The next two modules are approximately eight sessions each. The final module offers practice, skills enhancement etc. The first half of therapy is usually delivered weekly, then the second half is usually every 2 weeks. Although CBT-REG draws on some of traditional elements of Beckian CBT, the focus of CBT-REG interventions is shifted to the examination of thinking processes rather than thought content (as cognitive processing style may be a marker of risk for psychopathology) and to stabilization of the sleep-wake and physical activity-rest cycles (as opposed to daily activity planning).

The second module employs "behavioral regulation" (a modified version of behavioral activation that emphasizes the importance of preventing over-stimulation or excessive activation in those at risk of hypo/mania), alongside sessions targeting sleep-wake cycle or circadian regulation (with techniques derived from CBT for insomnia) (16, 17). Which interventions are initiated is determined by whether sleep disturbances are characterized by insomnia (which is often linked to arousal or anxiety), hypersomnia, unstable patterns, or prolonged sleep onset latency with late waking time (which may be a marker of circadian dysrhythmia) (17–20). Different modules or combined modules are used to regulate these sleep disturbances, although similar daytime interventions are used to manage physical activity across all cases (17, 21).

This next module uses techniques from rumination focused CBT (RfCBT) (22). Although this model has overlapping elements to mindfulness, we use RfCBT with youth for several reasons. For instance, it includes functional analysis and more behavioral elements, linking it well with the second module. Further, it is easier for a wide range of young people to work with RfCBT techniques, as it offers a more concrete approach with less reliance on some of the more subtle mindfulness skills. Additionally, this trans-diagnostic approach is helpful for rumination associated with distress, substance use, anxiety or depressive symptoms, and can also be used to deal with "positive repetitive self-focused thinking" (positive rumination or "basking") that has been reported in youth with cyclothymia, brief hypomania or other bipolar at-risk syndromes (20).

The RfCBT techniques and the activity-behavioral regulation techniques can also help tackle risk taking behaviors, which are sometimes employed as a maladaptive coping strategy to overcome negative rumination. These modules can be useful in helping to manage potentially harmful substance use and/or risky behaviors associated with sexual activity, etc.

The final sessions (about 4) can be extended over longer time periods if required and focus on recapping the skills and techniques that have been learnt and developing skills in identifying and managing early warning signs (primarily events, triggers, sleep and behavior change) that may indicate risk for increases in symptom levels or reductions in functioning.

The therapy is longer than many interventions for individuals at risk of BD. However, we suggest that this is helpful because it can take 6 months to produce a robust and sustained change in behavior patterns, and cognitive-emotional and sleep-circadian regulation. In addition, young people may prefer to take breaks or have pauses between modules, sometimes to take more time to practice skills from the recent module, but also because of ambivalence about the need to continue to attend sessions (which may be linked with "avoidance" or difficulty in accepting their increased "risk" status). Therapists need to be flexible in their approach, ideally allowing such pauses without formally discharging individuals from therapy, as this avoids difficulties in accessing sessions promptly (especially if symptoms or problems have worsened during any break).

Participants and Procedure

Participants in this open case series were drawn from individuals recruited to a cohort study entitled "Early identification and treatment of young people at high risk of recurrent mood disorders: a feasibility study." The cohort study and the pilot study of CBT-REG received ethical approval from the North East

TABLE 1 | Putative target mechanisms: circadian and cognitive-emotional regulation.

(a)→ Target Symptom: Sleep; Target Mechanism: Rest-Activity (Circadian) Regulation Prolonged sleep onset latency and delayed sleep phase both peak in young adults (about 14% show these patterns) and both phenomena show inverse associations with mood and cognitive functioning in non-depressed samples. Further, the degree of circadian disturbance is significantly more marked in those with emerging mood disorders, with >30% young adults with depression showing sleep phase delay according to objective actigraphy recordings. These rest-activity disturbances are reported in about 60% of those with emerging BD. Given the overlap between developmental and disease processes, we postulate that age-recognized shifts in rest-activity rhythms (usually a consequence of circadian dysregulation) act to precipitate or perpetuate illness in individuals at risk of BD or recurrent mood disorders and that targeting these abnormalities can improve outcomes.
(b)→ Target symptom: Rumination; Target Mechanism: Cognitive-Emotional Regulation Rumination is defined as a response to negative affect that involves "*repetitively and passively focusing on symptoms of distress and on the possible causes and consequences of the symptoms*." Rumination may comprise of two elements: an adaptive, reflective-distancing component (akin to "mindfulness") and a less adaptive, more toxic element referred to as "brooding," described as "getting depressed about being depressed." It is a critical marker of cognitive-emotional dysregulation as the individuals' focus on their distress (rather than on distraction to reduce dysphoria) and their passivity (rather than active problem-solving to resolve stressors) act together to intensify their negative affect. Ruminative response style is a robust risk factor for the development and maintenance of psychopathology, especially depression and recent evidence also implicates rumination in anxiety or comorbid anxiety-depressive states in younger (but not older) adults and in BD. Interestingly, those with high levels of rumination also show poorer sleep quality, and abnormal cortisol response to stress. Developmentally, the propensity to rumination peaks during middle and late adolescence (partly because of greater self-focus, etc.), and is more common in females.

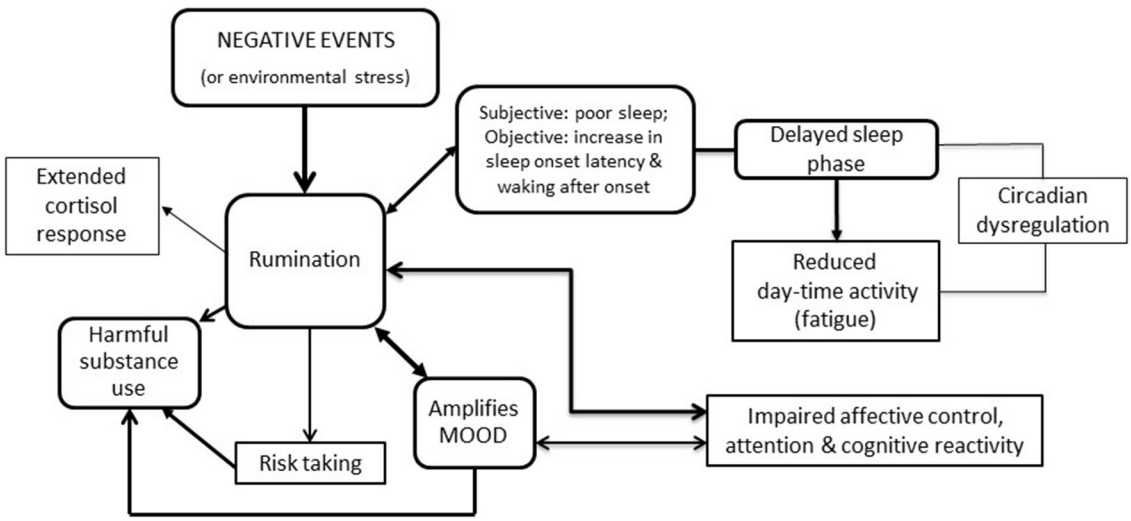

FIGURE 1 | Hypothesized links between rumination, risk taking, mood, substance use, sleep and activity (each link has been demonstrated empirically, but this working model is the first to draw connections between all the different elements).

of England Research and Ethics committee (Refs: 11/NE/0271 and 12/NE/0325).

The pilot study sought to recruit a minimum of 10 and a maximum of 15 youth aged 16–25 years. Inclusion criteria were: (i) Capable of providing written informed consent (with additional parental consent for those age < 18), (ii) Presented in the past 2 years for any problems that are/were considered to be mood-related according to a clinician working in primary care or secondary health services (such as GP clinics and/or Child and Adolescent Mental Health Services, Youth Drug and Alcohol services, adult psychiatry, crisis assessment and treatment, and/or Early Intervention in Psychosis services), and (iii) Currently help-seeking and identified as being "at risk" of BD (i.e., they met criteria for stage 0 or 1 for BD). The latter was ascertained by a comprehensive interview that included a structured clinical interview for Axis I and II diagnoses, a detailed assessment of family history, instruments used to screen for BD (e.g., General Behavior Inventory) (23), etc.

Exclusion Criteria were: (i) Evidence of the current or lifetime presence of a Bipolar I or Bipolar II Disorder diagnosed according to internationally recognized criteria (i.e., they already met criteria for stage 2 for BD), (ii) Currently being prescribed a mood stabilizer or long-term treatment with an atypical antipsychotic (iii) Clinical diagnosis of severe Borderline or Antisocial Personality disorder, and/or clinical high risk of deliberate self-harm or suicidal behaviors, (iv) Insufficient knowledge of English language, and/or (v) Other characteristics that were likely to significantly impair their ability to participate in a verbal therapy.

Individuals who met eligibility criteria, gave written informed consent, and completed the baseline assessment procedure were offered the opportunity to commence therapy.

Measures

Given the exploratory nature of this study, we included many different measurement scales (and some participants also used electronic monitoring) and findings from some of the observer, subjective and objective ratings have been reported elsewhere (8, 17, 24, 25). **Appendix 1** details the assessments, to summarize, we recorded-

1. Socio-demographics and clinical characteristics
2. Pre-and-post-therapy self-ratings of the 90-item Symptom Checklist (SCL-90R) (26), the Internal State Scale (ISS) (27) and the Work and Social Adjustment scale (WASA) (28). The ISS provided the main measure of symptoms over time (27). This self-rating comprises 16 items (each rated on 0–100 Likert scale) and allows simultaneous recording of manic, depressive, and psychotic symptoms. The 16 items are divided into four subscales: Activation (ISS-ACT); Depression (ISS-DEP); Perceived Conflict (a measure of psychotic symptoms: ISS-PC); and Well-Being (ISS-WB).

   To explore therapy targets we used the Ruminative Response Scale of the Response Styles Questionnaire (RSQ) (29) and extracted data for four key metrics selected from a self-rated sleep diary, namely: bedtime (BT), sleep onset latency (SOL), total sleep time (TST) and rise time (RT) for two consecutive weekends before and two consecutive weekends at the end of therapy. We report weekends as these represent un-entrained sleep patterns, which are likely to be better markers of sleep-wake cycle problems than weekdays (where routines are imposed by external factors such as educational class times) (20, 30).
3. Post-therapy we assessed acceptability of therapy by examining number of sessions attended and the number of dropouts. Also, we asked participants for feedback about CBT-REG regarding usefulness and difficulty of modules, satisfaction with therapy (rated 0-10) and whether would they recommend CBT-REG to others.
4. Course and Outcome: We examined clinical records for about 2 years post-therapy.

Data Analysis

We report means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous measures and counts or percentages for categorical measures. We estimated response to CBT-REG using within-group effect sizes (ES with 95% confidence intervals); large ES were defined as Cohen's $d \geq 0.80$, with medium ES defined as Cohen's $d \geq 0.40$ (up to 0.79).

RESULTS

The case series comprised 8 females and 6 males with a median age of 18.5 years (IQR-16.3–20.7), 50% ($n = 7$) resided with one or both parents; most ($n = 9$) were in late secondary or undergraduate tertiary education, two were in training, two were in paid employment and one was currently unemployed. Three individuals had a family history of BD with or without alcohol/substance misuse and two had a family history of major depression. Four individuals were seeking help for depressive and anxiety symptoms, five for intermittent or ongoing subthreshold hypomanic symptoms (with or without depression), two reported educational problems associated with cannabis and/or alcohol use, and the others reported less specific symptoms but identified a range of distressing problems such as social impairment, academic difficulties and sleep disturbances that impacted on functioning. Four individuals were receiving antidepressants for depressive or anxiety symptoms.

As shown in **Table 2**, large ES were observed for change in ISS-DEP, ISS-ACT, SCL, and RSQ (with positive 95% confidence intervals). Moderate ES were noted for ISS-PC and WASA, but 95% confidence intervals indicate these ES are less robust. It was notable that sleep metrics showed lower ES, with only RT demonstrating a medium ES ($d = 0.51$). The 95% confidence intervals indicate the need for careful interpretation, but the finding is noteworthy as RT is a core target for CBT-I and is especially linked to re-setting sleep-wake cycles. Also, it should be noted that reporting only mean BT, SOL, TST metrics over time may be misleading in youth as some individuals will report insomnia whilst others may report hypersomnia, etc. As such, the goal of therapy was to increase the TST (and/or shorten SOL) for the former group and to shorten TST (and modify SOL and RT) for the latter.

Acceptability was partly inferred from the CBT-REG completion rate. One individual attended only four initial sessions and dropped out after resolving some initial problems (interestingly, we discovered that they later returned to therapy). Two individuals dropped out after completing 14 sessions (i.e., they terminated therapy during sessions addressing sleep-wake cycle disturbances and development of preventative strategies). So, the attrition rate was 21% (lower than many studies of CBT or of psychological therapies in adults with clearly established diagnoses). The average number of sessions for CBT-REG completers was 22. Three individuals also received 2-3 family sessions. Twelve individuals provided feedback, the mean satisfaction score was of 8.40 (SD 1.95) and eight individuals stated they would and two probably would recommend the intervention to others. Two males reported some difficulties in undertaking rumination-focused interventions independently, and six individuals indicated they needed more time to implement all the different sleep-wake cycle interventions alongside developing long-term self-monitoring/self-management plans.

Follow-up revealed that two participants (one of whom had dropped out of therapy) had a full-threshold BD or psychotic disorder. One other youth, originally referred with depression and a family history of BD, was reported to have experienced a further depressive episode and had subthreshold hypomanic syndromes (but had not developed BD so far). Six individuals had been discharged from secondary care services and there was no evidence of any further significant mental health problems.

TABLE 2 | Scores pre- and post-CBT-R for 14 participants who commenced therapy.

Measure	Pre-therapy Mean (SD)	Post-therapy Mean (SD)	ES[a] and 95% CI	
Internal state scale			**ES**	**95% CI**
Depression	83.21 (69.87)	34.37 (26.57)	*0.92*	*0.12, 1.67*
Well-being*	108.97 (52.14)	130.14 (51.32)	0.41	−0.35, 1.15
Activation	104.73 (63.21)	62.98 (37.29)	*0.80*	*0.00, 1.55*
Perceived conflict	76.45 (67.22)	47.58 (32.91)	0.54	−0.21, 1.27
Symptom checklist	239.27 (53.39)	187.22 (50.42)	*1.00*	*0.02, 1.76*
Work and social adjustment*	9.91 (6.82)	14.70 (8.47)	0.63	−0.12, 1.36
Response styles questionnaire	57.81 (8.96)	42.33 (12.78)	*1.40*	*0.54, 2.18*
Sleep diary metrics				
Bedtime: 24 h clock (SD in hours)	00.35 (2.10)	23.67 (1.58)	0.37	−0.30, 1.13
Sleep onset latency in minutes	42.80 (34.71)	31.63 (22.47)	0.38	−0.31, 1.22
Total sleep time in minutes	417.00 (92.62)	425.45 (71.20)	0.10	−0.64, .86
Rise time: 24 h clock (SD in hours)	09:31 (1.65)	08:47 (1.24)	0.51	−0.02, 1.31

**Higher score for these variables indicates a better outcome (for all other self-report variables, lower scores indicate better outcomes).*
[a]ES, Effect Size, estimated as Cohen's d.
95% CI: 95% confidence intervals for the ES.
Data shown in italics indicate significant findings.

CONCLUSIONS

We are mindful that this is a small proof of principle study and that replication is required in larger-scale double blind randomized controlled trials in which the CBT-REG model described is compared with at least one other control condition. However, we are encouraged by the findings of this pilot study. Of course, the use of a case series design, reliance on self-report data to assess outcomes, and lack of adjustment of analyses for potential confounders (such as age, sex, clinical presentations, etc.) means the magnitude of the reported ES may be inflated, and the 95% confidence intervals serve as a reminder to interpret even moderately large ES carefully. Nevertheless, it is reassuring that large changes occurred in a broad range of distressing symptoms (as measured by the SCL) and in specific key targets namely depression and activation (as measured by the ISS) and rumination. Also, changes in social and behavioral regulation (as measured by the WASA) and RT were moderately large, albeit with varying confidence intervals. Given the robust data supporting the use of CBT in a wide range of major mental disorders and across all age groups, it is unsurprising that SCL and depression scores significantly decreased. Further, given the use of key strategies derived from RfCBT, is was anticipated that participants would show significant reductions in rumination. The modification/stabilization of activation (a proxy for manic psychopathology in the ISS) is notable, especially given that there was less evidence for the overall effect of CBT-REG on sleep-wake cycle disturbances. However, it is possible that the benefits of therapy on sleep disturbances may be under-estimated as we only extracted data for a few variables from the sleep diaries and focused only on average weekend measures of those metrics. This alternative explanation of the sleep findings should be born in mind as there is considerable evidence that variability in key sleep parameters may be more sensitive markers of the overall health of the sleep and circadian system, especially in BD (18, 30). Of course, given the feedback from participants that the strategies presented in the later sessions of CBT-REG were more difficult to instigate independently, it may be that more work needs to be undertaken on the balance of sessions within CBT-REG in an attempt to enhance the utility of the selected strategies (derived from CBT-I) in adolescent and young adult populations. Also, it needs to be emphasized that that the key problem(s) for which the individuals sought help was tackled first, meaning that the topics addressed later in therapy require a personal acknowledgment of a potentially increased risk for mental health problems (31).

Although case note follow-up only provides weak evidence, we do think it is worthwhile to get a snapshot of the course and outcome of case series participants. Recent research highlights that about 18% individuals with a family history of BD will develop BD or another major mental disorder during the peak age range for onset of adult pattern conditions (4, 6, 7, 31–34). Furthermore, about 10% of those with early expressions of psychopathology and about 30% of those with subthreshold manifestations of BD will develop a full-threshold mood or psychotic disorder over about 2–4 years (31–33). In those with a family history of BD and a subthreshold presentation of BD, the transition rate may be >50% over 2 years (31–34). In this pilot study of a small case series, we found evidence that about 21% could be viewed as having a poor clinical outcome with 7% of participants (one individual) developing BD, 7% a psychotic disorder, and 7% continuing to experience mood problems, but without transition to full-threshold BD (or perhaps transition

has been delayed). It is recognized that individuals who do not show transition from subthreshold to full-threshold disorders are not necessarily well, and many continue to experience a range of clinical and social impairments (4, 6, 7). As such, it is encouraging that 43% of the case series (six individuals) were known to be well enough to be fully discharged from mental health care.

A review of current interventions for individuals with emerging BD identifies that the available treatment protocols include the necessary elements to treat full-threshold BD and that the therapies give due consideration to maturational level or social context (eg. specific sessions focused on the young person's functioning at school, managing peer group pressures, individuation from parents, etc.) (8, 9). However, whilst this makes the therapies useful for young people at stage 2 of BD (i.e., already meeting criteria for a full-threshold syndrome) it is unclear if they provide sufficient strategies to comprehensively target individual needs or any unique prognostic indicators (12, 13). Also, we note that whilst family therapy is particularly efficacious in young people with emerging BD (8, 9) many of the individuals recruited to our study were already living independently (and some were residing at a long distance form their family) and only half the remaining individuals opted to engage in family sessions. This suggests that peer group or individual therapy will be an important option for many older adolescents and young adults. Also, few of the available therapies target underlying trans-diagnostic factors such as rumination (which may be associated with co-morbid substance misuse and other problems such as over-arousal, irritability and anxiety, etc.).

As early identification of individuals at risk of bipolar and other recurrent mood disorders is now being viewed as an important unmet need, we are likely to increase the service use by these groups (in the same was as was seen with early intervention in psychosis). A significant challenge is to develop more valid, evidence-based, timely interventions, that are appropriate for the early stages of BD and consider the reality of the trans-diagnostic outcomes seen in these groups of help-seeking adolescents and young adults. This requires considerable efforts from researchers in psychological therapies and potentially even greater rethinking of the underlying mechanisms that needed to be targeted by novel pharmacotherapies. We believe that our pilot study is a useful first step in trying to address the complex issues faced in trying to deliver a psychological intervention that might prevent transition to a specific disorder whilst addressing the pluri-potentiality of risk in this age and stage group, and also acknowledges the need to tackle any presenting problems or conditions that led the individual to seek clinical input in the first place. A key message from our work to date is that it is likely that the therapy for youth at risk of BD may need to be longer than anticipated, which means it is also worthwhile considering the optimal format for delivery (e.g., intermittent models with pauses, or a set of core modules with booster sessions, etc.).

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The Ethics Committee and study participants only gave permission to the EIMD researchers to use their data. Requests to access these datasets should be directed to jan.scott@newcastle.ac.uk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Cohort Study and the Pilot Study of CBT-REG received ethical approval from the North East of England Research and Ethics Committee (Refs: 11/NE/0271 and 12/NE/0325). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JS and TM were CI and senior PI respectively on the Early identification and treatment of young people at high risk of recurrent mood disorders: a feasibility study. They jointly supervised the research team, undertook the main study and the pilot study. JS wrote the preliminary draft of this report and TM undertook redrafting, both have approved the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.616829/full#supplementary-material

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Secondary Outcomes of Implemented Depression Prevention in Adolescents: A Randomized Controlled Trial

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Our most recent RCT provides evidence that indicated depression prevention is effective in reducing depressive symptoms in adolescents when implemented in the school community. In the present study we further test the potential effects of this prevention approach on symptoms related to depression: anxiety, suicidality, somatic symptoms, and perfectionism. We conducted exploratory analyses in 130 adolescents with elevated depressive symptoms aged between 12 and 16 years old ($M = 13.59$; $SD = 0.68$; 63.8% girls) who were randomly assigned to the experimental (OVK 2.0) or active control condition (psycho-education). Self-reported anxiety, suicidality, somatic symptoms, and perfectionism were assessed at pretest, post intervention, as well as 6- and 12-months follow-up. Latent growth curve analyses revealed that there was a significant decrease in anxiety in both conditions and that this decrease was significantly larger in the intervention condition than in the control condition. Somatic symptoms and socially prescribed perfectionism decreased significantly in the intervention condition and suicidality decreased significantly in the control condition. Yet there was no difference in decrease in suicidality, somatic symptoms, and perfectionism between the two conditions. This study suggest that screening on depressive symptoms and providing a CBT depression prevention program for adolescents with elevated depressive symptoms, can decrease comorbid symptoms of anxiety and therefore ensure better outcomes. We discuss the clinical implications as well suggestions for future research.

Clinical Trial Registration: The study is registered in the Dutch Trial Register for RCTs (NTR5725). Date registered: 11th of March 2016.

Keywords: cognitive behavior therapy, depressive symptoms, perfectionism, somatic symptoms, anxiety, suicidality, prevention, adolescence

INTRODUCTION

The number of adolescents experiencing depression is substantial, with ∼15.5% of adolescents experiencing depression between the ages of 11 and 19 (1). Moreover, these rates have increased in recent years, with a growing number of adolescents with untreated depression (2). The consequences of depression are tremendous, especially in adolescence. Important developmental processes take place in this phase of life, for instance the development of positive relationships and the maturation of skills that are important for life and work (3). It is therefore not surprising that the experience of depression in this developmental period is associated with several poor outcomes such as failure to complete secondary school, unemployment, and substance misuse (4, 5). Considering the negative outcomes, the prevention of depression should be a priority.

Several meta-analyses have shown that prevention programs could be effective in the prevention of depression, with the largest effect sizes for programs designed for adolescents who already have elevated depressive symptoms (6–10). Yet the implementation of these programs seems to suffer from practical barriers such as lack of communication between researchers and practitioners, poor financing, and interventions that are too complex, costly, or narrowly focused (11, 12). Until recently, it has been unclear whether the prevention effects that were found would remain when preventive interventions are implemented on a large scale.

Our most recent randomized controlled trial (RCT) about an integrated depression prevention approach (STORM: Strong Teens and Resilient Minds) examined the effectiveness of indicated prevention in reducing depressive symptoms in adolescents. This approach has a strong focus on collaboration between schools and (mental) health care partners and includes: (1) early screening for depressive symptoms and suicidal ideation, followed by clinical referral for students with acute suicidality; and (2) an indicated depression prevention program for adolescents with elevated depressive symptoms. The integration of STORM in the school community made it possible to examine the effectiveness of depression prevention under real life circumstances. In the RCT, the Cognitive Behavioral Therapy (CBT) based program entitled "Op Volle Kracht" 2.0 (OVK 2.0) was compared with psycho-education. The findings showed that OVK 2.0 was significantly more effective in reducing depressive symptoms than psycho-education 1 year after the prevention program, although it should be noted that depressive symptoms decreased in both conditions (13, 14).

These important findings are the basis from which to further unravel the potential effects of this program on other internalizing problems. It is possible that prevention strategies aimed at depression also affect other internalizing symptoms, suggesting that more adolescents with mental health needs might benefit from this prevention approach. Accordingly, the purpose of this study is to conduct exploratory analyses of the effect of indicated depression prevention on symptoms related to depression, which are: anxiety, suicidality, perfectionism, and somatic symptoms.

Anxiety, suicidality, somatic symptoms, and perfectionism are all strongly related to depressive symptoms and co-occur in a high degree (15–19). Moreover, they seem to share the same biomarkers, underlying mechanisms, and risk factors as depression, and might therefore respond similarly to a specific prevention approach (20). Despite the high comorbidity, in clinical practice it is not uncommon that these concepts cover up symptoms of depression. For example, headache and abdominal pain, which are the most frequent complaints in adolescents, are often triggered by stress and, when not acknowledged, could ultimately lead to symptoms of internalizing problems (21, 22). Also, adolescents high in perfectionism are often internally motivated to conceal internalizing symptoms, in fear of falling short of standards (23). This impedes the detection of underlying depressive symptoms, which is detrimental for several reasons, one of which is that untreated adolescent depression is related to a recurrence of symptoms in adulthood (24).

Although anxiety, suicidality, somatic symptoms, and perfectionism are related to depressive symptoms, it is unknown whether a prevention program aimed at depressive symptoms affects other symptoms too. Due to the high comorbidity and shared etiology, it could be expected that a decrease in depressive symptoms is associated with lower levels of other adverse outcomes. The outcomes of this study would add valuable information for further implementation as it is more efficient to implement interventions that also target coexisting problems. Although these analyses are largely exploratory, we hypothesized that prevention would lead to a reduction in symptoms. Specifically, we expect that adolescents who received OVK 2.0 would show larger reductions in anxiety, suicidality, somatic symptoms, and perfectionism than adolescents who received psycho-education.

METHODS AND MATERIALS

Participants

As is described elsewhere (14), in this study a total of 5,222 adolescents in the second year of secondary schools were screened for depressive symptoms. Of the 5,222 adolescents, 469 had elevated depressive symptoms and these adolescents were approached for further study. Besides elevated depressive symptoms according to the screening [score $\geq$ 14; CDI-2; (25, 26)], inclusion criteria were: sufficient knowledge of the Dutch language, and age between 11 and 15 years old. Exclusion criteria were: presence of high suicidality, already undergoing CBT for mood problems, and absence of parental permission. Ultimately, 130 adolescents aged between 11 and 15 years old participated ($M = 13.59$; $SD = 0.68$; 63.8% girls). School levels varied between vocational training (45.4%) and pre-university training (19.2%). The majority of the participants were of Dutch origin (85.4%). After obtaining informed consent from adolescents and parents, participants were randomly allocated to OVK 2.0 ($n = 66$; the intervention condition) or psycho-education ($n = 64$; the control condition). Randomization was stratified on school level and was performed by an independent researcher. Participants completed online surveys at baseline (T1), after the intervention (T2), at 6-month follow-up (T3), and at 12-month follow-up (T4). After

completion of each survey, participants received a gift voucher. More information about the participant flow is provided in **Supplementary File 1**, presenting a flow diagram of the study.

Interventions

OVK 2.0

OVK has its origin in the Penn Resiliency Program [PRP; (27)], which was developed in the United States and proved to be effective as universal prevention within a school setting (28). In the Netherlands, OVK was investigated on several prevention levels, and it was concluding that the program was not effective in the prevention of depressive symptoms on a universal and selective level (29, 30). In a shortened protocol (8 lessons instead of 16), OVK was proved to be effective in adolescent girls with elevated depressive symptoms (31). Consequently OVK 2.0 is a modified version of the original OVK program based on the program that was used in the study of Wijnhoven et al. (31). The goal of OVK 2.0 is to teach adolescents how to recognize their thoughts and emotions, and how these are related with each other and with their behavior. The training was given in eight 1-h lessons in groups of three to eight adolescents, and the techniques in the training were based on CBT. Trainers had to fill in a checklist of exercises after each lesson to measure the treatment fidelity. Adherence to the protocol ranged from 74.6 to 94.7%. The study protocol and article presenting the main effects present more details about the content of the program and the background of the trainers (13, 14).

Psycho-Education

Psycho-education consisted of a brochure with information about depressive symptoms and two e-mails with advice and tips on how to decrease depressive symptoms. For example, adolescents were encouraged to continue doing activities that used to give them a positive feeling.

Measures

Anxiety was measured with the State-Trait Anxiety Inventory [STAI; (32)]. We used the 20 items measuring state anxiety. Participants had to rate on a 4-point scale that ranged from 0 (almost never) to 3 (almost always) how they feel at the moment (e.g., "I feel nervous"). Cronbach's alpha ranged from 0.91 to 0.93 over the various assessment points.

Suicidality was measured with the VOZZ-Screen (33). This 10-item questionnaire assesses thoughts and actions about suicide, suicidal ideations, self-harm, and life. Items about life (e.g., "I feel worthless") are rated on a 5-point scale ranging from 1 (I totally agree) to 5 (I totally disagree). Items about self-harm and suicide (e.g., "I attempted suicide") are rated on a 5-point scale from 1 (never) to 5 (very often). Items about suicidal ideation in the past week (e.g., "I thought that suicide would be a solution for my problems") are rated on a 5-point scale from 1 (never) to 5 (every day). Cronbach's alpha ranged between 0.79 and 0.81 over the various assessment points.

A sum score of 23 or above is an indication of a serious suicide risk. Adolescents who appeared to be at high risk for suicidality by a score of 23 or above or by filling in the item about suicide in the CDI-2 with "I want to end my life," were seen by a professional of the public health service within the school. Subsequently, parents were informed, and eventual information about referrals were provided.

Somatic symptoms were measured with the Dutch version of the Children's Somatization Inventory [CSI; (34, 35)], consisting of 35 items on which participants had to rate on a 5-point scale from 0 (no suffering) to 4 (much suffering) to what extent they have been bothered by somatic symptoms in the past 2 weeks (e.g., "abdominal pain"). Cronbach's alpha was 0.92 at all timepoints.

Perfectionism was measured with the Dutch version of the Frost Multidimensional Perfectionism Scale [F-MPS; (36, 37)]. This questionnaire contains 35 items and six subscales of perfectionism: concern over mistakes, doubts, personal standards, organization, parental expectations, and parental criticism. Participants have to rate to what extent each statement fits them on a scale ranging from 1 (strongly disagree) to 5 (strongly agree). For the purpose of the present study, we only used the subscales concern over mistakes (e.g., "I hate being less than the best at things"), doubt about actions (e.g., "I usually have doubts about the simple everyday things I do"), and personal standards (e.g., "I set higher goals than most people").

In line with the literature on perfectionism (19), we distinguished two factors in perfectionism: personal standards perfectionism (PS; sum score of personal standards, 7 items) and concerns about mistakes and doubts perfectionism (CMD; sum scores of concerns about mistakes and doubt about actions, 13 items). PS represents self-orienting perfectionism (setting unreasonably high standards and goals) and CMD represents socially prescribed perfectionism [doubts and excessive concern for mistakes; (36, 38)]. Cronbach's alpha ranged between 0.86 and 0.88 for PS and between 0.91 and 0.94 for CMD over the various assessment points.

Strategy of Analyses

Data were analyzed with the statistical package Mplus version 7.2 (39). First, we used descriptive statistics and z-tests to analyze differences in the measured concepts at all timepoints. Next, we used Latent Growth Curve Models (LGCM) to test the longitudinal effectiveness of OVK 2.0 on secondary outcomes, according to the intent-to-treat principle. The Full Information Maximum Likelihood estimator [FIML; (40, 41)] was used to handle missing data under the condition that missings are at random. Little's MCAR test showed that completely missing at random was supported ($\chi^2_{[362]} = 394.81$, $p = 0.113$). Five participants were excluded from the analyses because of missing data at all four timepoints, two from the intervention condition and three from the control condition.

The procedure COMPLEX with the robust maximum likelihood estimator (MLR) was used to control for non-independence of the data because of nesting participants within the 13 schools. We used the following fit indices: Chi-square (*df*), the Root Mean Square of Approximation [RMSEA; values < 0.08 means acceptable fit; (42)], and the Comparative Fit Index [CFI; values > 0.90 means acceptable fit; (43)].

In the study for main effects of the RCT (14), a linear growth model for depressive symptoms was accepted above a quadratic

one, because a quadratic model was overfitting the data (44). This was also the case for the secondary outcomes, and a linear growth model for each of the secondary outcomes was accepted as most adequate. Parameters were intercept (*i*; initial estimated level) and slope (*s*; estimated degree of change over time) as latent growth parameters, and time was coded in months (0, 3, 6, and 12 months). For anxiety, the linear model showed a fit of $\chi^2_{(12)} = 33.35$, $p = 0.001$, RMSEA = 0.169, CFI = 0.904. For suicidality, the fit of the model was $\chi^2_{(12)} = 12.11$, $p = 0.437$, RMSEA = 0.012, CFI = 0.999. For somatic symptoms, the fit of the model was $\chi^2_{(12)} = 31.21$, $p = 0.002$, RMSEA = 0.161, CFI = 0.888. The model fit of PS perfectionism was $\chi^2_{(12)} = 34.75$, $p = 0.001$, RMSEA = 0.175, CFI = 0.866. Finally, the model fit of CMD perfectionism was $\chi^2_{(12)} = 11.28$, $p = 0.505$, RMSEA = 0.000, CFI = 1.000. The fit of three models was acceptable for the CFI with values > 0.90, but two models had a CFI-value somewhat below 0.90. Additionally, the fit for three models was less acceptable for the RMSEA (the models of anxiety, somatic symptoms, and PS perfectionism). However, for small samples cutoff values of 0.10 for RMSEA are too restrictive (45), and acceptable models might be over-rejected (46). Moreover, poor global fit indices (CFI and RMSEA) can be misleading: they may still be consistent with a good approximation of individual growth curves (47). Therefore, these models were accepted.

Next, we used the χ^2 difference test to test differences in intercept between the intervention and control condition, by comparing the χ^2 value of the unconstrained model with the χ^2 value of the growth model where both intercepts were constrained to be equal. A significant difference in intercept was indicated when the χ^2 value significantly differed between the conditions. For testing differences in slope, the testing procedure was repeated by comparing the equal intercept constrained model with the equal intercept and equal slope model.

RESULTS

As emerged from the screening, 469 adolescents reported elevated depressive symptoms. Of these adolescents, 130 participated in our study. The percentage of adolescents completing the surveys at baseline (T1), post-intervention (T2), 6-month (T3) follow-up, and 12-month (T4) follow-up were 88.5, 71.5, 80.0, and 80.0%. The descriptive statistics and test results of the comparison between intervention and control condition for all secondary outcomes are presented in **Table 1**. No significant differences between the intervention and control condition in suicidality, somatic symptoms, and CMD were found. Anxiety differed with marginal significance between the conditions at T4, with higher means in the control condition. In addition, PS differed significantly between the conditions at T2 and at T4, with higher means in the control condition. Correlations between the outcome variables and depressive symptoms are presented in **Supplementary File 2**.

TABLE 1 | Means, standard deviations, and z-values for differences on anxiety, suicidality, somatic symptoms, and perfectionism (PS and CMD) between the intervention and control conditions.

	Intervention condition (*N* = 64)		Control condition (*N* = 61)			
	M	*SD*	*M*	*SD*	*z*-value	*P*
Anxiety T1	42.73	10.21	42.51	11.18	0.13	0.896
Anxiety T2	38.72	11.15	39.38	11.35	−0.27	0.786
Anxiety T3	38.48	11.96	40.29	11.79	−1.17	0.241
Anxiety T4	34.65	11.07	38.50	10.58	−1.92	0.055
Suicidality T1	17.92	4.77	19.40	6.42	−1.23	0.219
Suicidality T2	17.76	6.22	19.24	6.50	−1.62	0.105
Suicidality T3	16.83	5.56	18.61	6.52	−1.70	0.089
Suicidality T4	16.70	5.76	18.06	5.90	−1.75	0.080
Somatic symptoms T1	20.01	13.76	22.24	18.63	−0.60	0.547
Somatic symptoms T2	19.22	16.49	18.17	17.03	0.44	0.660
Somatic symptoms T3	16.46	14.15	19.82	16.85	−1.21	0.226
Somatic symptoms T4	16.87	15.78	18.51	16.95	−0.37	0.715
PS perfectionism T1	15.19	7.15	15.24	6.26	−0.08	0.935
PS perfectionism T2	13.18	5.41	15.30	6.90	2.71	0.007
PS perfectionism T3	14.33	6.08	15.53	7.33	−1.58	0.114
PS perfectionism T4	13.80	5.61	15.34	6.94	−2.38	0.017
CMD perfectionism T1	26.97	10.91	27.88	10.92	−0.36	0.715
CMD perfectionism T2	24.14	10.46	25.38	11.48	−1.17	0.243
CMD perfectionism T3	25.15	11.36	26.56	12.93	−0.84	0.400
CMD perfectionism T4	22.93	11.07	25.53	10.61	−1.65	0.099

LATENT GROWTH CURVE MODELING

First, we examined the linear growth models of anxiety, suicidality, somatic symptoms, PS perfectionism, and CMD perfectionism for the intervention and control conditions. The results of these analyses are presented in **Table 2**. Besides the intercepts and slopes, the fit measures of the baseline models are also described in this table. The results show that slopes are significant for anxiety, showing that anxiety decreased over time in both conditions. The significant negative slopes for somatic symptoms and CMD perfectionism in the intervention condition indicate a decrease over time as well. Furthermore, suicidality decreased significantly in the control condition and showed a decreasing trend in the intervention condition.

Second, we tested whether intercept and slopes differed between the intervention and control condition (last four columns in **Table 2**). For anxiety only, the Chi-square difference tests between groups showed that the slopes in the intervention and control group were significantly different (see **Table 2**). The decrease in anxiety in the intervention condition (s = −0.62) was stronger than in the control condition (s = −0.24). **Figure 1** shows the course of anxiety in the intervention and control condition.

DISCUSSION

This study examined the effectiveness of depression prevention on anxiety, suicidality, somatic symptoms, and perfectionism in an implemented depression prevention approach for adolescents with elevated depressive symptoms. The findings from the present study showed that anxiety decreased significantly in both conditions and that the decrease was significantly greater in the intervention condition than the control condition. Furthermore, somatic symptoms and concerns about mistakes and doubts perfectionism decreased significantly in the intervention condition, and suicidality decreased significantly in the control condition. However, the decreases in somatic symptoms, concerns about mistakes and doubts perfectionism, and suicidality did not significantly differ between the two conditions. In addition to the significant effect on depressive symptoms (14), these findings show that the integrated prevention approach in this study might have broader effects than targeting depressive symptoms.

The significant effect of the depression prevention program on anxiety is encouraging, considering the evidence that 10–50% of the adolescents have comorbid levels of depression and anxiety (48, 49), and that the presence of comorbid anxiety predicts a severity in depressive symptoms (50, 51). In addition, the presence of both depression and anxiety predicts worse outcomes (e.g., increased risk of recurrence or poor treatment response) than either of these alone (52–54). The present study suggests that screening for depressive symptoms and providing a CBT depression prevention program for adolescents with elevated depressive symptoms can decrease comorbid symptoms of anxiety, and therefore has the potential to ensure better outcomes.

TABLE 2 | Results of latent growth curve analyses for the five outcome variables.

	Intervention group				Control group				Fit measures of baseline model				Test between groups			
													For intercepts		For slopes	
	i	*p*	s	*p*	i	*p*	s	*p*	$\chi^2(12)$	*p*	CFI	RMSEA	$\Delta\chi^2(1)$	*p*	$\Delta\chi^2$ (1)	*p*
Anxiety	41.91	0.000	−0.62	0.000	41.40	0.000	−0.24	0.001	33.35	0.001	0.904	0.169	0.08	0.777	5.76	0.016
Suicidality	17.84	0.000	−0.10	0.065	19.41	0.000	−0.11	0.001	12.11	0.437	0.999	0.012	2.42	0.120	0.26	0.610
Somatic symptoms	19.29	0.000	−0.21	0.036	20.62	0.000	−0.18	0.070	31.21	0.002	0.888	0.161	0.23	0.632	0.12	0.729
PS perfectionism	13.69	0.000	0.02	0.682	15.28	0.000	0.02	0.778	34.75	0.001	0.866	0.175	1.74	0.187	0.53	0.467
CMD perfectionism	26.15	0.000	−0.27	0.005	27.45	0.000	−0.16	0.150	11.28	0.505	1.000	0.000	0.44	0.507	1.10	0.294

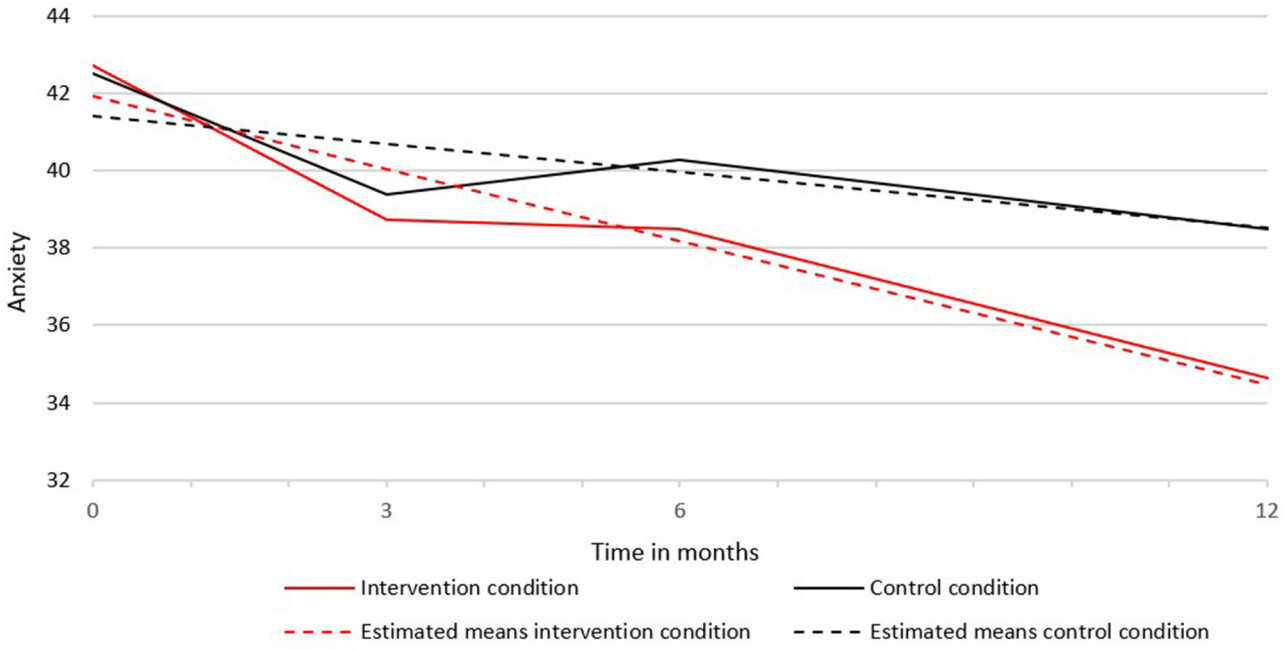

FIGURE 1 | Mean scores of anxiety over time in the intervention and control condition.

This finding is in line with research showing that CBT is effective for a wide range of emotional problems, including symptoms of anxiety (55). Although CBT programs for anxiety and depression vary in the strategies that are included, they share the same focus, which is cognitive restructuring by teaching the interplay between thoughts, feelings, and behaviors. Moreover, the CBT techniques might focus on the fundamental cognitive distortions that underlie both anxiety and depression (56). For example, the fear of rejection or the belief that one is not capable enough can cause both depressive symptoms and symptoms of anxiety. This overlap in techniques and focus might account for the significant effect of depression prevention on anxiety (20, 57).

However, the effect of depression prevention on anxiety is in contrast with [Garber et al. (56)], who tested in a meta-analytic review the cross-over effects of anxiety programs on depressive symptoms, and of depression programs on symptoms of anxiety. They found crossover effects for both depression and anxiety in treatment programs but not in targeted prevention programs, concluding that treatments for anxiety and depression may have broader effects than just the target they aimed at, but that prevention programs do not. Yet the review was focused on effects directly after treatment, which might underestimate prevention effects, as in our RCT significant effects were found 1 year after the program. Also, the mean level of depressive symptoms in our sample was near the level of clinical symptoms ($M = 15.76$, clinical symptom level ≥ 14), which might indicate that our findings are more comparable with treatment effects.

Still, the fact that despite the high comorbidity with depressive symptoms and their shared etiology, CBT depression prevention was not significantly more effective in the reduction of suicidality, somatic symptoms, and perfectionism than psycho-education, is thought-provoking. One explanation might be found in the content of the prevention program, which might not be sufficient in targeting these symptoms. Considering the content and therapeutic elements in interventions that target suicidality, somatic symptoms, and perfectionism, there are specific techniques that were not included in our prevention approach. For example, studies on adults support the use of CBT in the treatment of somatic symptoms, with 6–16 sessions of CBT leading to a reduction in symptoms (58). Yet these treatments include, besides the traditional CBT techniques, techniques that are more body oriented, such as relaxation techniques, mindfulness, guided imagery, and techniques that deal with specific somatic symptoms (59). Mindfulness is also suggested by researchers as an effective technique for treating perfectionism, in particular by learning to disengage from repetitive negative thinking (60). Furthermore, programs aimed at the reduction of suicidality contain interventions that differ from traditional CBT programs, such as techniques to increase help-seeking behavior, social support, and safety behavior (61). So, although CBT might have some benefits for these symptoms, they might require alternative or at least additional techniques.

According to this interpretation, the fact that not all comorbid problems respond to the same prevention strategy has some important implications for future research as well as for clinical practice. Since our main findings show that there is a substantial group of adolescents who did not respond to the CBT prevention in terms of a decrease in depressive symptoms (61.7%), we need to examine how prevention effects can be maximized. It is possible that there is a group of adolescents who did not

respond to CBT prevention because of comorbid symptoms that impede the prevention effect. Arguing that the presence of certain symptoms, for instance perfectionism, calls for another intervention might also suggest that CBT is less effective in reducing depressive symptoms when there is comorbid perfectionism. Although future research should disentangle this further, more knowledge about the group of non-responders might lead to a more personalized prevention approach.

STRENGTHS AND LIMITATIONS

The most important strengths of this study are the longitudinal design, the use of an active control group, and the implementation of preventive interventions in school communities. These strengths made it possible to examine the effectiveness of OVK 2.0 under real life conditions and to make substantial conclusions about the effectiveness. Also, the results are generalizable as the sample include both boys and girls from different school levels. Still, this study has some limitations. Although the sample was large enough to examine the effect on the outcome variables, it was insufficient to examine the effect on outcomes variables when controlling for depressive symptoms or as moderators in the effect on depressive symptoms. Such analyses would provide more information about the underlying mechanism of prevention and the additional effect of prevention on related symptoms when accounting for depressive symptoms. In addition, only 27% of the adolescents who emerged from the screening were willing to participate in the study, and therefore, selection bias must be considered [see also (14)]. Other limitations are the reliance on self-reports only, which might have caused socially desirable behavior, the lack of measurement of the fidelity of psycho-eduction, and the possible performance and assessment biases as allocation was not concealed. Finally, randomization was carried out on school level, which limited the random allocation of adolescents.

CONCLUSIONS

The findings of the present study show that integrated depression prevention seems to be effective in reducing symptoms of anxiety in adolescents with elevated depressive symptoms. Although these symptoms frequently co-occur with depressive symptoms and share the same risk factors, we argue that additional techniques are necessary to target these problems. Regarding suicidality, we recommend future prevention studies to continue monitoring the effect of prevention programs on symptoms of suicidality (with appropriate risk management). Although just a small number of adolescents with suicidal ideation proceed to make an actual suicide attempt, the consequences for the environment are tremendous and we are obliged to do everything we can to decrease the number of suicides at this young age.

In conclusion, given the high prevalence rates of depression in adolescents and the poor outcomes when there is comorbid anxiety, these findings are hopeful. Therefore, this study provides further support for the implementation of an implemented prevention approach in which adolescents with elevated risk for depression are identified and offered an evidence-based prevention program to reduce the risk of developing depression or other negative outcomes.

DATA AVAILABILITY STATEMENT

The data for the current study is not publicly available due to the containing information that could compromise research participant privacy, but they are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CMO Arnhem-Nijmegen. Written informed consent to participate in this study was provided by the participants and participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KJ-H, KE, SR, DC, and RE conceptualized and contributed to the design of the current study. KJ-H and KE were responsible for the coordination of the data collection. KJ-H wrote all the sections in the manuscript. SR reviewed and revised all sections of the manuscript. AV assisted in the planning, execution of data analyses, and description of the results. DC, RS, and RE all helped to draft the manuscript by providing feedback. All authors have made substantive intellectual contributions to the paper, read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.643632/full#supplementary-material

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REVIEW
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Repetitive Transcranial Magnetic Stimulation for Adolescent Major Depressive Disorder: A Focus on Neurodevelopment

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Adolescent depression is a potentially lethal condition and a leading cause of disability for this age group. There is an urgent need for novel efficacious treatments since half of adolescents with depression fail to respond to current therapies and up to 70% of those who respond will relapse within 5 years. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment for major depressive disorder (MDD) in adults who do not respond to pharmacological or behavioral interventions. In contrast, rTMS has not demonstrated the same degree of efficacy in adolescent MDD. We argue that this is due, in part, to conceptual and methodological shortcomings in the existing literature. In our review, we first provide a neurodevelopmentally focused overview of adolescent depression. We then summarize the rTMS literature in adult and adolescent MDD focusing on both the putative mechanisms of action and neurodevelopmental factors that may influence efficacy in adolescents. We then identify limitations in the existing adolescent MDD rTMS literature and propose specific parameters and approaches that may be used to optimize efficacy in this uniquely vulnerable age group. Specifically, we suggest ways in which future studies reduce clinical and neural heterogeneity, optimize neuronavigation by drawing from functional brain imaging, apply current knowledge of rTMS parameters and neurodevelopment, and employ an experimental therapeutics platform to identify neural targets and biomarkers for response. We conclude that rTMS is worthy of further investigation. Furthermore, we suggest that following these recommendations in future studies will offer a more rigorous test of rTMS as an effective treatment for adolescent depression.

Keywords: depression, rTMS, adolescence, neurodevelopment, individualized targeting

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INTRODUCTION

Adolescent depression is a leading cause of disability, yet its treatment remains unsatisfactory. Thus, there exists an urgent need for novel, neurodevelopmentally-informed, targeted therapeutics. Repetitive Transcranial magnetic stimulation (rTMS) has emerged as a promising treatment modality for adult major depressive disorder (MDD). rTMS is a non-invasive method to modulate brain network functioning through the application of pulsed magnetic fields (1). Several reviews concluded that rTMS could be a potentially safe and effective treatment for adolescent depression (2–6), however, empirical studies yield mixed results.

Indeed, the sole large-scale ($n = 103$) randomized controlled trial (RCT), an industry-sponsored effort to extend FDA clearance for rTMS to depression in adolescents, was negative (7), that is, did not show a difference between rTMS and sham control.

In light of this trial, this review focuses on how neurodevelopment creates challenges for development of rTMS protocols in this population and provides specific recommendations to overcome these complexities. We highlight the developmental pathophysiology underlying symptoms of adolescent depression and relate these to the putative mechanisms of action of rTMS. We propose that future studies employ experimental therapeutics approaches to identify predictive biomarkers of response and to develop individualized, neurodevelopmentally informed rTMS targets.

Relevant studies were ascertained via a literature search of PubMed and Google Scholar. The search was limited to English-language peer-reviewed articles. The search terms used were: "adolescent depression" and "TMS" or "rTMS." Also, to ensure that we accurately represented the full extent of the literature, we examined previously published review articles. We excluded studies that applied single-pulse TMS, paired-pulse TMS, or other non-therapeutic TMS protocols, trials. We also excluded studies that evaluated depressive symptoms in adolescents with other primary clinical conditions [e.g., Tourette syndrome or autism spectrum disorder (8, 9)].

A NEURODEVELOPMENTAL OVERVIEW OF ADOLESCENT DEPRESSION

The World Health Report suggests that depression is the leading cause of disability worldwide, affecting over 264 million people (10, 11). The prevalence of moderate-to-severe depressive symptoms in youth between the ages of 12 and 17 is estimated to be 5.7% (12) with a cumulative prevalence of around 10% by age 16 (13). Moreover, depressed adolescents are about 30 times more likely to commit suicide compared to their non-depressed counterparts (14). Suicide is one of the leading causes of death in adolescents in the US and adolescence is also the time of peak incidence of suicidal behaviors and suicidal ideation (15). Despite the substantial individual and societal impact associated with depression in youth, treatment options are limited (16, 17). Traditional treatment methods include psychopharmacology (e.g., serotonin reuptake inhibitors) and behavioral therapy [e.g., cognitive behavioral therapy (CBT)]. The Treatment of Adolescent Depression Study (TADS), however, found that only 37% of patients experienced full remission of symptoms after 12 weeks of these first-line treatments (18). Furthermore, even with the combination of two evidence-based treatment modalities, at least a third of youths treated for depression do not respond, 20–37% only have a partial response, and 40–70% experience a relapse or recurrence (19–21). Thus, there remains a significant need for the development of new treatments.

In addition to the morbidity and mortality, there is significant financial burden of adolescent depression including: costs of health care use, productivity lost, and time off of work for caregivers. Estimates of direct costs of adolescent depression amount to ∼$2,900 additional dollars per year. This does not consider the indirect costs of reduced/lost productivity, which in adult depression is estimated as high as $12,000 per year (22). Given this financial burden, the cost-efficiency of treatment options is also a consideration. Pharmacotherapy, estimated at $100 per month is the least expensive therapy, followed by psychotherapy, estimated at $100–$150 *per session*. Both pharmacotherapy and psychotherapy are significantly less expensive than rTMS for a given depressive episode. However, one industry-sponsored study of individuals who failed a single course of antidepressants, applied simulation modeling to compare costs of rTMS therapy to multiple serial medication trials and suggested that rTMS may cost less in over the course of the patients' lifetime (23).

Adolescence is not only a time when the incidence of depression increases (24), but also a period of substantial social, emotional, and biological development. These developmental changes may contribute to risk factors and mechanisms underlying adolescent depression (25). Synapses in the adolescent brain are highly dynamic; new synapses are formed and others eliminated at higher rates than seen in adults (26, 27). Proposed developmental models of the increased risk of psychopathology in adolescence point to a mismatch in the growth of brain networks supporting emotional reactivity and regulation. Compared to brain networks subserving emotion regulation, those pertaining to emotional reactivity develop more rapidly (28, 29). The prefrontal cortex (PFC) is a key node in the emotion regulation network underlying complex cognitive tasks such as inhibition, working memory, cognitive control, and attention. The PFC undergoes age-dependent functional changes well into late adolescence and early adulthood (30–32). Structural neuroimaging shows decreases in total gray matter PFC volume starting at around 11–12 years old (33, 34). This decrease is thought to be associated with synaptic pruning (27). In contrast, imaging metrics of myelination, axon density and white matter volume in frontal regions, show relatively linear increases across adolescence (35–39). It is postulated that an imbalance of the immature PFC and the more mature frontal subcortical systems regulating emotional reactivity might lead to a predominance of "bottom-up" emotional reactivity (40–44).

On a molecular level, these adolescent neurodevelopmental changes are thought to result from fluctuations in neurotransmitter concentration and receptor expression. Notably, fluctuations in neurotransmitter systems, such as GABA (45, 46), NMDA (47), and dopamine (48, 49) have profound impact on neural signaling in regions pertaining to emotion regulation. GABAergic and glutamatergic systems in the PFC and cingulate cortices have a direct impact on the excitability and plasticity in regions subserving emotion regulation (50). Fluctuating dopamine levels and emergence of dopamine receptor-mediated facilitation of NMDA (glutamate) receptor transmission and GABAergic interneuron excitability both have been proposed as a mechanism of increased sensitivity to rewards, novelty, or other salient stimuli (51–53). These cellular and molecular changes in adolescence lead to imbalances in excitation and inhibition, changes in cortical plasticity and

connectivity, and less effective transferring of information between critical emotion processing brain regions (50, 54).

The pathophysiology that underlies adolescent depression may differ from that in adults (54). Studies in clinical samples and animal models suggest that these aberrant maturational processes contribute to adolescent depression (55). In one magnetic resonance spectroscopy (MRS) study, adolescents with depression showed decreased levels of GABA in the anterior cingulate cortex (ACC), as compared to healthy adolescents. Furthermore, this difference was specifically related to anhedonic symptoms (56). Another study found that symptom severity in both adults and adolescents with depression correlated with GABA and glutamate + glutamine (Glx) concentrations in the PFC (57, 58).

Neurodevelopmental changes and pathophysiology need to be considered when designing trials of novel targeted therapeutics, such as rTMS. In the next section we review the literature on rTMS. We suggest that future rTMS protocols may benefit from applying neurodevelopmentally-informed approaches of modulating aberrant brain networks and neurotransmitters to treat adolescent depression.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN ADULT AND ADOLESCENT MAJOR DEPRESSIVE DISORDER

TMS is a non-invasive neuromodulation technique that is increasingly utilized in clinics and laboratories world-wide to study and treat a range of neurological and psychiatric disorders. In research, TMS can be applied in single pulses to depolarize a small population of neurons in a targeted brain region. Single-pulse TMS can be used to measure cortical excitability, study central motor conduction time, or the cortical silent period (a measure of intracortical inhibition), or map effective connectivity between the stimulated region and other brain regions (59). TMS can also be applied in pairs of pulses (i.e., paired-pulse stimulation); two pulses are presented in rapid succession to study intracortical inhibition and facilitation (60, 61).

During rTMS, trains of regularly repeating TMS pulses are applied at various stimulation frequencies (e.g., 1, 5, 10 Hz) and patterns [e.g., Theta Burst Stimulation (TBS) (62) or Quadrapulse Stimulation (QPS) (63)]. Compared to paired-pulse or single-pulse stimulation protocols, rTMS pulses temporally summate to produce longer lasting changes in neural activity (64). Stimulation frequencies 1 Hz or lower are thought to produce local cortical inhibition while those 5 Hz or higher are thought to generate local cortical excitation (64, 65). There are also specific patterned forms of rTMS including intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS). iTBS and cTBS protocols lead to long-lasting facilitation and suppression of cortical excitability, respectively. Compared to 30 min or more for the standard 10 Hz rTMS procedures, a single session of cTBS and iTBS takes ∼40 s and 3 min, respectively.

At a system-level, rTMS modulates excitability in targeted regions of stimulation (66–69) and exerts broader effects across networks connected to those regions (70–74). Thus, in adolescents with depression, rTMS applied to PFC could mitigate some regional prefrontal pathophysiology and aberrant functional connectivity between PFC and the limbic system. Furthermore, if successful, modulating these systems during adolescence, a critical period of PFC maturation, could potentially generate longer term clinical benefits than seen in adults. However, the degree and direction of neurophysiological effect of rTMS are influenced by the state of excitability of the targeted cortical region and the degree of functional connectivity across the targeted network (75, 76). In addition, as noted above, there is considerable inter-individual variability at the symptom and pathophysiological level. Thus, it is important to characterize the current brain state in terms of local cortical excitability and network connectivity in order to determine the optimal treatment protocol for a given individual. As will be described below, identifying the optimal target and protocol for a given individual remains theoretical due to the complex etiology of adolescent depression.

Safety and Mechanisms of Action of rTMS in Adult and Adolescent MDD

The safety of TMS in clinical practice and research has been evaluated through multiple meta-analyses (77–80). Safety guidelines have also been disseminated by the International Federation of Clinical Neurophysiology (81–83). Widespread application of several TMS protocols, across diverse populations and devices, show a low incidence of Adverse Events (AEs) (84). This safety record led to FDA clearance of rTMS for the treatment of adult MDD and adult obsessive-compulsive disorder (OCD) in 2008 and 2018, respectively.

Initial rTMS trials in depression were based on theory that the clinical symptoms might arise from an imbalance between PFC hypometabolism and the limbic system (85). Early studies aimed to increase excitability in regions of PFC that were thought to influence regulation of the limbic system (66, 86–88). Subsequent blood oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) studies suggest that rTMS modulates both activity and connectivity of the targeted region and related networks (74, 89–94). Of note, the cellular and molecular mechanism of action of rTMS is still under investigation (95). At a system level, the Human Connectome Project (96, 97) has led to development of resting state functional connectivity (RSFC) signatures that are being proposed as individualized rTMS targets (98–101). It has also been suggested that some of the changes seen on fMRI following rTMS may result from modulations in GABA and glutamatergic systems (2, 57, 102–106).

As compared to the adult literature, the data on the safety of rTMS in adolescent depression are lacking. However, the data that exist suggest a similar safety profile in older children and adolescents as compared to adults. Allen et al. (107) conducted a systematic review of TMS safety in pediatric populations (including healthy volunteers and youth with neurological and/or psychiatric disorders) in 2017. Forty-two single-pulse and/or

paired-pulse TMS studies (n = 1,205) and 26 rTMS studies (n = 360) were reviewed. Adverse event rates ranged from 3.4 to 10.11% and varied based on the patient population being studied, the form of TMS being applied, and the number of sessions applied. Those with known neurological disorders or those receiving epileptogenic medications for psychiatric disorders were more at risk of adverse events. Similarly, adverse events were more common in high-frequency and/or high intensity rTMS protocols and protocols that involved a higher number of sessions (107). In 2020, Zewdie et al. (108), who run a pediatric brain stimulation clinical research program, published a report on their experience with the safety and tolerability of TMS in a cohort of 384 youth (108). The individuals in this report included healthy volunteers (n = 118), patients with perinatal stroke (n = 101), patients with mild traumatic brain injury (n = 121), and patients with neuropsychiatric disorders (n = 37). They report no serious adverse events and excellent tolerability despite over a hundred patients who were at greater risk for seizure due to a neurological condition. As with previous reports, Zewdie et al. note that the most common side-effects were transient headache and neck pain. The authors conclude that standard TMS paradigms, including single pulse, paired-pulse, and rTMS, should be considered minimum risk and provide a safety and tolerability evaluation form for use in this population.

In 2015, Krishnan et al. conducted a safety review involving 35 studies (n = 322) focused on the use of rTMS in children and adolescents with range of conditions (109). Fifteen studies reported no adverse events or that the treatment was "well-tolerated," without specifying adverse events. The most common adverse events reported were headache (11.5% of patients) and scalp discomfort (2.5%). A third pediatric TMS safety study was conducted by Hong and colleagues in 2015 and focused specifically on the safety and tolerability a novel rTMS paradigm, namely TBS (110). This retrospective analysis (n = 76) reported adverse events in 10.5% of TBS sessions including: headache, arm/hand/other pain, numbness/tingling, and weakness (110). The rate and severity of adverse events reported in this study did not differ between those that received TBS and a comparator group of 89 youth who received single- and paired-pulse TMS. Similar rates were also reported for active and sham (placebo) TBS (110).

More serious adverse events in pediatric studies have been rare (occurring in ∼1–2% of participants). Two cases of syncope in children with pediatric stroke and six cases of seizures (four in adolescents with depression, one in an adolescent with migraines, and one in an adolescent with schizophrenia) have been reported (111–116). Factors that could have increased the risk of these serious adverse events include: concomitant medication use (in four of the cases), alcohol withdrawal (in one case), and clinical disorders associated with increased risk of syncope and seizure (i.e., pediatric stroke and migraine, respectively). More details about these case reports can be found in **Table 1**.

The most recent International Federation of Clinical Neurophysiology TMS safety guidelines indicate that the extant pediatric literature "provide reassurance regarding the safety of these techniques" in pediatric populations (82). However, as noted above, this "reassurance" is based on far less data than in the adult literature. Furthermore, the neurodevelopmental processes ongoing in children and adolescence, compounded by the pathophysiological processes affecting those with neuropsychiatric and neurodevelopmental disorders require consideration (117, 118). As it relates to adolescent depression, the aforementioned neurotransmitter fluctuations and potentially aberrant functional connectivity may result in an altered neurophysiological state (as compared to the adult brain). Thus, evaluating and adjusting for the physiological state of the brain may both reduce the risk of adverse events as well as potentially increase the intended effects.

Efficacy of rTMS in Adult and Adolescent MDD

Efficacy of rTMS in Adult MDD

In addition to publishing safety guidelines, the International Federation of Clinical Neurophysiology has also published a series of evidence-based guidelines on the therapeutic use of rTMS (119, 120). To develop these guidelines, experts in the field evaluated the level of evidence of rTMS efficacy for a number of indications. Consistent with the FDA label and based on a number of large-scale clinical trials (121–123), high-frequency (10 Hz) rTMS to the left dorsolateral prefrontal cortex (DLPFC) achieved a "Level A" (definite efficacy) for adult MDD. Since its initial FDA clearance, in 2008, multiple TMS devices and protocols have also received clearance for adult MDD. Consensus guidelines have also been established by the National Network of Depression Centers and the American Psychiatric Association Council on Research (124). Multiple meta-analyses of thousands of individuals have concluded that rTMS is safe, tolerable, and leads to a reduction in depressive symptoms in otherwise treatment resistant adult patients with MDD. Although the safety and tolerability of rTMS is consistent across trials, effect sizes vary greatly based on a number of factors including: rTMS parameters (e.g., intensity, location, and stimulation protocol) and interindividual factors such as brain size, shape, and neurophysiological state.

Intensity of stimulation is typically set in relation to the individual's motor threshold (MT). The MT is the stimulator output that is required to produce a contraction of the thumb or fingers half the time when applied to the primary motor cortex "hotspot." MT is used as a proxy of the intensity of stimulation necessary to activate other regions of cortex. Intensity of rTMS typically ranges from 80 to 120% of MT. At these intensity levels, current models indicate that standard coils induce an electrical field that can reach 2–3 cm from the scalp (125). Consistent with the FDA label for adult MDD, the DLPFC target is often approximated from measurements on the scalp (126). However, some studies have also used structural or functional MRI combined with a frameless stereotaxic neuronavigation system to target specific regions of interest (65, 127). Targeting rTMS based on fMRI and/or diffusion tensor imaging (DTI) mapping of an individual's brain network (128, 129) tends to result in larger effect sizes as compared to scalp-based approaches (127, 130, 131). Typical stimulation frequencies vary from 1 to 20 Hz. The most common frequency used for adult MDD

TABLE 1 | Case reports of TMS induced seizures in adolescents.

Publication	Patient status	Age, gender	TMS protocol	Intensity	Location	Stimulator model/ Coil type	Seizure description
Hu et al. (111) Journal of International Medical Research	MDD	15 (F)	10 Hz rTMS	100% RMT	L- Prefrontal Lobe	Magstim Figure 8 Coil	Generalized tonic-clonic seizure, started within minutes of 1st treatment
Chiramberro et al. (112) Brain Stimulation	MDD	16 (F)	10 Hz rTMS	Not reported	L-DLPFC	Magstim Figure 8 Coil	Generalized tonic-clonic seizure induced 20 min into 40 trains on the 12th day of stimulation
Cullen et al. (113) Journal of Child and Adolescent Psychopharmacology	MDD	17 (F)	18 Hz Deep TMS	120% RMT	L- Motor cortex	H1 Coil	Generalized tonic-clonic seizure induced on the 48th train of the 8th day of treatment
Wang et al. (114) Brain Stimulation	Migraine	16 (F)	10 Hz rTMS	110% RMT	L- Motor cortex	Magstim Rapid Figure of 8 Coil	Generlized tonic-clonic seizure induced 10 seconds into the 3rd train of the 1st session
Purushotham et al. (115) Brain Stimulation	Schizophrenia	15 (F)	iTBS	80% AMT	L-Motor cortex	Magstim Rapid Figure of 8 Coil	Generalized tonic-clonic seizure induced 30 seconds into the 1st session
Kallel and Brunelin (116) Journal of ECT	MDD	18 (F)	20 Hz rTMS	110% RMT	L-DLPFC	MagPro X30 Figure of 8 Coil	Generlized tonic-clonic seizure induced on the 26th train of the 3rd session on the 2nd day of stimulation

MDD, Major Depressive Disorder; rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; RMT, resting motor threshold; AMT, active motor threshold; L-DLPFC, left dorsolateral prefrontal cortex.

is 10-Hz. rTMS applied to the DLPFC at 10 Hz frequency per the FDA label is associated with an average of 30% response rate, compared with 10.4% with sham (placebo) rTMS, with an effect size of 0.55 (132–134) and a pooled odds ratio of response or remission of 3.3 (132). Furthermore, according to a recent meta-analysis, 66.5% of individuals who respond to the initial rTMS course have sustained response after 3 months, with responder rates decreasing to 52.9% after 6 months, and 46.3% of individuals still maintaining response 1 year after the initial treatment course (135).

Several approaches have been taken to address relapse and recurrence after initial rTMS response. These include various maintenance rTMS schedules as well as additional courses of rTMS treatments during periods of relapse. Though a number of studies have explored various maintenance rTMS schedules [see (136)], protocols vary across studies and clinics. Proposed maintenance regimen involve an initial tapering of sessions over the course of 3-4 weeks from five sessions per week down to one session every week and eventually one session every 2 or 3 weeks for many months to several years depending on the individual [see (137)]. Though this regimen may provide optimal protection against relapse, there may be alternative options for maintenance that are less burdensome including introduction and/or modifications of antidepressant medication or psychotherapy.

The effects of rTMS are not simply a matter of the stimulation parameters, but also how the stimulation is received and processed in the brain. The specific degree and location of stimulation of the targeted brain region depends upon the individually unique structural and functional architecture of each individual's brain. Given the putative mechanism of action of rTMS is the modulation of functional networks and the known interindividual structural and functional heterogeneity of these networks, the efficacy of rTMS depends upon the accurate targeting of the network of interest in that individual. Furthermore, although high-frequency and iTBS protocols typically lead to increased excitability of the targeted region, recent studies report considerable inter-individual and intra-individual (state-dependent) variability in cortical response, especially outside of the primary motor cortex (138, 139). Thus, efficacy can be optimized through careful characterization of both the functional network architecture and neurophysiological state.

Efficacy of rTMS in Adolescent MDD

Most of what is known about the effects of rTMS on the brain are based on adult studies. Less than 1,000 children and adolescents are represented in the published rTMS literature. Without FDA clearance, commercial marketing of rTMS for any pediatric indications is prohibited. While adolescents and children may be studied under an approved research protocol, any other use of TMS in individuals under age 21 is "off-label" in the United States.

The first published review on rTMS in adolescent depression (6) was based on two case series (140, 141) and one open-label

trial (142) ($n = 14$). With so few data, no meaningful conclusions could be made about efficacy. The authors suggested that the optimal stimulation parameters for adolescents might differ from those in adults. A subsequent review (3) included another open-label trial (143), a case report of an induced seizure in an adolescent (111), an open-label trial where depressive symptoms were evaluated in adolescents with Tourette syndrome (8), and a secondary analysis on the previous open-label trial. Despite the expanded number of publications, the rTMS literature was comprised of only 22 (inclusive of the one seizure report) adolescents with a primary diagnosis of MDD. A third review, a decade after the first (4), added three additional case reports (112, 113, 144), a case report of an individual with autism spectrum disorder and co-morbid depression who received rTMS for depressive symptoms (9), a case series (106), an open-label study (58), and three secondary analyses on previous datasets (145–147). By 2017, despite more publications, <50 adolescents with primary MDD had received rTMS and no studies included a placebo control group. The next review (2), in 2019, included two additional open-label trials (148, 149), more than doubling the previous total number of depressed adolescents treated with rTMS. This review focused on the effects of rTMS on GABAergic and glutamatergic neurotransmission and concluded by calling for larger, neurodevelopmentally-informed studies. The most recent review (5), included one additional case series (150), one new retrospective analysis of clinical data (151), and two more secondary analyses of existing datasets (152, 153) ($n = \sim$150). The authors (5) conclude by highlighting flawed study designs, calling for sham-controlled RCTs to properly assess the efficacy of rTMS.

Since the publication of the most recent review article, there is now one sham-controlled RCT of rTMS in adolescents with MDD (7) and two additional retrospective analyses of clinical data (154, 155). With the addition of these new data, the adolescent depression rTMS literature now encompasses 20 publications (**Table 2**) representing 12 unique datasets ($n = \sim$280 adolescent participants with MDD). Despite the calls for neurodevelopmentally-informed trials, the parameters have mimicked those in the adult studies. Intensity of stimulation has ranged from 80 to 120% of motor threshold. Protocols have largely followed the FDA clearance (for adults) applying 10 Hz unilaterally to the left DLPFC. Two studies took a different path. One (151) compared 1 Hz, unilateral right DLPFC stimulation with a bilateral (left followed by right) stimulation and another applied bilateral TBS stimulation (148). As for sample characteristics, studies have taken a conservative approach, enrolling relatively older adolescents (average age of 17.15), small sample sizes (7/12 datasets with sample sizes n≤10), and open-label designs or active stimulation case reports/retrospective analyses of clinical data (11/12 datasets). The sole exception is the large-scale RCT that enrolled 103 adolescents ∼18% of whom were age 12–14 years old (7).

Acknowledging the limitations of the method, open-label trials and case series/retrospective analyses of clinical data were generally positive, with large effect sizes open-label trials: Hedges's $g_{av} = 2.39$ and Glass's $\Delta_{pre} = 3.01$; case reports/retrospective analyses: Hedges's $g_{av} = 2.06$ and Glass's $\Delta_{pre} = 3.48$, [see (158) for explanation of effect size measures]. Average reduction in depressive symptoms for the open-label trials and case series/retrospective analyses equals 40 and 51%, respectively (with study averages ranging from 23 to 71%). Open-label trials and case series/retrospective analyses inherently inflate effect sizes and are influenced by regression to the mean, investigator biases, and confounding the effect of the active treatment with placebo effects (159). The only large-scale RCT of rTMS in adolescent depression yielded an effect size near zero (Hedges's $g = 0.10$). The active and sham rTMS groups showed comparable response (41.7% for the active and 36.4% for the sham group) and remission rates (29.2% for the active and 29.0% for the sham group) (7).

Sham TMS coils have been used in rTMS trials as an analog to pill placebo in drug trials. Sham coils do not apply a magnetic field but mimic the auditory, visual, and (in some cases) sensory experience of rTMS (160). The largest placebo effects have been seen in trials employing "physical placebo interventions" (e.g., a sham TMS coil) with subjective patient-related outcomes (e.g., self or parent reports or clinician administered interviews) (161). A meta-analysis of 61 studies using rTMS sham-controls for adult depression found a placebo effect size of 0.8 with the magnitude of the effect positively correlated with year of publication (162). Increasing placebo response over time may be an outgrowth of public/media attention, technologically more sophisticated devices (such as neuronavigation), enrollment of patients who are not "treatment resistant" (163, 164), and improved disguising of sham coils (165). The RCT in adolescents resulted in a sham effect size of 1.15 and a response rate of 36.4% (not significantly lower than the active rTMS effect size of 1.27 and response rate of 41.7%) (7). This higher placebo response rate in adolescents is also present in drug trials for adolescent depression (166) where placebo responses rates range from 24 to 60% (167–174).

To determine the efficacy of rTMS for adolescent depression, future RCTs will have to address the higher placebo effect rate. Aside from the conventional "active vs. sham" design alternative approaches such as inclusion of a placebo run-in, giving an active comparator, or applying statistical analysis techniques such as Growth Mixture Modeling (GMM) to capture unobserved subject heterogeneity in trajectories may be considered. The last approach requires dense collection of outcome measures over the course of rTMS and during follow-up. GMM was used to analyze data from an antidepressant trial; the placebo response trajectory deviated from the two active drug response trajectories (175). This technique has also been used to evaluate whether biomarkers, such as quantitative electroencephalography (qEEG), can predict antidepressant response (176).

Beyond the placebo response rate, other features in the study design for the RCT may have contributed to the failed outcome, including: the choice of the "5-cm rule" targeting strategy, broad inclusion criteria, within group variability in response, and insufficient sample size. The rTMS protocol, targeting strategy, frequency of stimulation, and dosage influence effect size in rTMS trials. Optimizing these factors in a neurodevelopmentally informed way could therefore increase effect sizes.

TABLE 2 | Previous literature on TMS for adolescent depression.

Publication	*n*	Age in years (Mean, Range)	Gender	Protocol	Number of sessions, Frequency of sessions	Depression outcome measure	Subject medications	Estimated effect size	Reported effects for depression outcome measure	Side-effects/Adverse events
Walter et al. (141) Journal of Child and Adolescent Psychopharmacology	$n = 3$	Ages: 16, 17, and 17	3 males	10 Hz rTMS, 90–110% RMT, over LDLPFC	10 treatment sessions over 2 weeks	HAM-D & BDI	None	Hedges's g_{av} = 1.53, Glass's Δ_{pre} = 3.37	Improvement of HAM-D from 28 (baseline) to 8 (week 4) for one participant Improvement of HAM-D from 34 (baseline) to 12 (week 4) for one participant No improvement for one participant	Adverse effects in only one patient—tension headache in two sessions
Loo et al. (140) Australasian Psychiatry	$n = 2$	Ages: 16, 16	Both female	10 Hz rTMS at 110% RMT; 40 trains of 5 second duration, 25 second ITI	29–36 treatment sessions over 6–11 weeks	MADRS, CGIS, BDI, Centre for Epidemiological Studies—Depression-Child Scale	$n = 1$: "psychotropic medication," $n = 1$: venlafaxine and methylphenidate	n/a	"Both subjects improved to a clinically significant degree with rTMS treatment	No adverse effects
Bloch et al. (142) The Journal of ECT *Mayer et al. (156)	$n = 9$	M = 17.3 Range = 16–18	2 males, 7 females	10 Hz rTMS at 80% RMT over LDLPFC (5 cm targeted); 20 trains, 2 s per train	20 treatment sessions over 2 weeks	CDRS, Screen for Child Anxiety-Related Disorders, Suicidal Ideation Questionnaire CGIS,Cambridge Neuropsychological Test Automated Battery	Not reported	Hedges's g_{av} = 1.50, Glass's Δ_{pre} = 2.63	Response rate of 33%	No adverse effects reported
Wall et al. (143) The Journal of Clinical Psychiatry *Croarkin et al. (147) *Wall et al. (146) *Croarkin et al. (153) *Somnez et al. (157)	$n = 7$	M = 16.5 Range =14.6–17.8	1 male, 6 females	10 Hz rTMS at 120% RMT over LDLPFC (5 cm targeted); train duration of 4 s, 26 s ITI, total 3,000 pulses	30 treatment sessions over 6–8 weeks	CDRS-R, QIDS-A17, CGI-S, Suicide Severity Scale	Not reported	Hedges's g_{av} = 4.51, Glass's Δ_{pre} = 5.05	CDRS-R scores improved from treatment 10 (mean = 50.9, SD = 12, $P < 0.02$) to treatment 30 (mean = 32.6, SD = 7.3, $P < 0.0001$), and at 6-month follow-up (mean = 32.7, SD = 3.8, $P < 0.0001$)	Scalp discomfort in 3 out of 8 participants
Yang et al. (106) The Journal of ECT	$n = 6$	M = 18.7 Range = 15–21	2 males, 4 females	10 Hz rTMS at 120% RMT over LDLPFC (structural-MRI targeted); 4 s trains, ITI 26 s, 75 trains, 3,000 pulses	15 treatment sessions over 3 weeks	HAM-D, BDI	Not reported	Hedges's g_{av} = 2.63, Glass's Δ_{pre} = 3.18	Response rate of 66% Responders had an 11% increase in glutamate levels from baseline	No adverse events reported

(Continued)

TABLE 2 | Continued

Publication	*n*	Age in years (Mean, Range)	Gender	Protocol	Number of sessions, Frequency of sessions	Depression outcome measure	Subject medications	Estimated effect size	Reported effects for depression outcome measure	Side-effects/Adverse events
Segev et al. (144) The Journal of ECT	$n = 1$	17	1 male	10 Hz rTMS, 100% RMT over LDLPFC (5 cm targeted), 42 trains of 4 s with an ITI of 30 s, 1,680 pulses per treatment	20 treatment sessions over 4 weeks	BDI-II, SIQ, Childhood Anxiety Related Disorder Questionnaire	Not reported	n/a	"…significant clinical improvement was demonstrated in anxiety symptoms and not in clinical measures of depression"	Headache, scalp pain, and scalp burning
Croarkin et al. (58) Psychiatry Research: Neuroimaging *Wall et al. (145) *Croarkin et al. (153) *Sonmez et al. (152)	$n = 10$	M = 15.4 Range = 13.9–17.4	6 males, 4 females	10 Hz rTMS at 120% RMT over LDLPFC (structural-MRI targeted); train duration of 4 s, 26 s ITI, total 3,000 pulses	30 treatment sessions over 6–8 weeks	CDRS-R, QIDS-A17-SR, CGI-S	Not reported	Hedges's g_{av} = 1.89, Glass's Δ_{pre} = 2.57	CDRS-R total score at baseline was 62.9 (SD = 8.2), total score at posttreatment was 41.8 (SD = 13.2), total score at 6-month follow up was 34.2 (SD = 15.3) Also reported, "…throughout the 6-month follow-up period, we estimated that a 1–scale unit increase (or decrease) in the CDRS-R total score (depression severity) was related to a mean decrease (or increase) in each Gln/Glu ratio"	Scalp discomfort, headaches, dizziness, neck stiffness, eye twitching, nausea, musculoskeletal discomfort
MacMaster et al. (149) Frontiers in Psychiatry	$n = 32$	M = 17.57 Range = 13–21	17 males, 15 females	10 Hz rTMS at 120% over LDLPFC (structural-MRI targeted); 4 s trains, ITI 26 s, 75 trains, 3,000 pulses	15 treatment sessions over 3 weeks	HAM-D	Not reported	Hedges's gav = 1.82, Glass's Δpre = 1.71	Response rate of 56% Remission rate of 44%	Limiting headaches and mild neck pain
Zhang et al., pooled analysis *Zhang et al. (150) Brain Stimulation *Zhang et al. (155) Journal of Affective Disorders *Zhang et al. (154) Journal of ECT	$n = 70$ 2 weeks $n = 23$ 4 weeks	M = 14.86 Range = 10–17	26 males, 44 females	10 Hz rTMS at 120% MT over LDLPFC (5 cm targeted); 80 trains, 30 pulses per train, 12s ITI, 2,400 pulses or 1 Hz rTMS at 120% MT over RDLPFC (5 cm targeted); 2 trains, 700 pulses per train, 1 s ITI, 1,400 pulses	20 treatment sessions over 4 weeks	HAM-D & HAMA	Sertraline, venlafaxine, duloxetine, mirtazapine $n = 1$: agomelatine, bupropion, deanxit. and clomipramine	Hedges's g_{av} 2 weeks = 1.65, Glass's Δ_{pre} 2 weeks = 1.40 Hedges's g_{av} 4 weeks = 2.85, Glass's Δ_{pre} 4 weeks = 1.98	2-week response rate of 50% 2-week remission rate of 54.3% 4-week response rate of 100% 4-week remission rate of 91.3%	No serious adverse events reported. Limited headaches or musculoskeletal discomfort

(Continued)

TABLE 2 | Continued

Publication	*n*	Age in years (Mean, Range)	Gender	Protocol	Number of sessions, Frequency of sessions	Depression outcome measure	Subject medications	Estimated effect size	Reported effects for depression outcome measure	Side-effects/Adverse events
Rosenich et al. (151) Early Intervention in Psychiatry	$n = 15$	M = 20.69 Range = 17–25	7 males, 8 females	Unilateral treatment = continuous 1 Hz rTMS over RDLPFC for 15 min ($n = 2$) or 30 min ($n = 9$); Bilateral treatment ($n = 4$) = intermittent 10 Hz rTMS 5 s intervals, 25 s ITI for 1,500 pulses over LDLPFC and followed by 15 min of 1 Hz unilateral treatment for 900 pulses over RDLPFC (all 6 cm targeted). All stimulation at 110% RMT	18 treatment sessions over 6 weeks	HAM-D, MADRS, and Zung Self Rating Depression Scale	Not reported	Hedges's g_{av} = 1.24, Glass's Δ_{pre} = 1.41	Partial response rate of 86.7% Response rate of 40% Remission rate of 13%	No serious adverse events, only mild headache, fatigue, and localized discomfort
Dhami et al. (148) Journal of Affective Disorders	$n = 20$	M = 20.9 Range = 16–24	10 males, 10 females	Bilateral theta burst stimulation: iTBS on LDLPFC and cTBS on RDLPFC at 80% RMT (structural-MRI targeted)	10 treatment sessions over 2 weeks	HRSD-17, BDI-II, Q-LES-Q, CDRS-R	Not reported	Hedges's gav = 2.21, Glass's Δpre = 3.07	Response rate of 20% Remission rate of 10%	Headache, scalp pain, chest tightness, anxiety, nausea, gastrointestinal symptoms, nasopharyngitis, restlessness, general discomfort
Croarkin et al. (7) Neuropsychopharmacology *Active arm*	$n = 48$	M = 17.6 Range = 12–21	18 males, 30 females	10 Hz rTMS at 120% over LDLPFC (5 cm targeted); 4 strains, 26 s ITI, 75 trains, total 3,000 pulses	30 treatment sessions over 6 weeks	HAM-D, MADRS, CRS-R, QIDS-A-SR, CGI-S	zaleplon, zolpidem, zopiclone, or lorazepam	Hedges's g_{av} = 1.27, Glass's Δ_{pre} = 1.86	Response rate of 41.7%; remission rate of 29.2%	Four serious adverse events reported, all having to do with suicidal ideation or worsening depressive symptoms determined unrelated to rTMS treatment
Croarkin et al. (7) Neuropsychopharmacology *Sham arm*	$n = 55$	M = 17.4 Range = 12–21	18 males, 37 females	Sham	30 treatment sessions over 6 weeks	HAM-D, MADRS, CRS-R, QIDS-A-SR, CGI-S	zaleplon, zolpidem, zopiclone, or lorazepam	Hedges's g_{av} = 1.15, Glass's Δ_{pre} = 1.53	Response rate of 36.4%; remission rate of 29.0%	One serious adverse event of suicidal ideation definitely unrelated to rTMS treatment

(Continued)

TABLE 2 | Continued

Publication	*n*	Age in years (Mean, Range)	Gender	Protocol	Number of sessions, Frequency of sessions	Depression outcome measure	Subject medications	Estimated effect size	Reported effects for depression outcome measure	Side-effects/Adverse events
Croarkin et al. (7) Neuropsychopharmacology *Active* vs. *Sham*	*n* = 103 (54 active)	M = 17.35 Range = 12–21	36 males, 67 females	10 Hz rTMS at 120% over LDLPFC (5 cm targeted); 4 s trains, 26 s ITI, 75 trains, total 3,000 pulses	30 treatment sessions over 6 weeks	HAM-D, MADRS, CRS-R, QIDS-A-SR, CGI-S	zaleplon, zolpidem, zopiclone, or lorazepam	Hedges's g_s = 0.10,	"There were no statistically significant differences in clinical outcomes between the active TMS and sham TMS groups"	Five serious adverse events reported, all having to do with suicidal ideation or worsening depressive symptoms determined unrelated to rTMS treatment

rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation; RMT, resting motor threshold; MT, motor threshold; ITI, intertrain interval; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; HAM-D/HRSD, Hamilton depression rating scale; HAM-A, Hamilton anxiety rating scale; BDI, Beck depression inventory; MADRS, Montgomery-Asberg depression rating scale; SIQ, suicidal ideation questionnaire; CGIS, clinical global impressions scale; CDRS-R, depression rating scale for children revised; QIDS, Quick Inventory of Depressive Symptomatology; Q-LES-Q, quality of life enjoyment and satisfaction questionnaire; SSRI, selective serotonin reuptake inhibitor.

**Follow up studies/post-hoc analysis using the same participant data.*

LIMITATIONS OF THE EXISTING LITERATURE AND PROPOSED RESOLUTIONS

Impact of Stimulation Parameters on Effect Size

The majority of clinical trials for both adult and adolescent depression have applied 10 Hz left hemisphere DLPFC rTMS. However, a meta-analysis of rTMS RCTs, encompassing over 4,000 patients and 81 trials, concluded that sequential bilateral stimulation to the right (1 Hz) and left (10 Hz) DLPFC was the most effective method (177). Only two adolescent depression trials used bilateral stimulation. Though safety and efficacy are the primary goals of novel treatment development, feasibility and tolerability also need to be considered. The standard 10 Hz protocol is burdensome for the patient and provider; daily sessions require over half an hour (up to an hour for bilateral stimulation protocols) and at least 6 weeks of treatment. Use of iTBS protocols can reduce this burden with a single session of iTBS taking only 3 min, allowing for accelerated protocols and shorter treatment courses (62).

iTBS protocols were designed to closely mimic endogenous theta/gamma rhythms of the brain and induce long-term potentiation-like (LTP-like) plasticity. Though early iTBS studies targeted primary motor cortex, this protocol has also been applied to other brain regions including the DLPFC. iTBS over the DLPFC has been shown to induce long-term changes in local cortical excitability (178, 179), reduce GABA and glutamate/glutamine levels, and alter network connectivity (180). On a behavioral level, iTBS led to improved performance on the ability to inhibit automatic responses and working memory tasks in a small study of healthy volunteers (181). In a non-inferiority study iTBS and 10 Hz rTMS both reduced symptoms of depression in adults with similar safety, tolerability and efficacy (182). A meta-analysis of adult studies showed a response rate of iTBS of 35.6% (42/118) vs. 17.5% (18/103) with sham, a pooled odds ratio of response and remission of 2.7 and 1.9, respectively, and an effect size of 1.0 (183). Though promising in adults, iTBS has not been evaluated in an RCT in adolescents and faces the challenge of the aforementioned higher sham response rates. However, the mechanism of action of iTBS may be particularly well-suited to the intrinsic neuroplasticity of the adolescent brain. Furthermore, the ability of iTBS to modulate aberrant neurotransmitter function and pathological connectivity is well-matched to the reported DLPFC pathophysiology of adolescent depression.

Different rTMS targeting strategies yield differences in precision, reliability, and effect size. In six of 12 studies (**Table 2**) of adolescent depression the targeting strategy was scalp-based, four used MRI-guidance, and two provide no data. Scalp-based targeting is unreliable and imprecise for localizing DLPFC (184–188). MRI-based neuronavigation used for rTMS shows larger effect sizes (127, 130, 131). For treatment of depression, one study in 51 depressed adults found a moderately larger effect for MRI-based neuronavigation than standard targeting (Hedges $g_s = 0.64$) (127). Even when using MRI-based neuronavigation,

there are uncertainties about the optimal target for treating depression. Most studies target DLPFC, a large cortical area that is functionally connected to the Frontoparietal Network (also known as the Central Executive Network), the Default Mode Network, and the Salience Network (93, 189). All of these networks may be affected in depression and could be influenced by DLPFC stimulation. Using a standard "figure of 8 coil," a shift of as little as 0.5–1 cm can differentially affect one or more of these networks (190). Furthermore, there is a large variation in individual functional brain circuitry (191). Thus, especially during adolescence when these networks are in flux, using patient-specific functional neuronavigated rTMS to precisely target and modulate one or more of these networks, could lead to larger effect sizes (192).

Larger effect sizes are also seen in protocols that apply more sessions and more pulses *per session* (193–195). A meta-analysis of number of sessions and pulses/session to treat depression found the average effect size increased from 0.43 to 2.74 when the number of sessions increased from 5 to 20; the maximum mean effect size (5.47) was seen with 20 or more sessions and more than 1,200 pulses/session (193). However, only five of the 12 studies of adolescent depression applied 20 or more sessions. Increasing the number of sessions *per day* above the convention of one session daily would increase efficiency. The conventional procedure results in a standard course of treatment of 6 weeks or more. Accelerated protocols with 2–10 session per day applying the same number of total sessions appear to show equivalent safety and efficacy (157, 195–199) with the pace of improvement showing a direct relationship with the cumulative number of sessions. Additionally, neuroimaging studies find that, like standard protocols, accelerated protocols result in changes on neurochemical and functional connectivity biomarkers of depression (103, 200). When applying more than one session daily, intersession interval influences additive effects. Basic research studies on LTP find that the level of LTP is doubled when a second TBS train is applied after 60 min, but if applied after only 10, 30, or 40 min there was no cumulative effect (201). That being said, neurodevelopmental factors could affect optimal intersession intervals and has yet to be determined. Piecing these protocol parameters together, a proposal for the most favorable balance of feasibility, efficacy and efficiency is up to five sessions/day, a 60-min intersession interval, and at least 20 total sessions (202). Such a treatment course can be completed in 1 week (instead of 6 weeks for once daily treatments). The value of swift antidepressant interventions becomes particularly relevant during the COVID pandemic, when access to therapy can be hindered and also adherence to longer therapy is a greater problem (203).

Within-Group Variability: Impact of Inter-individual Heterogeneity and Intra-individual Brain State on Effect Size

Clinical heterogeneity may contribute to reduced therapeutic response in studies of adolescents (204, 205). Adolescent patients present with a diverse range of symptoms (205), clinical courses (206), and responses to treatment (16, 204, 207, 208). We and others have thus suggested that underlying pathophysiology may account for the observed clinical heterogeneity (209). Given this heterogeneity, one would not expect to find a single "one size fits all" optimal treatment for adolescent depression (210). To address clinical heterogeneity, one could increase the sample size, allowing for subgroup analyses, or focus on a narrower phenotype.

Attempts have been made to define clinical subtypes and brain-network-based biotypes, but these have been difficult to replicate (211). One promising symptom domain for targeted treatment is anhedonia/dysphoria. Anhedonic/dysphoric symptoms seem to be reliably associated with PFC-cingulate network dysfunction (212–215) and have been shown to be particularly responsive to neuronavigated rTMS to the DLPFC (100). This raises the possibility that reducing sample heterogeneity by enrolling with primarily anhedonic/dysphoric symptoms might increase power to observe an effect. Such an approach was successfully used in a recent pharmacological trial (216).

A different approach is to focus treatment on suicidal ideation, the most serious risk to patient safety. The literature on efficacy of rTMS for suicidality paints a mixed picture. A pooled analysis of 19 depressed adolescents who received open-label rTMS showed decreased suicidal ideation over the course of treatment (153). This decrease in suicidality, corresponded to an overall decrease in severity of depression symptoms (153). A retrospective analysis of 332 depressed adult patients who received rTMS also reported improvements in suicidality (217) and a review ($n = 593$) and naturalistic study ($n = 43$) of rTMS in adult MDD found consistent improvements in depressive symptoms and suicidality in open-label trials. These positive findings are contrasted with results from sham-controlled trials that have failed to show significant group differences in the reduction of suicidal ideation (210). While it is possible that, compared to conventional pharmacotherapy, rTMS might be a safe, faster means of reducing suicidal ideation; larger, sham-controlled RCTs employing the most current sophisticated methods will be needed to conclusively demonstrate efficacy. Furthermore, the immediate therapeutic effects of ketamine may soon become the standard for speed of reducing suicidality against which all other interventions must be compared.

For both safety and feasibility, most adult and adolescent rTMS studies have allowed participants to continue their current medications (218). Safety reviews suggest that rTMS in those receiving stable doses of antidepressant medication does not increase the risk of adverse events (82); however, this increases within-group variability in neurochemical state and decreases statistical power. To control for variability in neurochemical state, investigators could enroll only participants who have been withdrawn from all psychotropic medications; however, withdrawing symptomatic patients from their medications introduces safety concerns of increased suicidal ideation and withdrawal-related side-effects. It demands close medical monitoring. A more feasible approach would be to require participants to maintain a steady medication dose and to apply a within-subject model controlling for baseline severity as the primary outcome measure. While this would not

eliminate variability across participants, it reduces the effects of neurochemical brain state on the primary outcome measure. Combining rTMS and pharmacological treatment is another novel multimodal intervention being developed in adults that could be extended to adolescents (219). Notably, recent data suggest that combining antidepressant medication with a course of rTMS may in fact have a greater benefit in adolescents than in adults (150).

In order to increase tolerability of the treatment, adolescent studies have allowed patients to read, watch TV, or listen to music during rTMS sessions. The difference in behavioral engagement/arousal this causes is another potential source of within-group variability. While these distraction strategies are common in everyday practice with rTMS, they are a concern for treatment trials. Factors such as attention, arousal and mood state have been shown to affect modulation of excitability by rTMS (220–223). Thus, if the adolescent is even passively engaged in an unrelated activity, this may impact the effect of the rTMS. Applying shorter stimulation protocols (e.g., iTBS) may reduce the need for co-occurring activities to make the session more tolerable. Alternatively, one can transiently modify the patient's cognitive state by presenting stimuli or engage them in a task that engages the same brain networks as the rTMS target. In this way, rTMS can be combined with the behavioral task in order to amplify the impact on the targeted network (76). Studies of rTMS for post-traumatic stress disorder (PTSD), smoking cessation, and OCD have shown increased treatment response when the participant's symptoms were provoked [e.g., by asking questions about thoughts, images, or impulses related to their obsessions or compulsions or asking the patient to perform a task related to their symptoms (224)] immediately prior to rTMS stimulation (225–227). One could also consider pairing stimulation with concurrent behavioral interventions such as CBT (228).

The Importance of Imaging Biomarkers in rTMS Treatment Development

Given the significant time-investment necessary for rTMS treatment, many have sought to identify early predictors of later response. A recent retrospective study of 101 patients who received 4 weeks of rTMS treatment found that a lack of clinical response at the midway point predicted non-response with 88% accuracy (229). However, this still requires the patient to undergo 10 treatment sessions. Identifying intrinsic neurophysiological signatures or measures that can be obtained after one or two rTMS sessions would be preferable (229). Brain imaging techniques are increasingly capable of obtaining measures of brain function at cellular/molecular and network levels (96, 97, 230, 231). MRS can yield measures of GABA and glutamate neurotransmitter functioning (230, 231). BOLD fMRI and RSFC (96, 97) have been proposed as tools for neuroimaging biomarkers. RSFC as measured by fMRI is stable across development (232, 233) and reproducible (234) at a group level. RSFC in adolescent depression has been shown to differentiate (at a group-, not at the individual-level) symptom severity (235), symptom domains (213, 236, 237), onset (238), and course of disease (239, 240). Furthermore, RSFC in fronto-parietal, cingulo-opercular/ventral attention, and default mode networks has been used to predict individual differences in adolescent brain maturity and executive functioning (241). Within individuals, however, most commonly used sequences are too short to produce reliable RSFC measures (242), but with longer sequences (243, 244) or novel sequence types (244) it may be a reliable measure. rTMS trials in adolescent depression would benefit from dense collection of reliable neuroimaging measures at baseline, post-treatment, and follow-up. At baseline, neuroimaging measures may allow investigators to customize treatment to the unique neurodevelopmental state of each adolescent's developing cortex. Though group data appear promising, the benefit of using RSFC profiles for patient-specific treatment decisions is currently only theoretical.

Neuroimaging measures can also serve as predictive biomarkers for response to rTMS. Multiple studies have linked intrinsic functional connectivity between the targeted region of PFC and ACC, anterior insula and striatum with later response to rTMS (74, 125, 200, 245–254) and other antidepressant treatments (101, 255–258). Interleaved rTMS/fMRI has shown acute effects on BOLD activation of both local and distal brain regions immediately following 1 Hz DLPFC rTMS in adults with MDD (89). Though research is promising in this area, replication and prospective examination of these predictive biomarkers will be critical prior to clinical implementation.

To facilitate clinical translation of such biomarkers, the National Institute of Mental Health (NIMH) has introduced "fast-fail" trials. This initiative employs an experimental therapeutics platform to quickly identify devices, protocols or compounds that should be considered for more extensive testing (259). These types of trials may be especially useful in adolescent depression where there is a clear urgent public health need for novel therapeutics, but still a great deal of uncertainty in the neural targets and biomarkers that reliably predict treatment response. The "fast-fail" initiative has recently led researchers to report successful target-engagement of a novel kappa-opioid receptor antagonist for the treatment of anhedonia in adult MDD (216). Thus, extending this approach to adolescents is both timely and feasible.

CONCLUSIONS

Treating adolescent depression is fraught with the challenges of heterogeneity of the clinical phenotype, the high placebo response rate, and the breadth of neurodevelopmental changes during puberty. While the efficacy of rTMS for adults with treatment resistant MDD is supported by multiple, adequately powered RCTs, evidence in adolescent depression is scanty and has many limitations. The safety profile of rTMS for adolescent depression appears to be desirable but many parameters, including the most favorable approaches, have yet to be determined.

rTMS is worthy of further investigation for this vulnerable population. We propose that future adolescent depression rTMS trials: (1) be designed with 20 or more sessions (2) select a narrow clinical phenotype (e.g., select for anhedonia); (3) test for the possibility of individualization by including neuroimaging biomarkers (e.g., RSFC); (4) employ an experimental therapeutics approach (5) allow for robust inferences by being adequately controlled and powered with realistic effect size estimates. Such trials, if successful, may establish paradigms for larger, pivotal trials that clarify whether rTMS is an effective treatment for adolescent depression. Furthermore, they are likely to advance our understanding of the pathophysiology of this disorder.

AUTHOR CONTRIBUTIONS

LO drafted and revised the manuscript. MH conducted the literature review under the supervision of LO. DN, KT, SL, and AS contributed to the drafting and revision of the manuscript. All authors approved the final submitted manuscript.

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REVIEW
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Online Indicated Preventive Mental Health Interventions for Youth: A Scoping Review

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Objective: Between the ages of 12 and 25 the onset of mental disorders typically occurs, and the burden of mental health problems is greatest for this group. Indicated preventive interventions to target individuals with subclinical symptoms to prevent the transition to clinical levels of disorders have gained considerable traction. However, the threshold to seek help appears to be high even when help is needed. Online interventions could offer a solution, especially during the COVID-19 pandemic. This scoping review will present an overview of the recent research of indicated online preventive interventions for youth (12–25 years) experiencing the early stages of mental health complaints with the aim of identifying the nature and extent of the research evidence.

Methods: The 5-stage framework by Arksey and O'Malley was used. Academic literature published from 2013 onwards in printed or electronic format was included from Scopus, PsychINFO, and Ovid MEDLINE(R) ALL.

Results: The search yielded 11,122 results, with the final selection resulting in inclusion of 30 articles for this review. In total, the articles included 4,950 participants. 26.7% of the selected articles focused on youth between 12 and 25 years. Of the articles 60% did not screen for, nor exclude participants with clinical levels of symptoms. Most studies used a common evidence-based therapy for the disorder-category targeted. More than half of the online interventions included some form of human support. Adherence levels ranged between 27.9 and 98%. The results indicate general effectiveness, usability and acceptability of online indicated preventive interventions. The most commonly used approach was CBT ($n = 12$ studies). Studies varied in their size, rigor of study, effectiveness and outcome measures. Online interventions with a combination of clinical and peer moderation ($n = 3$ studies) appear to result in the most stable and highest effect sizes.

Conclusion: Online indicated preventive mental health interventions for youth with emerging mental health issues show promise in reducing various mental health complaints, and increasing positive mental health indicators such as well-being and

resilience. Additionally, high levels of usability and acceptability were found. However, the included studies show important methodological shortcomings. Also, the research has mainly focused on specific diagnostic categories, meaning there is a lack of transdiagnostic approaches. Finally, clear definitions of- as well as instruments to measure- emerging or subclinical mental health symptoms in youth remain are missing.

Keywords: indicated prevention, mental health, e-health, youth, scoping review, digital, well-being, early detection and intervention

INTRODUCTION

Mental health can be defined as "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" (1). Nonetheless, this state is disrupted in half (2) to almost three quarters (3) of all people living in the western world at some point in their life, and in 1 in 4 in any given year (4). The onset of mental disorders typically occurs in childhood and adolescence (2, 5), with 75% of mental disorders beginning before the age of 25 (5, 6). The waiting lists to receive care accordingly are continually growing (7), and costs associated with mental illness are substantial [e.g., (8)], and growing (9). Moreover, the burden of mental health problems is substantial for these individuals and is indicated by negative effects upon quality of life (10), life expectancy (11) social functioning, ability to work (10), and (self-)stigmatization (10, 12, 13). This burden has been found to be the greatest in young people aged between 15 to 25 years (6).

Increased attention has been paid at interventions aimed at youth with emerging symptoms to treat them as early as possible in the development of a mental disorder, for example, during the peak period of risk for onset, with a focus on both symptomatic as well as functional recovery (14). Prevention and early intervention are recognized as key elements for minimizing the psychosocial and economic impacts of any potentially serious health condition (15, 16). Previous research has shown the effectiveness of face-to-face psychosocial preventive interventions for youth. Improvements in behavioral and social outcomes were observed as well as a decrease in the proportion of participants transitioning from mental health complaints to mental disorders (17, 18). Unfortunately, the gap between needing help and seeking help is substantial. Only one in three young people seek help for their mental health problems (19, 20), and most individuals present to services at a much later stage (21–23). Subsequently these individuals present with more developed and severe problems that are more difficult to treat, and have more functional and social consequences since the mental illness strikes in a critical developmental period where social, vocational and educational milestones were to be achieved (15, 24). In other words, even though help for mental health problems is needed in adolescence or young adulthood, the threshold to seek it appears high. Perceived barriers for help-seeking in young people include negative attitudes toward seeking help (e.g., internalized stigma or shame), practical concerns (e.g., costs and transportation), believing they have to manage the problem on their own, downplaying their problems, doubts concerning the effectiveness of treatment, the unavailability of help (19, 25) and perceived public mental-health stigma (26).

Online interventions might offer a solution to the perceived barriers. Advantages of online interventions are the possibility to receive help anonymously, and increased convenience because individuals can choose when and where they access help (27–29). Moreover, online interventions have the potential to reach people who are unwilling or unable to receive face-to-face help, for example, those who live in remote areas or those with decreased mobility (30). Online interventions may be especially appealing to young people as most youth are familiar and competent with using digital technology. This is illustrated by data that indicate that 96% of European youth (aged 16–24) use the internet regularly (31). Furthermore, research shows that young people report using the internet to find information pertaining to mental health (32), they have positive perceptions about using the internet for mental health related-issues (33), and clinicians hold positive attitudes toward using technology for treatment too (34). Moreover, online interventions hold the potential to decrease costs for the individual and the healthcare system. Lastly, online interventions offer mental health care from home during the current COVID-19 pandemic (35, 36) which may be especially important for individuals with emerging complaints who are prone to developing more severe mental health issues (37).

Online indicated preventive interventions for individuals with an indicated need for care, that is, youth with emerging complaints, offer a promising approach to address this unmet need. From a resource perspective, it may be more feasible to target individuals with subclinical symptoms than non-symptomatic individuals who may not have a need for an intervention (38). The clinical staging model (39, 40) illustrates the differentiation between subclinical symptom clusters (stage 1a or 1b) and the onset of more discrete syndromes or clinical entities (stage 2, 3, and 4). Previous meta-analyses investigating face-to-face preventive interventions in youth have also shown that indicated preventive interventions have larger intervention effects than universal preventive interventions (38, 41).

The effectiveness of online indicated mental health preventive interventions for young people has been addressed in four systematic reviews and two meta-analyses between 2014 and 2016. In these reviews "youth" is defined as between the ages of 12 and 25, in concordance with most international definitions of youth as well as governmental and youth mental health institutions (42, 43). Interestingly, the majority of participants included in these reviews are youth with subclinical symptoms (stage 1a or 1b), however some participants might be in a later

stage since a clinical diagnosis was not an exclusion criterion in most included studies. Also, the transition to clinical disorders, which is the established primary outcome of indicated preventive treatment trials, was generally not measured. Lastly, the reviews varied quite substantially in their scope. Rice et al. (44) conducted a systematic review including studies focusing on online and social networking as indicated preventive interventions for the treatment of depressive symptomatology in youth (12–25 years). The overall finding was that online interventions appear to be promising in reducing depression symptomatology in young people. The systematic review of Ali et al. (45) included six studies targeting online peer-to-peer support for young people (12–25 years) with emerging mental health problems. Two out of six studies found support for the effectiveness of online peer-to-peer support although an overall lack of quality of the studies was found, and the type of moderation used in the studies was poorly reported. In 2015, Pennant et al. (46) included 27 studies in their systematic review and meta-analysis researching both indicated and universal preventive computerized therapies for anxiety and depression in children and young people (12–25 years). It was found that indicated and general preventive intervention had positive effects for reducing symptoms of anxiety and depression. However, follow-up data about long-term effects was scarce, and the authors stated that the magnitude of the effects needed to be interpreted cautiously due to the heterogeneity associated with a number of outcomes and predominantly low quality of the evidence. In all three systematic reviews it was not specified whether the indicated prevention had an effect on the rate of transition to clinical disorders, since outcome measures included solely measures of symptom severity.

O'Dea et al. (47) reviewed the evidence for online interventions for universal and indicated prevention targeting depression and anxiety symptoms and disorders in youth (12–18 years). They included six studies, and found positive effects on symptoms in all but one trial. They concluded that there are a number of gaps in the literature, for example a lack of cost-effectiveness data, and heterogeneity in sample sizes, randomization procedures, and outcome measures, making it difficult to compare trial results. There was only one study that measured the effect of indicated prevention on the development of clinical levels of depression; it was found that Cognitive Behavioral Therapy (CBT) lowered this risk. Ebert et al. (48) conducted a meta-analysis including internet and computer-based cognitive behavioral therapy for anxiety and depression in children and youth (< 25 years). They included 13 Randomized Control Trials (RCTs) and found an overall effect size of $g = 0.72$, reflecting a decrease in symptom severity. Again, the authors reported high heterogeneity and long-term effects of the studies. In the most recent meta-analysis of Conley et al. (49) the impact of universal and indicated preventive technology-delivered interventions for higher education students (age not specified) was investigated. They included 22 universal and 26 indicated prevention studies, and found larger positive treatment effects for indicated preventive interventions than universal preventive interventions. The authors reported important limitations on the experimental rigor and recommended that future research should for example provide more details on participant characteristics, and intervention content; and collect follow-up data.

While Rice et al. (44), Ali et al. (45), Pennant et al. (46), O'Dea etal. (47), Ebert et al. (48), and Conley et al. (49) included online indicated preventive interventions in their reviews, universal preventive interventions were included as well. To our knowledge no more recent reviews have been published. Moreover, there have been no reviews specifically of studies focusing on the effect of indicated preventive interventions provided online for youth. This scoping review will present an overview of the recent research of indicated online preventive interventions for youth experiencing the early stages of mental health complaints with the aim of identifying the nature and extent of the research evidence.

METHODS

Framework

We utilized the 5-stage framework by Arksey and O'Malley (50) developed for reporting a scoping review. This framework entails the following stages: (1) identifying the research question, (2) identifying relevant studies, (3) selection of studies, (4) charting the data, and (5) summarizing and reporting the results.

Research Question

The focus of this review was to present an overview of indicated online preventive interventions for emerging mental health symptoms in youth and aimed to identify the nature and extent of the research evidence. This led to the following guiding question: *What is known in the literature about the use of indicated online preventive interventions for youth with emerging mental health problems?*

Search Strategy

A search was conducted together with the university librarian with experience in conducting reviews (JD). **Appendix 1** displays the used search terms. Academic literature published in printed or electronic format was included from the following sources: Scopus, PsychINFO, and Ovid MEDLINE(R) ALL. Articles written in the English and Dutch language were retrieved. In order to ascertain recent findings, articles from 2013 onwards were included in this review. Study designs were limited to randomized controlled trials, quasi-experimental study designs and experimental studies without a comparison group. See **Supplementary Material** for the search criteria.

Eligibility Criteria

The eligibility criteria were determined to find all articles relevant to the research question. A highlighted summary of the main inclusion/exclusion criteria covered here is provided in **Table 1**.

Population

Studies eligible for inclusion were those containing a sample of youth, defined in concordance to most international, governmental and youth institutional definitions (42, 43) as participants aged 12–25, who have signs or symptoms of a mental disorder that are either self-reported or assessed via a screening

TABLE 1 | Eligibility criteria.

	Inclusion	Exclusion
Population	Youth (majority included 12–25 years old) Signs or symptoms of a mental health disorder	Children (<12 years old) and adults (>25 years old). Known mental health disorder
Intervention	Online prevention interventions (online-, internet-, web-, or mobile-based) Online *indicated* preventions	Interventions primarily face-to-face, Universal prevention, Selective preventive interventions
Comparison	Online prevention program, website, app, game, social media or smartwatch intervention compared to intervention, waiting list, or face-to-face intervention	–
Outcomes	Negative mental health indicators Positive mental health indicators Well-being indicators	Outcomes that are not indicative of mental health and well-being
Timing and setting	From 2013 onwards	–
Language	Articles written in English or Dutch	Other
Study design	RCTs, Quasi-experimental study designs, Experimental studies without comparison group	Descriptive studies, protocols

process. Studies were included if they included participants below age 12 or above age 25 as long as the majority of the participants was between ages 12–25. This was assessed by the mean age of the participants, the standard deviation of age, and the proportion of participants within this age range (studies were included only when more than half of the participants fell within the range). Articles were excluded when the age range of the included participants was outside 12–25 and the mean age was not reported.

Studies were also excluded if they had selected participants with a known mental disorder (either self-reported or diagnosed by a clinician). However, since most indicated preventive interventions did not screen for the presence of a mental disorder, studies were not excluded if they did not screen for mental disorders. The risk of reducing specificity by including these articles was deemed essential in order to have a broader scope to best summarize the relevant research.

Intervention

Interventions needed to be delivered primarily in an online (digital) setting (defined as: online-, Internet, Web-, or mobile-based) and focused on indicated prevention of mental disorders in youth aged 12–25 with signs or symptoms of a mental disorder. Only online indicated preventive interventions were included [defined as: preventive online interventions which target individuals who are showing early symptoms and signs of a disorder to prevent progression from clinical stages 1a and 1b to stages 2–4; (40)].

Interventions that are primarily face-to-face with some additional online content were also excluded. Lastly, process evaluation studies were excluded (although important implementation findings may be highlighted in the identified studies).

Comparison and Study Type

Studies comparing online prevention programs, websites, apps, games, social media or smartwatch interventions compared to no intervention, waiting list, or face-to-face interventions were included. No exclusion criteria were applied to the type of comparator used. RCTs, quasi-experimental study designs and experimental studies without a comparison group were eligible for inclusion in this review. No minimum follow-up time period was specified. Observational studies or protocols were excluded. There were no restrictions by timing or type of setting. Only articles written in English or Dutch were included.

Outcomes

The following a priori determined outcome measures were included: negative mental health indicators, for example, depression, anxiety, psychological distress and suicidal behavior, and transition to symptom levels above clinical diagnostic threshold; positive mental health indicators, for example, self-efficacy, coping skills, resilience, emotional well-being, self-esteem; and well-being indicators, for example, social participation, quality of life, social functioning, empowerment, communication, social support. Outcomes that were not indicative of mental health and well-being were excluded.

Charting the Data

Data were extracted by two out of five reviewers independently and in duplicate with the use of standardized data extraction forms. Any disagreements were resolved through discussion and by a third reviewer. To ensure accuracy, the extracted data was reviewed by experts in the field based on relevance. Data that was extracted included: intervention characteristics, methodology, program outcomes and information about program completion, engagement rate, and inclusion of human support.

The following data items were extracted: (1) intervention name, author, country where research was conducted, year of publication, (2) intervention characteristics (type of intervention, duration, target group), (3) method (study design, sample, selection biases, confounders, blinding, data collection, analysis, intervention integrity), (4) program outcomes, and (5) adherence (non-completion/dropout rates). In case of deficient or missing outcome data, authors were contacted and data were requested.

Summarizing and Reporting Results

To determine the extent and nature of the studies, a numerical analysis was conducted, using tables and chart mappings. Using conventional content analysis the descriptive data was analyzed. The user-centered design framework was followed, which states that two reviewers have to examine the data and identify codes relative to the findings. The codes were grouped according to themes to summarize the literature and answer the research question.

RESULTS

The search conducted by the university librarian (JD) yielded 11,122 results. After the screening process, the remaining 77 articles were assessed for relevance using the eligibility criteria in **Table 1** by six experts (DN, MAJ, JG, TvA, AP, and CM), and an additional two articles were provided by experts, resulting in the final inclusion of 30 articles for this scoping review. For the study selection procedure, see the PRISMA diagram in **Figure 1**.

For all study characteristics, see **Table 2**.

Timeline

Six studies were published in 2016. The number of studies regarding preventative online measures for youth saw a slight decline in the years 2017 ($n = 5$) and 2018 ($n = 4$), followed by a spike in publications occurring in 2019 ($n = 13$). At the present moment, there have been an additional two studies published in 2020.

Geographic Location

The included studies were predominantly conducted in Australia ($n = 9$) and the United States of America ($n = 7$), accounting for more than half (53%) of the contributions in this scoping. The remaining studies were conducted in the Netherlands ($n = 5$), Canada ($n = 1$), Finland ($n = 1$), Germany ($n = 1$), Japan ($n = 1$), Sweden ($n = 1$), Switzerland ($n = 1$), and the United Kingdom ($n = 1$). See **Table 2**.

Study Design

The included studies consisted primarily of RCTs ($n = 23$). Of these 23 RCTs, two were stratified and one was clustered. The remaining were experimental designs without comparison groups ($n = 6$). Another study that was included based on the preliminary inclusion criteria was identified as a mixed design ($n = 1$). Almost half (46%) of all included studies made use of a follow-up procedure, either within 3 months ($n = 4$), between 3 to 6 months ($n = 6$), or after 7 months and beyond ($n = 4$). See **Table 3**.

Sample Size and Study Population

See **Table 2** for sample characteristics. In total, the 30 articles included 4,950 participants in their studies, (165 participants per study on average), ranging from 14 to 536 participants. In total, 26,7% of the selected articles focused on young people between the ages of 12 and 25, 30% focused solely on youth from the ages 11 to 19, and 43,3% focused on adolescents of 17 years and older. The weighted mean age of participants over all articles was 18,9 years. In all articles but 1 (77), the majority of participants were female. 33,3% of the articles focused on depression symptoms or disorders, 10% on anxiety related symptoms or disorders, and 20% on either depression or anxiety symptoms or disorders. 6,7% of the articles focused on symptoms of psychosis, 3,3% on suicide, and 3,3% on depression or psychosis symptoms. 23,3% of the articles focused on elevated stress and had a transdiagnostic approach.

Of the included articles 40% focused solely on indicated prevention and excluded participants who met criteria for a mental disorder. The other 60% did not screen for, or exclude participants with presence of a mental disorder. Therefore, these studies were not strictly indicated prevention studies despite using the terms "prevention" or "indicated" in the publications. The measures used to establish whether a participant had emerging complaints vs. a known mental disorder varied

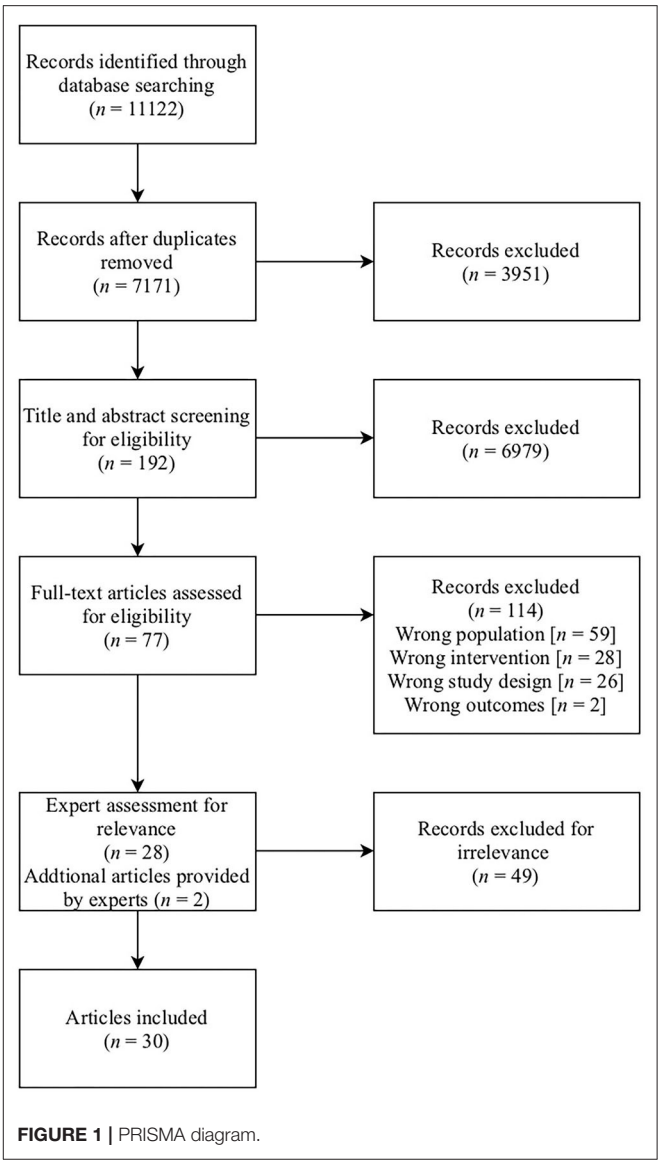

FIGURE 1 | PRISMA diagram.

TABLE 2 | Study characteristics.

Author	*N*	Mean age (SD)	Gender	Type of complaints	Disorder excluded?*	Adherence	Location
Alvarez-Jimenez et al. (51)	14	20.3 (3.4)	78% female	At risk for psychosis	CAARMS	57% participants completing at least 6 therapy modules and 43% completing 9 or more therapy modules	Australia
Alvarez-Jimenez, et al. (52)	157	19.1 (2.3)	77% female	Self-reported mental health concerns	No	Unclear	Australia
Anttila et al. (53)	46	16 (?)	74% female	Depressive or anxiety symptoms	No	100% adherence ($n = 5$ withdrew before start, $n = 24$ non-response)	Finland
Aubel et al. (54)	55	21 (2.43)	73% female	Depressive or psychotic symptoms	Currently under treatment or need for more care assessed by psychiatrist	92.59%	Netherlands
Berg et al. (55)	71	17.2 (1)	94% female	Depressive symptoms	No	70.0% fully completed, on average 81% of 8 modules	Sweden
Cook et al. (56)	235	20.41 (?)	83% female	Depressive symptoms	Instrument not specified	Unclear	UK
Deady et al. (57)	60	21.74 (2.22)	60% female	Depressive symptoms and alcohol use	No	63.3%	Australia
Dickter et al. (58)	83	17.5 (2.04)	56.2% female	Depressive symptoms	PHQ-A interview	26.5% no modules, 24.1% 1–5 modules, 20.5% 6–13 modules, 28.9% entire program	USA
Farrer et al. (59)	200	22 (4.1)	77.5% female	Transdiagnostic	No	75.8% used program at least once	Australia
Fitzpatrick et al. (60)	70	22.2 (2.33)	67% female	Depressive/anxiety symptoms	No	52% (used provided e-book at least once)	USA
Harrer et al. (61)	150	24.1 (4.1)	74.7% female	Elevated stress	No	71.2%	Germany
Hickie et al. (62)	449	?	63% female	Distress symptoms	No	Weekly use 18%, 1–2 times a month or less 82%.	Australia
Hides et al. (63)	169	19.9 (2.5)	79.3% female	Distress symptoms	No	54.44%	Australia
Hill et al. (64)	80	16.67 (1.7)	68.8% female	Suicide prevention and burdensomeness	No	43.90%	USA
Hullu et al. (65)	240	13.6 (?)	72.5% female	Social anxiety symptoms	No	41.86%	Netherlands
Lattie et al. (66)	39	16.23 (.99)	74.4% female	Depressive symptoms	M-health history assessed by psychiatrist	Unclear	USA
Levin et al. (67)	79	20.51 (2.73)	66% female	Transdiagnostic: in distress	No	55% completed all, 75% completed half, 17.5% didn't participate.	USA
Levin et al. (68)	234	21.61 (5.48)	76.9% female	Depressive, anxiety and distress symptoms	Self-report no former diagnoses	ACT: 1st lesson completed 85%, 2nd lesson completed 55% - Online Education 1st lesson completed 100%, 2nd lesson completed 86%	USA

(Continued)

TABLE 2 | Continued

Author	*N*	Mean age (SD)	Gender	Type of complaints	Disorder excluded?*	Adherence	Location
Mccall et al. (69)	65	21.86 (5.51)	72% female	Social anxiety symptoms	Self-report no former diagnoses	98.0%	Canada
Mcdermott et al. (70)	350	18.75 (1.63)	73.2% female	Depressive symptoms	No	77.2% completed	Canada
Motter et al. (71)	46	21 (3.7)	71.7% female	Depressive symptoms	No	76.09%	USA
Poppelaars et al., (72)	208	13.35 (.71)	100% female	Depressive symptoms	No	95.39%	Netherlands
Radomski et al. (73)	536	16.6 (1.7)	71.3% female	Anxiety symptoms	No	27.90%	Canada
Sanci et al. (74)	413	20.7 (2.3)	83.3% female	Symptoms of distress and negative affect	No	71% responded to 2-week, 1-month, 3-month follow-up.	Australia
Simmons et al. (75)	66	18.5 (3.42)	82% female	Depressive symptoms	Instrument not specified	76.0%	Australia
Staples et al. (76)	424	21.5 (2)	82.8% female	Depressive or anxiety symptoms	PHQ-9	100% 1 lesson, 88% 2 lessons, 79% 3 lessons, 64% completed all (4) lessons	Australia
Takahashi et al. (77)	22	20 (.62)	27.3% female	Depressive symptoms	Self-report no former diagnoses	50.0%	Japan
Topper et al. (78)	251	17.45 (?)	83.7% female	Depressive or generalized anxiety disorder symptoms	Self-report no former diagnoses + PHQ-9	86.83%	Netherlands
Traber-Walker et al. (79)	30	16.1 (?)	61% female	At risk for psychosis	Self-report no former diagnoses	-	Switzerland
De Voogd et al. (80)	108	14.45 (1.53)	66.7% female	Depression and anxiety symptoms	No	43.8%	Netherlands

**This section specifies whether there was screened for known mental disorders, and if people with a mental disorder were excluded.*

SD, standard deviation; PHQ-9, patients health questionnaire-9; PHQ-A, patients health questionnaire-9 modified for adolescents; m-health, mental health; CAARMS, comprehensive assessment of at risk mental states; CBT, cognitive behavioral therapy; IPT, interpersonal therapy; ACT, acceptance and commitment therapy.

TABLE 3 | Study outcome measures and results.

Author	Study design	Intervention type	Duration of intervention	Outcome measures	Human support	Findings
Alvarez-Jimenez et al. (51)	Experimental study without comparison with 2-month follow-up	Mindfulness and strength based intervention	2-months	Psychotic Symptoms, Depression, Stress, Social and Global Functioning, Mindfulness, Personal Strengths, Social Provision, Life Satisfaction, Self-Efficacy, Self-Esteem, Loneliness	Peer and clinically moderated	Large improvement in social functioning ($d = 1.83$), subjective well-being ($d = 0.75$), strengths usage ($d = 0.70$) and mindfulness skills ($d = 0.66$) at follow-up.
Alvarez-Jimenez, et al. (52)	Experimental study	CBT, mindfulness, self-compassion and positive psychology	9 weeks	Nonspecific Psychological Distress, Mental Well-being, Stress, Depression, Loneliness, Psychological Needs, Friendship Strength, Use of Strength, Mindfulness, Platform Usability	Peer and clinically moderated (clinician guidance, chat counseling, and peer moderators)	Improvements in psychological distress ($d = -0.38$), perceived stress ($d = -0.37$), psychological well-being ($d = 0.38$), loneliness ($d = -0.33$), social support ($d = 0.25$), and autonomy ($d = 0.50$).
Anttila et al. (53)	Mixed Methods descriptive study	Self-determined by participants	6 weeks	Quality of Online Services	Clinically moderated (feedback on exercises by research nurse)	89% rated web-based support system reliable and safe. 93% rated the content on web-based support systems relevant
van Aubel et al. (54)	RCT with 6 and 12-month follow-up	ACT	6 weeks	Depression, Psychotic symptoms, Anxiety, General psychopathological symptoms, Psychological Flexibility, Negative and Positive Affect	Clinically moderated (weekly group sessions with trained therapist)	Decrease in depressive symptoms ($p = 0.027$) compared to control. Increased mean negative affect ($p = 0.011$), relative to active controls.
Berg et al. 2019	RCT	CBT	8 weeks	Depression, Psychological Knowledge	Clinically moderated (weekly chat contact and feedback on exercises)	Improvements in psychological knowledge in ICBT compared to attention control (between-group $d = 1.25$). Non-significant correlation between change scores in knowledge and BDI-II change scores
Cook et al. 2019	RCT with 3- and 15-month follow-up	CBT	6–12 weeks	Depression, Anxiety, Worrying, Rumination	Clinically moderated (feedback by clinicians)	Reduced risk of depression by 34% using guided i-RFCBT relative to usual care (hazard ratio = 0.66). Significant improvements in rumination, worry, and depressive symptoms.
Deady et al. (57)	RCT	CBT and motivational interviewing	4 weeks	Depression, Alcohol use	None	Reduction in depressive symptoms ($d = 0.71$; 6-month follow-up: $d = 0.39$), reductions in alcohol use quantity ($d = 0.99$; 6-month follow-up: $d = -0.09$) and frequency $d = 0.76$; 6-month follow-up: $d = 0.24$) compared to control.
Dickter et al. (58)	Experimental study, without comparison	CBT and IPT	Not specified	Suicidal ideation, Hopelessness, Low self-esteem, Social isolation	None	Decrease in suicidal ideation ($d = 0.60$).
Farrer et al. (59)	RCT	Psychoeducation, CBT and mindfulness	6 weeks; young people choose amount of modules	Depression, Anxiety, Non-specific Psychological Distress, Social Anxiety, Quality of Life, Self-efficacy, Academic Self-Efficacy	None	Reductions social anxiety ($d = -0.03$; 3-month follow-up $d = -0.17$). Improvements in academic self-efficacy ($d = 0.10$; 3-month follow-up $d = 0.60$).

(Continued)

TABLE 3 | Continued

Author	Study design	Intervention type	Duration of intervention	Outcome measures	Human support	Findings
Fitzpatrick et al. (60)	RCT	CBT	2 weeks	Depression, Anxiety, Positive and Negative Affect	Robot	Decreased depressive symptoms in the Woebot condition ($d = 0.44$) over control. Reduced anxiety symptoms in both groups ($d = 0.37$)
Harrer et al. (61)	RCT with 3-month follow-up	CBT and 3rd wave techniques	5–7 weeks	Perceived stress, Depression, Anxiety, Well-being, Emotional exhaustion, Dysfunctional perfectionism, Resilience, Self-compassion, Self-esteem, Academic work impairment, Academic productivity, Academic self-efficacy, Academic worrying	Clinically moderated (guidance by psychology student; check adherence, give feedback on exercises)	Improvements in stress ($d = 0.69$), anxiety ($d = 0.76$), depression ($d = 0.63$), college-related productivity ($d = 0.33$), academic work impairment ($d = 0.34$) compared to control. Effects remained at follow-up
Hickie et al. (62)	Experimental study without comparison with 15, 30, 60, 90 day follow-up	Decision aid for treatment	90 min	Non-specific Psychological Distress, Suicidality, Personal concerns, Positive Mental Health, Happiness, Program Usability	Clinically moderated (a health professional present)	Significant reduction in psychological distress, body image issues, depression, and coping with stress. Improvement in health and mental health rating.
Hides et al. (63)	Stratified RCT with 1, 2, 3, 6-month follow-up	Music therapy	1-month	Emotion Regulation, Non-specific Psychological Distress, Positive Mental Health	None	Significant improvements in 5 of the 6 emotion regulation skills, mental distress, and well-being at 2, 3, and 6-months. No significant differences between groups
Hill et al. 2016	RCT with 6 week follow-up	CBT	2 weeks	Interpersonal Needs, Perceived Burdensomeness, Thwarted Belongingness, Depression, Suicide Ideation, Satisfaction with Services	None	Lower perceived burdensomeness scores (partial η^2 =0.10; follow-up: partial $\eta^2 = 0.21$), lower depressive symptoms (follow-up: partial $\eta^2 = 0.12$), and lower thwarted belongingness (follow-up: partial $\eta^2 = 0.16$) compared to control.
de Hullu et al. (65)	Clustered RCT	Cognitive bias modification internet-based vs. CBT f2f	10 weeks	Social phobia, Test anxiety, Self-esteem, Prosocial behavior, Fear of Negative Evaluation, Self-esteem, Implicit Cognition	None	Decrease in social and test anxiety (2-year follow-up: $d = 0.86$, and 0.82 respectively). Positive changes in self-esteem ($d = -0.67$), prosocial behaviors ($d = -0.57$), and fear of negative evaluation ($d = 0.49$).
Lattie et al. (66)	RCT	CBT	8 weeks	Depression, Positive Affect, Perceived Stress, Alcohol and Drug use, System Usage and Usability	Peer and clinically moderated (for guidance and technical support)	Decreased depressive symptoms ($\eta_{p^2} = 0.061$) and perceived stress ($\eta_{p^2} = 0.159$); significant increase of positive effect from baseline to midpoint in both groups ($\eta_{p^2} = 0.321$)
Levin et al. (67)	RCT	ACT	4 weeks	Depression, General Anxiety, Social Anxiety, Academic Concern, Eating Disorder Symptoms, Hostility, Alcohol use, Distress, Psychological Inflexibility, Positive mental Health, Personal values, Mindfulness, Cognitive fusion, Program Usability	None	Decrease in total distress ($d = 0.66$), social anxiety ($d = 0.78$), academic concern ($d = 0.62$), MHC total score, ($d = 0.58$), and MHC social well-being ($d = 0.69$). Significant time by condition interactions were found for PHLMS acceptance (d =0.053), and VQ obstacles ($d = 0.65$)

(Continued)

TABLE 3 | Continued

Author	Study design	Intervention type	Duration of intervention	Outcome measures	Human support	Findings
Levin et al. (68)	RCT with 3 week follow-up	ACT	3 weeks	Depression, Anxiety, and Stress Symptoms, Psychological Inflexibility, Positive Mental Health, Personal values, Relationship and Education, Mindfulness, Knowledge of ACT core concepts, Program Usability	None	No differences between conditions at post or follow-up.
Mccall et al. (69)	RCT with 4-month follow-up	CBT	4-months	Social Anxiety, Fear of Negative Evaluation, Quality of life	None	Reduction in social anxiety in treatment condition (SIAS: d =0.72; FNE: d = 0.82) then control condition (SIAS: d =0.56; FNE: d = 0.97)
Mcdermott et al. (70)	RCT	CBT vs. attention bias modification	6 weeks	Neuroticism, Non-specific Psychological Distress, Depressive Symptoms Anxiety and Stress	None	Greater improvement in depressive symptoms in CBT condition vs. attentional bias modification (d = 0.37 and d = 0.48; follow-up: d = 0.57 and d = 0.65).
Motter et al. (71)	RCT	Cognitive training	8 weeks	Depression, Social dysfunction, Letter Fluency, Cognitive Flexibility	None	Greater improvement in coding (d = 0.45), executive functioning and processing speed in EF/PS group compared to verbal group. Improvements in self and clinician-rated depressive severity, everyday functioning, and cognition in both groups.
Poppelaars et al. 2016	RCT with follow up at 3-, 6-, 12-month interval	CBT	8 weeks	Depression	Clinically moderated (in one condition combined face-to-face therapy with e-health)	Decrease depressive symptoms in all conditions ($p < 0.001$; 1-year follow-up: partial $\eta^2 = 0.14$), no difference between conditions.
Radomski et al. (73)	RCT with 6 week follow-up	CBT	6 weeks	Anxiety, Experience of E-Health Interventions	Clinically moderated (one coaching session by clinician)	Total user experience was significantly more positive for the interactive online platform than for respondents using a webpage.
Sanci et al. (74)	RCT with 1 and 3-month follow-up	Decision aid	Not specified	Non-specific Psychological Distress, Positive and Negative Affect, Help-Seeking Behavior	None	Decrease in negative effect compared to control (p = 0.02; 1-month follow-up: p = 0.001). Increase in help seeking behavior compared to control (3-month follow-up: p = 0.04
Simmons et al. (75)	Experimental study without comparison	Decision aid for treatment and life style advice, and psychoeducation	50 min	Depression, Decisional conflict, satisfaction with decision	Clinically moderated (clinician present during session)	Clients were more likely to make a guideline congruent decision for treatment (93 vs. 70%; P = 0.004), had reduced decisional conflict and reduced depressive symptoms (follow-up: 7 points lower on PHQ).
Staples et al. (76)	RCT using data from an already completed study	CBT	8 weeks	Depression, Anxiety, Non-specific Psychological Distress, Treatment Satisfaction	Clinically moderated (one condition with support clinician)	Symptom reductions on all measures at post-treatment and 3-month follow-up both conditions. Within-group effect sizes were large (d >1.0) and high levels of treatment satisfaction.

(Continued)

TABLE 3 | Continued

Author	Study design	Intervention type	Duration of intervention	Outcome measures	Human support	Findings
Takahashi et al. (77)	Experimental study without comparison	Motion picture-reproducing app	5 weeks	Depression, General Mental Health, Social Anxiety, Self-Efficacy, Salivary Interleukin-6 levels, Program Usability	None	Decrease depressive symptoms ($d = 0.94$).
Topper et al. 2017	RCT with 3-month and 12-month follow-up	CBT	6 weeks	Worrying, Rumination, Perseverative Thinking, Depression, General Distress, Mood and Anxiety, Eating Disorder Symptoms, Alcohol Use	Clinically moderated (weekly group session and feedback on online exercises by a therapist)	Reduced RNT ($d = 0.53$ to 0.89; 12-month follow-up: effects maintained), and symptoms of anxiety and depression ($d = 0.36$ to 0.72; 12-month follow-up: effects maintained) in both interventions. Significantly lower 12-month prevalence rate of depression and generalized anxiety disorder in both intervention groups compared to the waitlist
Traber-Walker et al. (79)	RCT	Adjunct to therapy; e.g. information, registrations	16 weeks	Global and Social Functioning, Quality of Life, Self-Efficacy, Treatment Satisfaction	Clinically moderated (weekly individual sessions)	Ongoing
de Voogd et al. (80)	Stratified RCT with 6-month follow-up	Attentional bias modification	4 weeks	Anxiety, Depression, Perseverative Thinking, Mental Recognition Task, Strengths and Difficulties, Self-Esteem, Emotional-Visual Cognition, Cognitive Recognition	Clinically moderated (sending of reminders and technical support)	Reductions in symptoms of anxiety and depression; and an increase in emotional resilience. Attentional bias modification reduced attentional bias compared to both control groups.

N, number of participants; RCT, randomized clinical trial; ACT, acceptance and commitment therapy; CBT, cognitive behavioral therapy; d, Cohen's d; ηp2, partial eta- squared; p, p-value; PHQ, patient health questionnaire; EF/PS, executive functioning and processing speed; ICBT, internet-based cognitive behavioral therapy; BDI-II, becks depression inventory II; MHC, mental health continuum; PHLMS, the philadelphia mindfulness scale; VQ, valuing questionnaire; SIAS, Social Interaction Anxiety Scale; FNE, the fear of negative evaluation scale; RNT, repetitive negative thinking; i-RFCBT, internet-based rumination-focused cognitive behavioral therapy; f2f, face-to-face.

substantially over the studies, ranging from self-report (e.g. "Have you ever been diagnosed with a mental disorder?") to a structured DSM-5 interview with clear cut-offs for clinical levels of mental disorders. A specific and validated clinician-rated instrument was used only for identifying the subclinical complaints of psychosis (UHR-state) (51). Lastly, the studies used different at-risk definitions, which indicates that a clear consensus on definitions is also missing.

Intervention Type and Duration

Most of the studies used a common evidence-based therapy for the disorder-category targeted. The most commonly used approach was CBT ($n = 17$), of which several studies ($n = 5$) combined this approach with another, for example Interpersonal Therapy (58), Motivational Interviewing (MI) (57), third wave techniques (61), mindfulness (59), and strength-based interventions such as mindfulness, self-compassion and positive psychology (52). One study researched Cognitive Training (CT) (71), and another mindfulness and strength training (51). Three studies investigated Acceptance and Commitment Therapy (ACT) (54, 67, 68). One study used cognitive bias modification (65), and two attentional bias modification (70, 80). Less common approaches were used by Takahashi et al. (77) using a motion picture producing app; Anttilaet al. (53) who used self-determination as a framework and allowed participants chose relevant subjects to discuss; and Hides et al. (63) using Music Therapy. In the study by Traber-Walker et al. (79), an app was used as an adjunct to face-to-face therapy; for example, containing information and registration forms. Lastly, three studies offered a decision aid to help find the right treatment, and find information (e.g., lifestyle advice, psychoeducation); and did not provide further treatment on their platforms (62, 74, 75). More than half of the online interventions included some form of human support, ranging from sending reminders, to group or individual sessions with clinicians. In most studies the treatments were based on specific theoretical bases for the disorder-category being targeted, for example, CBT for depressive symptoms, with standard modules and options to tailor the treatment to the individual's needs. See **Table 3**.

The range of duration of the online intervention was 50 min to 16 weeks. See **Table 3**. The three decision aid programs had the shortest duration, namely only one session (50 or 90 min; and not specified). Not taking these three studies into account, the online treatment programs varied in duration from 2 weeks to 16 weeks.

Adherence

The included studies showed a varied range of adherence to the programs, see **Table 2**. The adherence percentages were either adopted directly from the reported number provided by the authors of the included papers, or calculated based on the percentage of participants who either completed at least half of the program in the experimental condition, or dropped out during the experimental phase. Adherence levels ranged from 27.9% of participants (73) to 98% of participants (69) with a mean adherence percentage of 63.81%. However, caution should be exercised in the depiction of these numbers due to the lack of consensus in measuring adherence.

Outcome Measures

Outcome measures consisted/included factors such as: depression, anxiety, social anxiety, distress, eating pattern disturbances, excessive drinking, suicidal ideation, mindfulness, self-efficacy, self-esteem, cognitive functioning, psychological inflexibility, social dysfunctioning, quality of life, rumination, emotional regulation and various other factors. Noticeable in the selected articles is that many different questionnaires (with varying validity) were used to measure a single psychological construct such as depression. For a complete overview, see **Table 3**.

Key Findings

For a full overview of the overall findings, including the outcome variables, the study design, the number of participants in each study and whether human support was used in the intervention, see **Table 3**.

The quality of the selected articles differed considerably. Firstly, the number of participants included in the selected studies showed a wide range (from $n = 14$ to $n = 536$). Moreover, various articles did not provide data on effect sizes of significant effects ($n = 7$). In addition, some articles deconstructed or created questionnaires without reporting their psychometric properties. Lastly, some studies did not have a control group to compare the effects of the interventions to ($n = 6$). Therefore, the results are to

TABLE 4 | Number of studies and effect sizes per intervention type and form of support.

Intervention type	*N*	Support	Effect size (*d*)
CBT	6	Clinical	0.36–1.25
	1	Clinical & peer	0.51–1.37
	1	Robot	0.37–0.44
	4	None	−0.76–1.03
CBT combined	1	Clinical	0.33–0.76
	1	Clinical & peer	−0.38–0.50
	3	None	−0.17–0.99
ACT	1	Clinical	No effect sizes reported
	2	None	0.053–0.78
Cognitive bias modification	1	Clinical	No effect sizes reported
	2	None	−0.67–0.86
Decision aid for treatment	2	Clinical	No effect sizes reported
	1	None	No effect sizes reported
Music therapy	1	None	No effect sizes reported
Cognitive training	1	None	0.45
Motion picture-reproducing app	1	None	0.94
Adjunct to therapy; e.g., information, registrations	1	Clinical	Ongoing
Mindfulness and strength-based intervention	1	Peer & clinical	0.66–1.83
Self-determined	1	Clinical	No effect sizes reported

N, number of participants; ACT, acceptance and commitment therapy; CBT, cognitive behavioral therapy; CBT combined, cognitive behavioral therapy combined with other approach; d, Cohen's d.

be interpreted with caution, and the authors refrain from making conclusive comparisons between studies.

The results of the selected articles show that online preventive interventions are generally effective in reducing negative outcome measures such as depressive symptoms ($n = 16$), anxiety ($n = 5$) and stress ($n = 6$). As for the positive outcome measures, the majority of articles measuring positive health indicators showed that online preventive interventions significantly improves positive mental health factors such as well-being ($n = 4$) and social functioning ($n = 2$). However, a large part of the selected articles measuring positive health indicators also showed non-significant improvement

TABLE 5 | Study characteristics for studies excluding participants with clinical levels of symptoms.

References	Screening instrument	Intervention type	Human support	Findings
Alvarez-Jimenez et al. (51)	CAARMS	Mindfulness and strength based intervention	Peer and clinically moderated	Large improvement in social functioning ($d = 1.83$), subjective well-being ($d = 0.75$), strengths usage ($d = 0.70$) and mindfulness skills ($d = 0.66$) at follow-up.
van Aubel et al. (54)	Currently under treatment or need for more care assessed by psychiatrist	ACT	Clinically moderated (weekly group sessions with trained therapist)	Decrease in depressive symptoms ($p = 0.027$) compared to control. Increased mean negative affect ($p = 0.011$), relative to active controls.
Cook et al., 2019	Instrument not specified	CBT	Clinically moderated (feedback by clinicians)	Reduced risk of depression by 34% using guided i-RFCBT relative to usual care (hazard ratio = 0.66). Significant improvements in rumination, worry, and depressive symptoms.
Dickter et al. (58)	PHQ-A interview	CBT and IPT	None	Decrease in suicidal ideation ($d = 0.60$).
Mccall et al. (69)	Self-report no former diagnoses	CBT	None	Reduction in social anxiety in treatment condition (SIAS: $d = 0.72$; FNE: $d = 0.82$) then control condition (SIAS: $d = 0.56$; FNE: $d = 0.97$)
Lattie et al. (66)	Mental health history assessed by psychiatrist	CBT	Peer and clinically moderated (for guidance and technical support)	Decreased depressive symptoms ($\eta_{p^2} = 0.061$) and perceived stress ($\eta_{p^2} = 0.159$); significant increase of positive effect from baseline to midpoint in both groups ($\eta_{p^2} = 0.321$)
Levin et al. (68)	Self-report no former diagnoses	ACT	None	No differences between conditions at post or follow-up.
Simmons et al. (75)	Instrument not specified	Decision aid for treatment and life style advice, and psychoeducation	Clinically moderated (clinician present during session)	Clients were more likely to make a guideline congruent decision for treatment (93 vs. 70%; $P = 0.004$), had reduced decisional conflict and reduced depressive symptoms (follow-up: 7 points lower on PHQ).
Staples et al. (76)	PHQ-9	CBT	Clinically moderated (one condition with support clinician)	Symptom reductions on all measures at post-treatment and 3-month follow-up both conditions. Within-group effect sizes were large ($d > 1.0$) and high levels of treatment satisfaction.
Takahashi et al. (77)	Self-report no former diagnoses	Motion picture-reproducing app	None	Decrease depressive symptoms ($d = 0.94$).
Topper et al. 2017	Self-report no former diagnoses + PHQ-9	CBT	Clinically moderated (weekly group session and feedback on online exercises by a therapist)	Reduced RNT ($d = 0.53$ to 0.89; 12-month follow-up: effects maintained), and symptoms of anxiety and depression ($d = 0.36$ to 0.72; 12-month follow-up: effects maintained) in both interventions. Significantly lower 12-month prevalence rate of depression and generalized anxiety disorder in both intervention groups compared to the waitlist
Traber-Walker, et al. (79)	Self-report no former diagnoses	Adjunct to therapy; for example, information, registrations	Clinically moderated (weekly individual sessions)	Ongoing

SD, Standard Deviation; PHQ-9, Patients Health Questionnaire-9; PHQ-A, Patients Health Questionnaire-9 modified for adolescents; CAARMS, Comprehensive Assessment of At Risk Mental States; CBT, Cognitive Behavioral Therapy; IPT, Interpersonal Therapy; ACT, Acceptance and Commitment Therapy; f2f, face-to-face.

intervention on factors such as self-efficacy ($n = 4$) and self-esteem ($n = 4$).

For studies using CBT as the intervention, small to large effect sizes were found (Cohen's d (d) between 0.36 and 1.25). Studies that combined CBT with other approaches reported small to large effect sizes ($d = -0.17$ to 0.99). CT was found to have a small effect size ($d = 0.45$). ACT interventions reported a medium effect size ($d = 0.62$ to 0.78). Mindfulness and strength-based interventions found medium to large effect sizes ($d = 0.66$ to 1.83). Cognitive bias modification found a large effect size ($d = 0.86$) and attentional bias modification a medium effect size ($d = 0.57$). The motion picture producing app found a large effect size ($d = 0.94$). For an app used as adjunct to face-to-face therapy a small to medium effect size was reported ($d = 0.25$ to 0.50). For music therapy and the decision aids the Cohen's d was not reported. Online interventions without human support resulted in small to large effect sizes ($d = -0.09$ to 0.99). Online interventions with robot support yielded small effect sizes ($d = 0.37$ to.44). Studies that included clinical moderation found small to large effect sizes ($d = 0.33$ to 1.25). Finally, online interventions with the combination of clinical and peer moderation found small to large effect sizes ($d = 0.25$ to 1.83).Overall, studies varied in their size, rigor of study, effectiveness and outcome measures; the effect sizes were highest for the mindfulness and strength-based intervention (1 study, $n = 14$; social functioning $d = 1.83$), CBT ($n = 12$ studies; $d = 0.36$ to 1.25), and the motion picture app (1 study, $n = 22$, no control; $d = 0.94$ depressive symptoms). Online interventions with a combination of clinical and peer moderation ($n = 3$ studies; $d = 0.25$ to 1.83) appear to result in the most stable and highest effect sizes. See **Table 4** for an overview.

Even though the scope of this review was indicated prevention, 60% of the articles did not exclude participants who met criteria for a mental disorder. However, clinical stages 1a and 1b are not synonym with the absence of a mental disorder as assessed with the DSM/ICD (ref). But to give a complete overview, we summarize the 12 studies that excluded participants with a mental disorder below and in **Table 5**. These studies show varying results. Overall, no effects to large effect sizes were found ($d = 0$ to 1.83). Studies using CBT as the intervention found small to large effect sizes ($d = 0.36$ to >1.0). One study using an ACT intervention found no significant treatment effects, and one found significant effects ($p = 0.027$, no effect size reported). The motion picture app found a large effect size ($d = 0.94$). Mindfulness and strength-based interventions found medium to large effect sizes ($d = 0.66$ to 1.83). Online interventions without human support resulted in no effect to large effect sizes ($d = 0$ to 0.94). Studies that included clinical moderation found small to large effect sizes ($d = 0.36$ to 89). Finally, online interventions with the combination of clinical and peer moderation found medium to large effect sizes ($d = 0.5$ to 1.83). Overall, studies using mindfulness and strength-based interventions, a motion picture app or CBT found the highest effect sizes. The studies using ACT as the intervention type show varying results and no effect sizes are known for one study, making it difficult to draw conclusions on the effectiveness of ACT. Moreover, online interventions with the combination of clinical and peer moderation appear to result in the most stable (smaller range of effectiveness findings) and highest effect sizes.

The most robust data for the effectiveness of online preventive interventions are from the following three articles due to their high number of participants (n-range of studies from 413 to 536) and their RCT design. These studies provide general support for the effectiveness of online preventive interventions for youth. (1) Radomski et al. (73) used CBT as the intervention type, and did not find significant differences between conditions but user experience was significantly more positive in the intervention group compared to the control group. (2) Sanci et al. (74) researched a decision aid, and found a significantly stronger reduction in negative affect in the intervention group compared to the control group post-intervention and at the 1-month follow-up. In addition, a significant increase in help-seeking behavior was measured in the intervention group compared to the control group at the 3-month follow-up. (3) Staples et al. (76), also used CBT as the intervention type, and found significant reduction in symptoms of depression, anxiety and non-specific psychological distress with large within-group effect size ($d > 1.0$), high levels of treatment satisfaction and no significant differences between the online intervention group and the routine care group.

Overall, young people commonly reported high satisfaction and usability of online interventions. For example, high levels of treatment satisfaction were reported (76). Moreover, safety, reliability (53) and positive user experience (73) of online platforms were found.

DISCUSSION

The focus of this review was to present an overview of indicated online preventive interventions for emerging mental health symptoms in youth (12–25 years). We aimed to identify the nature and extent of the relevant research evidence from treatment studies. This led to the following guiding question: *What is known about the use of indicated online preventive interventions for youth with emerging mental health problems?*

The findings of the included articles of the scoping review indicate the overall importance of online indicated preventive intervention. The results show that online preventive interventions are generally effective to reduce subclinical symptoms of various mental illnesses and improve several outcome measures such as quality of life and mindfulness. In addition, young people commonly reported good satisfaction, acceptability and usability of online interventions.

However, the included studies pose several limitations and therefore conclusions should be made with caution. Also the research published to date has focused predominantly on specific diagnostic categories, suggesting there is a lack of studies that have targeted transdiagnostic mechanisms. Finally, clear definitions of- as well as instruments to measure- emerging or subclinical mental health symptoms are missing. In the next section, the found gaps in the research, and the limitations of this scoping review will be discussed, as well as recommendations for future research.

Gaps in the Literature

Overall, the included articles show that online indicated preventive mental health interventions for youth with emerging mental health issues show promise in reducing various mental health complaints, and increasing positive mental health indicators such as well-being and resilience. From the 30 articles selected for our scoping, the vast majority of the included studies were RCTs with adequate use of control groups ($n = 24$). Nonetheless, the included studies showed important shortcomings. For example, effect sizes were often not reported, psychometric qualities of used instruments were not investigated, and control groups were missing. Moreover, it remains unclear how long these positive effects last. The majority of articles had no follow-up data exceeding 3 months, and only four articles had follow-up data exceeding 7 months. The limited availability of long-term data is an issue, since it does not provide adequate insight whether online indicated preventive interventions for youth with emerging mental health issues delays the onset of a consequent mental illness, or whether it prevents the onset altogether. To provide an answer to this issue, future research regarding online indicated preventive interventions needs to investigate the long-term effects.

We note that there is an emerging consensus among researchers of the potential importance of indicated preventive interventions for young people. However, clear definitions of subclinical mental health complaints vs. clinical mental health disorders are missing, as well as instruments to measure these different stages. For example, in a considerable number of studies participants were only asked whether they were ever formally diagnosed with a mental illness. Thus, the external validity of available indicated prevention research is limited, and the findings of the studies should be interpreted with caution. The clinical staging model of McGorry et al. (40) might offer a way to differentiate subclinical mental health complaints from clinical mental health disorders using different stages of mental health disorders. The model provides clear descriptions and cut-offs [e.g., (81)]. To the best of our knowledge a clinical instrument to operationalize these stages has not yet been developed. When looked at online indicated prevention research, it becomes clear that the clinical staging model has not been fully implemented and that there is critical fundamental work still to be undertaken. Additionally, indicated prevention in terms of the clinical staging model entails the prevention of severe mental health conditions. Light mental disorders in the affective spectrum would fall in stage 1b (40). In other words, the clinical staging model does not have the same cut offs as the DSM/ICD categories. This also shows that it is relatively difficult to apply the clinical staging model at the current moment. An interesting finding from studies in at-risk populations is that emerging mental health complaints are often diffuse and non-diagnosis specific. Also, emerging complaints have divergent trajectories, potentially leading to different mental disorders as well as remission or recovery (40). Within the included research of this scoping review, however, the focus lies almost exclusively on specific disorder categories, for example, youth with depressive symptoms. Moreover, the interventions used were disorder-oriented and less individually tailored. Since emerging complaints are often diffuse, have divergent trajectories, and are underpinned by overlapping mechanisms, a transdiagnostic approach would potentially make indicated preventive interventions more useful.

Only a small proportion of the found articles focused on youth within the age of 12–25. Most studies either looked at children younger than 18 years old, or at adults above 18 years old. This finding highlights a common obstacle in the modern day psychiatry, namely the gap that exists between child and adult psychiatry. The transition from child to adult psychiatry holds a risk for disruption in continuity of care (82, 83). Despite this, the onset of disorders (5, 6), as well as the strongest health burden (6) and multilevel life transitions (82) lie within this period. The group of youth between the ages of 12–25 years old is traditionally being divided in two groups based on age, labeled 'child' and "adult," while the characteristics and complaints of these individuals might suggest treating this group as a whole. More and more this need is emphasized, and currently being implemented in for example the Dutch health care system (84). The mean age of the sample of this scoping review was 18 years old, right at this cut, which also emphasizes the need to lift this boundary in scientific research and clinical practice.

To date a range of different platforms, websites and apps for online selective preventive interventions have been developed. Most studies used evidence-based therapies or frameworks for these programs. There was a great variance in the inclusion of additional human support to these interventions; ranging from sending reminders to weekly therapy sessions with a clinician. One study found no beneficial effect of inclusion of human support (76); however there is extensive research that adding human support enhances clinical effectiveness of online interventions (85, 86). The additional value of different types of human support should be investigated more extensively to be able to draw firm conclusions.

The mean adherence to the included programs varied substantially among the included studies. However, caution in interpreting this data is advised for various reasons. The biggest issue with interpreting the adherence rates in the present scoping review stems from the fact that the included papers were not using a standard method to describe the adherence to their program: therefore, there is no clear convention or determining "adherence." For example, adherence could be described by using the program in the experimental condition "at least once (59)," or "completing at least one module (out of a total of 4 modules (57)." Consequently, rates may seem artificially high due to the unclear demarcation of "adherence." Beintner et al. (87) found that out of a total of 216 publications that measured adherence in their analysis, 23 (10.6%) used one metric, 46 (21.3%) used two, 56 (25.9%) used three, and 63 (29.2%) included the use of four or more metrics. Indeed, it is a challenge to compare adherence rates in different studies with each other due to a missing common standard, as concluded by Beintner et al. (87). A possible solution to this methodological challenge is to introduce a-priori measurements to generate more meaningful data in future studies measuring adherence to and use of online programs, in accordance with the reasoning of Alvarez-Jiménez et al. (88). Additionally, adherence rates may be artificially

inflated due to recruitment setting or participation incentive as described in the study of Mccall et al. (69) (98% adherence rate) where student participants received extra course credit contingent on the amount of modules they completed and must be taken into account when interpreting data.

The majority of studies measuring usability and acceptability (defined by how intuitive and easy a program was to use and whether the program was satisfactory and acceptable, respectively) reported acceptable levels [e.g., (57, 60, 61, 66, 68)]. However, as it was critically noted by Deady et al. (57), the largely unguided nature of online preventative interventions might negatively impact adherence. About half of the studies included in this scoping review made use of some form of human support. However, it is difficult to make inferences about the possible impact of human support on adherence since the inclusion of human support as well as the measurements of adherence varied substantially among the included studies. It is important to carefully examine the advantages of providing largely unguided interventions with low adherence vs. interventions that require more guidance but yield higher adherence rates. Moreover, it could be valuable to investigate new ways to increase adherence in unguided settings.

LIMITATIONS AND STRENGTHS

Several limitations and strengths to this review should be highlighted. First of all, this study is a scoping review as opposed to a systematic review. Although this review has an ambitious breadth, it is not meant to be exhaustive in nature. For example, only three databases were searched. However, the advantage of a scoping review is that it aims to map key concepts, main sources, types of evidence available, volume, nature and characteristics rapidly, especially in areas where less research has been conducted. In contrast to most systematic reviews, the scoping review included not only RCTs, but different methods and study designs, implicating that the literature is potentially described more broadly (50). In addition, a scoping review is descriptive in nature (50), and no quality assessment of studies has been done. Therefore, further mechanisms and quality of evidence could not be provided.

Another limitation is that studies with certain disorder categories were excluded, for example eating disorders. One could argue this disorder would justify inclusion. Moreover, even though clear inclusion and exclusion criteria were drafted a priori, it was difficult to apply these criteria with a high degree of precision. Existing studies were often not explicitly based on concepts of clinical staging. Furthermore, the majority of the studies treated youth between the ages of 12 and 25 as two separate groups, contrary to our conceptualization of treating this age group as a whole. As a result, the identified articles varied in nature, population, methods, definitions and outcome measures, making it difficult to draw conclusions about online indicated preventive interventions for youth.

A strength of this review is that we used a transparent methodological framework to find key trends in the literature, which potentially gives a preliminary basis for future systematic reviews. Further, the review identified important gaps in the existing literature. Lastly, to our knowledge, this review is the first in the past 5 years to shed light on indicated preventive mental health intervention for youth.

FUTURE RESEARCH

Overall, high-quality investigations of the effectiveness of online indicated preventive interventions with follow-up data exceeding a few months for youth are missing. Further good quality research is needed to assess the effectiveness of the different online interventions using different therapeutic approaches. We suggest that researchers develop standardized definitions and instruments concerning subclinical symptoms in addition to clear definitions of "adherence." Moreover, a gap in transdiagnostic approaches is evident; as well as research that has specifically targeted the adolescent population in the age range from 12 to 25 years, which crosses the divide between the child and adult mental healthcare systems. Future research should include clinical trials of indicated preventive interventions for youth between the ages of 12 and 25 based on the clinical staging model with a focus on transdiagnostic mechanisms.

RECOMMENDATIONS

In order for effective online interventions to be implemented in large numbers of youth with emerging mental health issues, it is the authors' opinion that representatives of this youth should be involved in the development process of the interventions and the online platform (e.g., co-creation). The platform should be adaptive and improve continuously in response to feedback, thereby enabling idiosyncratic or personalized support. The review also shows that there are many different platforms and online interventions. Uniformity could prevent reinventing the wheel and contribute to the improvement of quality over time, both of the interventions and platforms, through research and the sharing of experiences. Lastly, it is of importance to that these services are financially compensated on a structural basis, for example from governments to enable ongoing innovation and development and keep up with the fast pace of development of technology. This requires commitment of governments and participation of "offline" (in-person) care parties to improve blended online and offline care adjusted to the needs of young people at different time points during their development.

AUTHOR CONTRIBUTIONS

MD, DN, ME, and KA completed initial study design. MD, ME, LN, KA, and ER assessed the provided articles. MD, ME, and LN made the final inclusion selection. DN, JDa, CM, AP, and TvA provided an expertise assessment and contributed extra articles

to the scoping. The manuscript was written by MD, ME, and LN. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.580843/full#supplementary-material

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Substance Misuse Trajectories and Risk of Relapse in the Early Course of Bipolar Disorder

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Substance misuse is highly prevalent in bipolar disorder even in the early illness phases. However, the trajectories of misuse of different substances after treatment initiation is not well-studied. Also, knowledge on how substance misuse trajectories influence the early course of bipolar disorder is limited. We recruited 220 individuals in first treatment of bipolar disorder of which 112 participated in a 1-year follow-up study at the NORMENT center in Oslo, Norway. Misuse was defined as having scores above cut-off for harmful use on the Alcohol or Drug Use Disorders Identification Tests (AUDIT or DUDIT). We investigated rates of stopping and continuing misuse of alcohol, cannabis and other illicit substances and daily nicotine use over the follow-up period, and whether such misuse trajectories predicted the risk for affective relapse. The prevalence of cannabis misuse was reduced from 29 to 15% and alcohol misuse was reduced from 39 to 21% during follow-up. Continuing alcohol misuse significantly and independently predicted affective relapse, whereas there was no difference in relapse risk between individuals stopping alcohol misuse and never misusing alcohol. Cannabis misuse trajectories did not significantly predict relapse risk although we cannot exclude interactions with alcohol misuse. In conclusion, substance misuse decreased in the early phase of bipolar disorder treatment but should be further reduced with interventions specifically addressing substance misuse. Stopping alcohol misuse is likely to yield substantial benefit on the clinical course of bipolar disorder.

Keywords: bipolar disorder, substance use disorders, alcohol misuse, cannabis misuse, relapse, longitudinal, early course

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INTRODUCTION

Around half of individuals with bipolar disorder (BD) develop cannabis-, alcohol-, or other substance use disorders during their lifetime (1–3). While necessary to describe the full range of substance use levels and -patterns, the diversity in thresholds and definitions used in the field may challenge dissemination. In the current study, "use" refers to any use of substances, "use disorders" refer to substance use meeting formal diagnostic criteria, while "misuse" is used as an umbrella

term also covering other definitions of potentially harmful substance use. There are indications that substance misuse is often present already at the onset of—or during the early phases of BD (4). In a recent first episode mania study, lifetime cannabis use disorder (CUD) was found in 34%, alcohol use disorder (AUD) in 15%, and other illicit substance use disorders (other SUD) in 11% of the participants (5). However, it is not well-known whether the rates of substance misuse decrease, increase or is stable during the early phases of BD. In one of the relatively few studies to date following BD individuals after their first manic episode, the proportion with alcohol misuse was found to be stable over the first 5 years of illness; 17.6% at baseline and 18.4% at follow-up. Misuse of illicit substances increased slightly from 45.9 to 52.6% (6). However, this study only investigated individuals with bipolar I disorder (BD I) and did not specifically report rates of cannabis misuse which is the most used illicit substance. Thus, while highly relevant when planning early intervention strategies, the different trajectories of misuse in representative populations of BD have been investigated to a limited extent.

Substance misuse, especially of cannabis but also of alcohol, is associated with more severe clinical characteristics in BD including earlier onset of the disorder, increased suicide risk and increased rates of rapid cycling (3, 7, 8). As these associations have mainly been established in cross-sectional studies, the current understanding of the direction of the relationship between substance misuse and BD illness severity is limited. Do individuals with BD experience more frequent episodes as a consequence of substance misuse, or are substances used more heavily as a response to symptoms in those with a more severe form of BD? This question can only be addressed through longitudinal studies, preferably during the first treatment phase where significant changes in substance misuse and clinical status are likely to take place. A previous prospective study comparing BD individuals who had never used cannabis with those who either stopped or continued their cannabis use over a 2 year period, found that those who stopped had similar relapse rates and functional outcomes to those who had never used cannabis (9). This indicates that preventing and ending cannabis (mis)use is an important clinical goal to reduce unfavorable outcomes in BD. However, the study included patients with a relatively long illness history and with low rates of cannabis use, possibly due to methodological issues such as under-reporting or sampling. In one of the few longitudinal studies on first episode mania to date, both the time in active cannabis misuse and the time in active alcohol misuse was associated with the time in affective episodes over the 5-year follow-up period (10, 11). In another longitudinal study of a first-treatment mania sample partly overlapping with the current study sample, we found that continued cannabis use was associated with higher levels of current manic symptoms and lower levels of current global functioning at 1-year follow-up compared to no use or stopped use (12). Recurrences of misuse after remission also appear to be common, further supporting the need to study misuse trajectories as a supplement to the study of lifetime comorbidity (10, 11). We have now expanded our first treatment BD sample, including participants with bipolar II disorder (BD II) and BD not otherwise specified (BD NOS). This enables a more detailed investigation of the trajectories of misuse of alcohol, cannabis and other illicit substances during the first year of treatment and their relationship to the risk of early relapse. We hypothesized that individuals with continued misuse of cannabis and/or alcohol would have significantly higher risk for relapse than patients without misuse, with intermediate risk in individuals who stopped their misuse.

MATERIALS AND METHODS

Sample

Participants were recruited to the on-going naturalistic multi-center Thematically Organized Psychosis (TOP) Study at the NORMENT Center for Mental Health Research at Oslo University Hospital and the University of Oslo from May 2003 to November 2019. All participants provided written informed consent to participate in this study. Exclusion criteria were a history of severe head injury, IQ below 70, age outside the range of 18–65 years, and inability to give informed consent. Inclusion criteria were being in the first treatment for a primary diagnosis of BD I, II, or NOS according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (13). First treatment was defined as giving informed consent to participate (a) within 12 months following the start of first adequate treatment or (b) while still not receiving adequate treatment. Adequate treatment was defined as taking mood stabilizing or atypical antipsychotic medication in an effective dose. Participants were not considered to be in first treatment if they previously on any occasion (before the index treatment) had received adequate treatment for more than 12 weeks. Participants who had experienced previously untreated self-remitting manic, mixed, or hypomanic episodes were also included, as were both previously, recently and never hospitalized individuals.

The TOP study is conducted in line with the Helsinki declaration of 1975 (as revised in 2008 and 2013) and has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Clinical Assessments

Diagnosis was established using the Structural Clinical Interview of Diagnosis for DSM-IV, Axis I disorders (SCID-I), modules A–E. The SCID-I was also used for assessment of age at illness onset and number of illness episodes. All interviewers completed a training course in SCID assessment based on the training program at UCLA (14) and participated in regular diagnostic consensus meetings led by a clinically experienced professor of psychiatry. Diagnostic reliability is assessed with regular intervals in the TOP study and has been found to be very good, with Cohen's kappa for diagnosis in the range between 0.92 and 0.99 across different assessment teams. For the main analyses, participants with BD NOS were coded as BD I if they had ever experienced manic episodes and as BD II if they had experienced hypomanic and depressive episodes. Age at onset of BD was defined as the age when the participant first met DSM-IV criteria for a major depressive, manic, hypomanic, or mixed episode. Duration of illness was calculated from age at inclusion in the study minus age at the first affective episode. Number of manic,

hypomanic, mixed, and depressive episodes according to DSM-IV criteria during lifetime and during the follow-up period were recorded. The number of episodes per illness year at baseline was calculated as the total lifetime number of affective episodes divided by duration of illness. Our main variable of interest was "any relapse," which was defined as having a new affective episode of any polarity during the follow-up period. We also explored "depressive relapse" and "(hypo)manic relapse," which refer to having a new depressive or elevated episode during follow-up, respectively. All such episodes were defined by DSM-IV criteria. Medication use of antipsychotic agents, lithium, and antiepileptics was recorded from interview with additional information from medical records.

Substance Use Assessments

Use of alcohol and illicit substances were assessed in-depth for each participant. Lifetime DSM-IV diagnoses of abuse or dependence of all substances were established using the SCID-I E-module. Abuse or dependence of substances other than alcohol and cannabis was compiled into a single "other substance use disorders" (other SUD) variable. The Alcohol Use Disorders Identification Test (AUDIT) (15) and the Drug Use Disorders Identification Test (DUDIT) (16) were used both at baseline and follow-up to evaluate the degree of current harmful alcohol and drug consumption, respectively. For AUDIT, scores $\geq$10 for males and $\geq$8 for females were coded as "misuse," and for DUDIT, scores $\geq$3 for males and $\geq$1 for females were coded as "misuse." These cut-off scores have been demonstrated as suitable for capturing substance use disorders in first episode psychosis (17). In addition, a semi-structured interview was used for assessment of recent substance use: Participants were asked whether they had used the following illicit substances: cannabis, cocaine, amphetamines, ecstasy, hallucinogens, heroin and other opiates, solvents, and non-ascribed sedatives/hypnotics during the last 6 months before baseline and follow-up assessments, as well as how many times illicit substances were used during this period. To enhance reliability, the participants were assured that no information about substance use would be shared with their clinician or others unless they explicitly gave permission. Cannabis misuse was defined as having a DUDIT score above cut-off and reporting cannabis use during the previous 6 months. DUDIT scores were missing for 13 participants at baseline and 20 participants at follow-up, and these were coded with cannabis misuse if they reported cannabis use and at least weekly use of illicit substances during the previous 6 months ($n = 1$ at baseline and $n = 3$ at follow-up). AUDIT scores were missing for 18 participants at baseline and 22 at follow-up, and these were coded as misuse if their average number of alcohol units consumed per week the previous 6 months exceeded 7 for females and 14 for males ($n = 2$ at both baseline and follow-up), in line with recommendations for maximum alcohol consumption in the Nordic countries (18). Finally, current daily use of nicotine was recorded both at baseline and follow-up since nicotine use is strongly related to all other forms of substance use or misuse (19), and has also been found to be associated with psychiatric outcomes such as suicidal risk in BD (20).

Substance Misuse Trajectory Groups

To investigate the relationship between misuse trajectories and relapse during the follow-up period, the sample was categorized as follows: (1) no lifetime use disorder or misuse at baseline or follow-up (NO), (2) lifetime use disorder and/or misuse at baseline but not at follow-up, i.e., stopped misuse (STOP), and (3) misuse at follow-up (with or without misuse at baseline so this group also included individuals which had started misusing) (CONT). The sample was categorized in this manner for both alcohol and cannabis misuse and in this way independent misuse trajectory variables for alcohol and cannabis were constructed.

Statistics

Categorical data are described as counts (percentage) and continuous data as medians (interquartile range, IQR) since all continuous variables had skewed distributions according to the Shapiro-Wilk-test (all p-values < 0.001). Except from the initial analyses comparing the baseline characteristics of those who completed and those who dropped out of the study (as shown in **Table 1**), only cases which completed follow-up were included in the further analyses and data presentation. The distributions of sociodemographic and clinical variables were tested against each of the substance misuse variables (NO, STOP, and CONT for alcohol and cannabis). For bivariate analyses of continuous variables, we conducted Kruskal-Wallis H-tests. For categorical variables we used χ^2-tests or Fisher's exact-tests when calculation tables for categorical variables had cells with <5 expected cases. Statistical significance was set at $p < 0.05$, two-tailed for bivariate analyses. Significant overall effects were followed up with group-wise comparisons, which were Bonferroni corrected for multiple testing. Variables representing previously implicated predictors of relapse were examined as potential confounders in the multivariate analyses, such as age at onset (21), bipolar disorder subtype (22), frequency/number of previous episodes (23), duration of illness (24), and use of medication with mood stabilizing properties. Those significantly associated with the misuse trajectory variables ($p < 0.05$) by overall effects were entered as independent variables into hierarchic blockwise logistic regression analyses to ascertain the specific contribution of misuse trajectory on "any relapse" after controlling for potential confounders. Socio-demographic factors (if any) were entered in the first block, clinical variables including other substance related variables in the next, and substance misuse trajectories in the last block. The multivariate analyses were run twice on the whole sample to explore whether alcohol or cannabis use trajectories predicted relapse risk, and thus the level of significance was Bonferroni corrected to $p < 0.025$.

RESULTS

A total of 220 individuals with bipolar disorder (BD I $n = 151$, BD II $n = 59$, and BD NOS $n = 10$) were included in the study at baseline. Of these, 112 patients (51%) participated in a personal follow-up examination after 1 year. Of the 108 patients without data at follow-up, 20 were not planned for follow-up, 31 had moved or could not be reached, 13 had withdrawn from the study, 15 did not want to participate, 2 patients had died, and

TABLE 1 | Baseline sociodemographic and clinical characteristics of followed-up vs. lost to follow-up sample.

	Followed-up ($n = 112$)	Lost to follow-up ($n = 108$)	Statistics	
	Median (IQR)		Mann-Whitney *U*-test	*p*-value
Age	27.0 (13.0)	25.5 (13.0)	6713.0	0.158
Education, years	14.0 (3.0)	13.0 (3.0)	5504.0	0.182
Age at onset of BD	19.0 (10.0)	18.0 (6.8)	6010.5	0.972
Duration of illness, years	7.0 (11.0)	6.0 (9.75)	6287.5	0.530
No. of affective episodes per illness year at baseline	1.0 (1.3)	1.07 (1.3)	5266.0	0.943
AUDIT at baseline*	7.0 (9.0)	6.0 (8.0)	5506.5	**0.039**
DUDIT at baseline#	0.0 (5.0)	0.0 (3.0)	5066.5	0.637
	n (%)		Chi²-test	*p*-value
Gender, females, *n* (%)	69 (61.6)	62 (57.4)	$\chi^2 = 0.403$	0.526
Bipolar disorder type			$\chi^2 = 0.540$	0.764
Bipolar I disorder, *n* (%)	77 (68.8)	74 (68.5)		
Bipolar II disorder, *n* (%)	31 (27.7)	28 (25.9)		
Bipolar NOS disorder, *n* (%)	4 (3.6)	6 (5.6)		
Lithium or other mood stabilizer	50 (44.6)	49 (45.4)	$\chi^2 = 0.012$	0.914
Antipsychotic medication	53 (47.3)	57 (52.8)	$\chi^2 = 0.655$	0.418
Any adequate medication	73 (65.2)	75 (69.4)	$\chi^2 = 0.454$	0.500
Alcohol use disorder, *n* (%)	20 (17.9)	14 (13.0)	$\chi^2 = 1.008$	0.315
Cannabis use disorder, *n* (%)	12 (10.7)	14 (13.0)	$\chi^2 = 0.267$	0.606
Other substance use disorder, *n* (%)	9 (8.0)	9 (8.3)	$\chi^2 = 0.006$	0.936
Current daily nicotine use, *n* (%)	58 (51.8)	55 (50.9)	$\chi^2 = 0.016$	0.899

**Twenty-six missing: 18 in the followed-up group and 8 in those lost to follow-up.*

#Twenty-two missing: 13 in the followed-up group and 9 in those lost to follow-up.

IQR, Interquartile Range; BD, Bipolar Disorder; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test; NOS, Not Otherwise Specified. Significant p-values are marked in bold.

for 27 reasons were unknown. Sociodemographic and clinical characteristics of the sample at baseline, including a comparison of those who completed the study and those lost to follow-up, are presented in **Table 1**. The only significant difference in baseline demographic and clinical characteristics between participants who completed follow-up and those who did not out was a higher median AUDIT score in the followed-up participants (**Table 1**).

In the sample included in the further analyses i.e., participants who completed follow-up, median age at baseline was 27 years and median age at BD onset was 19 years. Sixty-five percent of the participants used mood stabilizing and/or antipsychotic medication, with a median age at initiation of medication of 27 years. The remaining participants had either no medication or no mood-stabilizer/antipsychotics at baseline. These were 23.5% BD I and 64.5% BD II.

Substance Misuse at Baseline

Of the 112 participants who completed follow-up, 57 (49%) participants had misuse of alcohol, cannabis or other drugs at baseline. Thirty-two (29%) participants had cannabis misuse (including $n = 11$ with lifetime CUD). Also, one participant had lifetime CUD but no report of cannabis use the 6 months prior to baseline, indicating that the CUD was in remission. Of the 32 with cannabis misuse, 21 (19%) also had alcohol misuse. A total of 44 (39%) participants had alcohol misuse (including $n = 20$ with lifetime AUD). Also, 3 participants had lifetime AUD but AUDIT scores below cut-off at baseline, indicating that the AUD was in remission. Ten (9%) participants had misuse of other substances (including $n = 9$ with lifetime other SUD). Of these, only 2 did not have additional alcohol or cannabis misuse. Fifty-eight participants (52%) reported daily nicotine smoking at baseline. Of note, although misuse of illicit substances is present in a substantial proportion of the sample, the majority of did not have such misuse, thus the median DUDIT score at baseline is 0.0 (**Table 1**).

Substance Misuse at Follow-Up

At follow-up, 33 participants (29%) had any substance misuse. Seventeen of the 32 participants with cannabis misuse at baseline had reduced their DUDIT score to below cut-off at follow-up. Two participants with reports of cannabis use increased their DUDIT score to above cut-off from baseline to follow-up. Thus, 17 participants (15%) had cannabis misuse at follow-up. Of these, 10 (9%) also had alcohol misuse. Of the 44 participants with alcohol misuse at baseline, 24 had reduced their AUDIT score to below misuse cut-off at follow-up. Four participants increased their AUDIT score to above cut-off from baseline to follow-up. Thus, 24 participants (21%) had alcohol misuse at follow-up. Of the 10 participants with other substance misuse, 4 had stopped the misuse of these substances at follow-up. Fifty-seven participants (52%-−3 with missing data) reported daily nicotine smoking at follow-up. Nine participants had stopped smoking and 9 had started smoking during the follow-up period.

Rates of substance misuse at baseline and follow-up are presented in **Figure 1**.

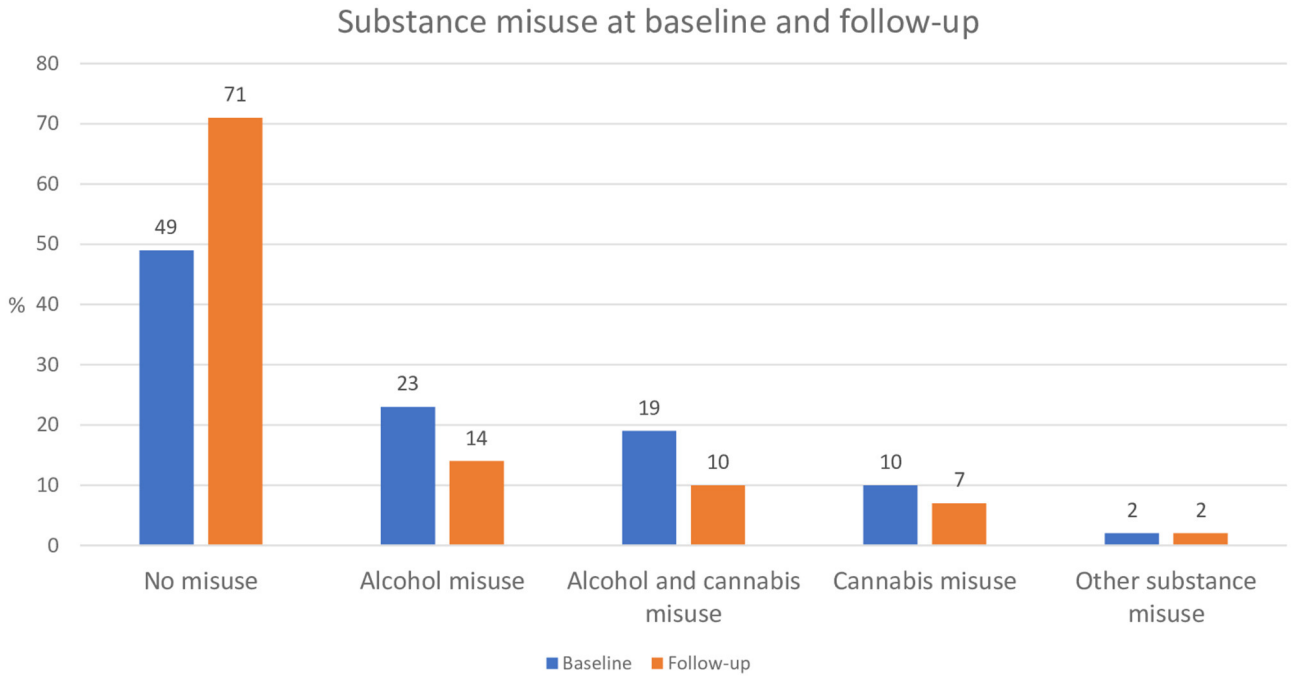

FIGURE 1 | Substance misuse at baseline and follow-up ($n = 112$). Data is based on participants who completed follow-up only (i.e., baseline data on participants lost to follow-up is not included).

Substance Misuse Trajectories and Relapse

Cannabis

Sociodemographic and clinical characteristics including "any relapse" across cannabis misuse trajectories are presented in **Table 2**. There were no significant differences in the rate of "any relapse" between the three groups, or in the rates of depressive or (hypo)manic relapse. There were significant group differences in age at onset, and in the prevalence of alcohol misuse and daily nicotine use at follow-up.

To rule out a role of possible confounders in the putative relationship between "any relapse" and the cannabis misuse trajectory ($p = 0.058$), a multivariate analysis was conducted. Cannabis misuse trajectory did still not significantly predict relapse after controlling for age at BD onset, alcohol misuse and daily nicotine use at follow-up. The model was significant ($\chi^2 = 15.312$, df $= 5$, $p = 0.009$), but only alcohol misuse at follow-up was significantly associated with relapse risk (**Table 3**).

Alcohol

We then investigated the relationship between relapse and alcohol misuse trajectories. Sociodemographic and clinical characteristics including "any relapse" across the alcohol misuse trajectories are presented in **Table 4**. There was a significant overall effect of alcohol misuse trajectory on "any relapse." *Post-hoc* analyses showed a higher relapse rate in the CONT group compared to both the NO group ($p = 0.004$) and the STOP group ($p = 0.01$), but no significant difference between the STOP group and the NO group ($p = 0.892$). There were also significant group differences in depressive relapse rates, and in the prevalence of misuse of other substances than alcohol and cannabis and in daily nicotine use at follow-up.

In the multivariate analysis controlling for the potential confounders; other substance misuse and daily nicotine use at follow-up, alcohol misuse trajectory was independently associated with "any relapse" with a significantly higher relapse risk in the CONT group compared to the NO group (**Table 5**). The model was significant ($\chi^2 = 10.867$, df $= 4$, $p = 0.028$), with a Nagelkerke pseudo R^2 of 12.9%.

DISCUSSION

In the current study of a first treatment BD sample, we found that the proportion of participants with any substance misuse was reduced from 49% at baseline to 29% at 1-year follow-up. We also found that participants with continued alcohol misuse were at higher risk for BD relapse during the follow-up period than participants with no history of alcohol misuse. This risk appeared to be primarily related to depressive episodes. Participants who stopped their alcohol misuse during follow-up had similar relapse risk to those who never had misused alcohol. Misuse of cannabis or other illicit substances or daily nicotine use did not independently predict the risk for BD relapse.

Participants were recruited during the initiation of the first adequate treatment, and the current study indicates that starting BD treatment contributes to reducing substance misuse. Still, one could argue that with 29% still misusing substances despite treatment initiation, additional interventions targeting substance misuse are needed. Unfortunately, we did not have any data on substance misuse-related interventions during follow-up, but

TABLE 2 | Sociodemographic and clinical characteristics across cannabis misuse trajectories.

	NO (A)	STOP (B)	CONT (C)	Statistics		
	n = 78	*n* = 17 Median (IQR)	*n* = 17	Kruskal Wallis *H*-test	*P*-value	*Post-hoc*
Age	29 (16)	24 (9)	25 (8)	$H = 5.688$	$p = 0.061$	
Age at illness onset	20 (14)	16 (4)	17 (10.5)	$H = 8.193$	**$p = 0.017$**	A > B
Duration of illness, years	7 (11)	9 (11.5)	6 (11.5)	$H = 1.805$	$p = 0.406$	
No. of episodes/year of illness at baseline	1.0 (1.3)	1.2 (1.4)	1.8 (1.1)	$H = 1.838$	$p = 0.399$	
		n (%)		X^2/Fishers Exact-test	*p*-value	
Sex, female	51 (65)	10 (59)	8 (47)	$X^2 = 2.047$, df = 2	$p = 0.399$	
Bipolar I disorder (vs. II)	59 (76)	9 (53)	13 (76)	Fisher's Exact-test = 3.576	$p = 0.187$	
Alcohol misuse at follow-up	14 (18)	8 (47)	8 (47)	Fisher's Exact-test = 11.743	**$p = 0.002$**	A < B, C
Other substance misuse at follow-up	2 (3)	2 (12)	2 (12)	Fisher's Exact-test = 4.509	$p = 0.111$	
Daily nicotine use at follow-up	33 (43)	10 (63)	14 (82)	$X^2 = 9.223$, df = 2	**$p = 0.010$**	A < C
Antipsychotic medication at follow-up	45 (58)	9 (53)	10 (59)	$X^2 = 0.152$, df = 2	$p = 0.927$	
Mood-stabilizer at follow-up	37 (47)	6 (35)	7 (41)	$X^2 = 0.930$, df = 2	$p = 0.628$	
Any adequate medication	62 (80)	11 (65)	13 (76)	$X^2 = 1.712$, df = 2	$p = 0.425$	
Depressive relapse	26 (34)	10 (59)	9 (53)	$X^2 = 4.686$, df = 2	$p = 0.096$	
(Hypo)manic relapse	21 (28)	9 (53)	4 (27)	Fisher's Exact-test = 3.979	$p = 0.141$	
Any relapse	35 (46)	12 (71)	12 (71)	$X^2 = 5.687$, df = 2	$p = 0.058$	

Data are presented as median and interquartile range (IQR), and numbers and percentage.
NO = No misuse at baseline or follow-up, STOP = lifetime use disorder and/or misuse at baseline but not at follow-up, i.e., stopped misuse, CONT = Misuse at follow-up (with or without misuse at baseline i.e., including individuals which had started misusing). Significant p-values are marked in bold.

TABLE 3 | Prediction of "any relapse" with cannabis misuse trajectories.

	B	SE	Sig.	OR	95% CI for OR
Age at illness onset	−0.04	0.023	0.088	0.961	0.917–1.006
Alcohol use at follow-up	1.096	0.543	**0.042**	2.994	1.033–8.673
Daily nicotine use at follow-up	−0.008	0.438	0.985	0.992	0.420–2.340
Cannabis misuse trajectory (ref. NO)					
STOP	0.640	0.675	0.343	1.896	0.505–7.116
CONT	0.559	0.636	0.380	1.749	0.502–6.087

NO = No misuse at baseline or follow-up, STOP = lifetime use disorder and/or misuse at baseline but not at follow-up, i.e., stopped misuse, CONT = Misuse at follow-up (with or without misuse at baseline i.e., including individuals which had started misusing). Significant p-values are marked in bold.

participants were included from general psychiatric services where the focus on substance misuse is limited.

As different methods have been used across early phase BD studies to characterize trajectories of substance misuse, our findings are difficult to compare to previous results. Still, the misuse rates appear to vary considerably between studies, being surprisingly stable from baseline to 1-year follow-up for both alcohol and drug misuse in one study of first mania (6); while in another, rates of both cannabis and alcohol misuse were substantially reduced at 60 weeks follow-up (from 48 to 10% for cannabis misuse and from 42 to 1% for alcohol misuse) (10, 11). The rates for stopping misuse found in the current study fall somewhere in between these two studies, which may be explained by the current sample including both BD I and II disorders and previously hospitalized and non-hospitalized participants. The substantial reduction seen in the study by Strakowski et al. may for instance be due to the inpatient setting from which participants were included (10, 11), as hospitalization reduces the likelihood that patients continue substance misuse.

Somewhat contrary to expectation, we did not find significantly higher BD relapse risk in individuals with continued cannabis misuse compared to those who stopped or never misused cannabis. In bivariate analyses, there were trends for group differences in both "any relapse" and depressive relapse, but the putative association for "any relapse" appeared to be confounded by age at onset and alcohol misuse. Regarding (hypo)manic relapse, albeit not on a trend level, there was a notable numerically higher rate in those who stopped misusing cannabis compared to those who never misused or continued misusing. Although the multivariate analyses clearly indicated that the trend level for "any relapse" was driven by confounders, this is an intriguing result in the opposite direction of what one may have expected. One could speculate whether discontinuing cannabis use may trigger (hypo)mania through

TABLE 4 | Sociodemographic and clinical characteristics across alcohol misuse trajectories.

	NO	STOP	CONT	Statistics		
	n = 57	*n* = 25 Median (IQR)	*n* = 28	Kruskal Wallis *H*-test	*P*-value	*Post-hoc*
Age	30 (16)	27 (13)	24.5 (8)	$H = 5.531$	$p = 0.063$	
Age at illness onset	20 (16.5)	17 (9)	17 (7.5)	$H = 5.694$	$p = 0.058$	
Duration of illness, years	6 (10)	10 (9.5)	6 (11.75)	$H = 2.075$	$p = 0.354$	
No. of episodes/year of illness at baseline	1.2 (1.3)	1.0 (0.9)	1.0 (1.3)	$H = 2.313$	$p = 0.315$	
		n (%)		X^2/Fishers Exact-test	*P*-value	*Post-hoc*
Sex, female (vs. male)	32 (56)	16 (64)	19 (68)	$X^2 = 1.212$, df = 2	$p = 0.545$	
Bipolar disorder type I (vs. II)	46 (81)	15 (60)	20 (71)	$X^2 = 3.931$, df = 2	$p = 0.140$	
Cannabis misuse at follow-up	5 (9)	4 (16)	8 (29)	Fisher's Exact-test = 5.416	$p = 0.060$	
Other substance misuse at follow-up	0 (0)	3 (12)	3 (11)	Fisher's Exact-test = 6.660	**$p = 0.015$**	A < B, C
Daily nicotine use at follow-up	33 (43)	10 (63)	14 (82)	$X^2 = 8.230$, df = 2	**$p = 0.015$**	A < C
Antipsychotic medication at follow-up	29 (51)	14 (56)	21 (75)	$X^2 = 4.554$, df = 2	$p = 0.099$	
Mood-stabilizer at follow-up	30 (53)	8 (32)	12 (43)	$X^2 = 3.086$, df = 2	$p = 0.223$	
Any adequate medication at follow-up	45 (79)	17 (68)	24 (86)	$X^2 = 2.470$, df = 2	$p = 0.291$	
Depressive relapse	19 (33)	8 (32)	18 (64)	$X^2 = 8.504$, df = 2	**$p = 0.014$**	A < C
(Hypo)manic relapse	16 (29)	7 (29)	11 (29)	$X^2 = 0.987$, df = 2	$p = 0.611$	
Any relapse	26 (46)	11 (44)	22 (79)	$X^2 = 9.409$, df = 2	**$p = 0.009$**	A, B < C

NO = No misuse at baseline or follow-up, STOP = lifetime use disorder and/or misuse at baseline but not at follow-up, i.e., stopped misuse, CONT = Misuse at follow-up (with or without misuse at baseline i.e., including individuals which had started misusing). IQR, Interquartile Range. Significant p-values are marked in bold.

TABLE 5 | Prediction of "any relapse" with alcohol misuse trajectories.

	B	SE	Sig.	OR	95% CI for OR
Daily nicotine use at follow-up	0.249	0.426	0.558	1.283	0.557–2.955
Other substance misuse at follow-up	1.305	1.187	0.272	0.369	0.360–37.738
Alcohol misuse trajectory (ref. NO)					
STOP	−0.290	0.528	0.583	0.748	0.266–2.106
CONT	1.256	0.547	**0.022**	3.512	1.203–10.252

NO = No misuse at baseline or follow-up, STOP = lifetime use disorder and/or misuse at baseline but not at follow-up, i.e., stopped misuse, CONT = Misuse at follow-up (with or without misuse at baseline i.e., including individuals which had started misusing). Significant p-values are marked in bold.

e.g., neuroadaptive effects or indirectly through withdrawal symptoms such as insomnia (25). The current findings of no significant differences in relapse rates between the cannabis misuse groups are in contrast to our previous finding of a relationship between continued cannabis use and higher levels of manic symptoms at follow-up (12). However, it is also possible that cannabis use induces subsyndromal symptoms rather than full-blown (hypo)manic episodes. These and other possible hypotheses should be followed up in future studies. Although some previous studies have indicated associations between cannabis use and relapse risk, longitudinal studies specifically addressing this relationship are very few. Cross-sectional studies, however, have repeatedly found associations between cannabis misuse and more severe clinical features in BD (3). The rate of alcohol misuse was however high in the group that stopped cannabis misuse, which may explain the lack of significant group differences. Indeed, when specifically addressing alcohol misuse, we found that alcohol misuse trajectory independently predicted relapse, with higher relapse rates in continued alcohol misusers compared to those with no alcohol misuse. Furthermore, there was no significant difference in relapse rates between participants with no alcohol misuse and those who stopped their alcohol misuse. This is an important clinical message, as the subsequent clinical course appears to be unaffected if alcohol misuse is stopped. However, the full model appeared to explain a modest proportion of the variance (pseudo $R^2 = 13\%$). While such a level of explanation is common in naturalistic clinical studies, these relationships need further investigation in future studies.

Of note, although there was no significant difference in rate of continued cannabis misuse across the alcohol misuse trajectories, the rate of continued cannabis misuse was relatively high in the continued alcohol misusers. One can therefore not exclude an interaction effect, i.e., that the higher relapse rate in the continued alcohol misuse group is partly explained by the continued cannabis misuse in this group. The fact that the clinical

course is improved when alcohol misuse stops may indicate that individuals with substance misuse do not comprise a subgroup of BD with an underlying more severe illness form. Hence, substance misuse may elicit affective episodes and lead to a more severe BD course rather than the opposite. This hypothesis, however, needs to be further addressed in future studies.

The study has some limitations. Attrition rate was high, yielding a modestly sized sample and relatively small subgroups. Isolating the specific effects of different substances of misuse and considering the full range of misuse severity (from mild to heavy dependence) on the outcome variable is thus challenging. Also, the limited sample size hampers taking other potential confounders and risk factors into full consideration, such as comorbid anxiety disorders, personality features (e.g., impulsivity) and childhood trauma, which may also influence episode recurrence (26, 27). Although higher AUDIT scores in the participants who completed follow-up compared to those who were lost was the only significant difference between the groups at baseline, we cannot rule out that participants with misuse during follow-up were more likely to drop out of the study, which may have biased the results e.g., by inflating the reduced misuse rates at follow-up. However, individuals in the early phase of BD may be particularly difficult to retain in research, and the current study is based on one of the world's largest samples to date. Another limitation is that data were not collected regarding substance misuse-related interventions during follow-up, which would have been informative. Furthermore, the substance misuse data is based on self-report, which may be biased. However, we have previously demonstrated good correspondence between urine samples and self-reports of drug use, which is also confirmed by a meta-analysis (28, 29). The study also has several strengths. Since the sample is naturalistic and catchment area based it is likely to be representative for BD I, II and NOS individuals presenting for treatment in Norway. Furthermore, the sample is thoroughly characterized also with regards to substance use, enabling a detailed analysis of trajectories of misuse of all relevant substances. Still, there is an urgent need of further longitudinal studies to disentangle the complicated relationships between BD illness course and substance misuse, preferably with collection of more continuous and parallel data on affective symptoms and substance use.

In conclusion, this study demonstrates that the high rates of substance misuse in the early phases of BD are somewhat reduced after initiation of treatment, but also indicates that there is room for improvement in the treatment of comorbid BD and substance misuse. The risk for BD relapse over a 1-year follow-up period is higher in individuals who continue their alcohol misuse compared to individuals who have never misused alcohol, while stopping alcohol misuse appears to be of substantial clinical benefit. While the effect of alcohol misuse on the early course of BD was significant, the effect of cannabis misuse needs to be further addressed in longitudinal studies.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The aggregated data on each individual may be identifiable. Requests to access these datasets should be directed to Trine Vik Lagerberg, t.v.lagerberg@medisin.uio.no.

ETHICS STATEMENT

The study was reviewed and approved by REK Sør Øst—Regional Committee for Medical and Health-related Ethics. The patients/participants provided written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

TL and IM designed the study. TL conducted the data analyses and drafted the manuscript. IM and RI contributed to data analyses, interpretation, and with revising the paper. SA, EB, MN, MH, and SO collected data. TB was responsible for data management and security. All authors were involved in critically reviewing the manuscript before approving the final version.

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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.

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Using Imagery Rescripting as an Early Intervention for Depression in Young People

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Innovation is urgently needed for school-based early interventions for depression. Imagery rescripting for aversive memories has been shown to be a valuable therapeutic approach in adults. Yet it is rarely applied to young people or to depression. This is surprising given that intrusive images of aversive memories are implicated in the development and maintenance of depression. We review the literature and describe the co-development of an imagery rescripting protocol for young people (age 16–18) with high symptoms of depression. To contextualize and illustrate this approach, we identify three themes of negative images emerging from the 37 participants who completed imagery rescripting and provide a detailed case example for each theme. The identified themes are *failure*, *interpersonal adversity,* and *family conflict or disruption*. Given that there is some therapist concern about using imagery rescripting, we highlight any reported negative consequences of engaging in imagery rescripting. We propose that imagery rescripting is an acceptable and potentially effective tool for early intervention in depression, which is significantly underutilized in current practice.

Keywords: depression, adolescence, early intervention, imagery rescripting, mental imagery

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INTRODUCTION

Impairing symptoms of depression are present in 5% of young people (YP) aged 17–19 (1). However, ∼75% of YP with depression do not receive an intervention (2) and current evidence-based psychotherapies for YP show little advantage over usual care, if any (3, 4). Novel early interventions are needed, particularly those that target cognitive mechanisms known to drive and maintain depression (5, 6). Traditionally, interventions for adolescent depression focus on verbal restructuring of negative thoughts and/or behavioral activation. Intrusive memories are a key maintaining factor for depression and imagery rescripting (IR) is a psychological technique aiming to reduce distress caused by aversive memories. IR is a highly effective transdiagnostic technique in adults and is likely to be developmentally appropriate. For example, young people rely more heavily on image-base processing (relative to adults) and neurocognitive development during adolescence may impact on vulnerability to distressing mental imagery (7). More generally, adolescence is a period characterized by increased flexibility and learning potential (8), and targeting mental imagery in interventions could have long-lasting benefits (9).

IMAGINE (Integrating Memories and Generating New Experiences) is a novel intervention aiming to reduce depression in YP aged 16–18. It combines IR with techniques to enhance positive future images and autobiographical memory specificity (10, 11). IMAGINE consists of

four, 90 minute sessions delivered face-to-face in schools. The intervention is manualised and accompanied by a workbook. It has been initially tested in a case series (12) and feasibility RCT (13, 14) with promising results. Here, we focus on using IR with YP. First, we review the literature. Second, we describe the co-design of the IR protocol and developmental adaptations. Third, we review the types of images reported by 37 participants, identifying key themes, each with a case example. This aims to identify the types of images amenable to IR, presenting in the context of adolescent depression. Finally, we report any negative consequences (e.g., risk issues, decline in mood) from IR. This is important as IR is rarely used in current practice, perhaps due to fears associated with worsening symptoms.

CURRENT LITERATURE

A meta-analysis of 19 trials using IR in adults across different disorders (15) demonstrated large effects of IR in reducing symptoms from pre-treatment to post-treatment and at follow-up (Hedges' $g = 1.22$ and 1.79, respectively). In young adults (age 18–24), two RCTs (16, 17) have examined IR to reduce social anxiety. They showed large within group effect sizes ($d = 2.10$; $d = 1.09$; $d = 3.00$), and large effects compared to passive [$d = 0.83$; (17)] and active control groups [$d = 1.02$; (16)]. IR has also been applied to other types of memories, for example a case series (18) ($n = 9$) indicated that two-sessions of IR could reduce test anxiety in university students. Excluding our work, only 2 single case studies (19, 20) have used IR in YP under age 18; these showed promising results in reducing anxiety.

Some studies have examined the mechanism of action, with suggestions that IR reduces distressing negative images through reducing avoidance, enabling emotional processing, and/or updating the meaning/content of the image. Studies with unselected samples (in the 18–24 age range) have illustrated that IR can update the meaning and reduce the distress and anxiety associated with an aversive memory (21, 22). Whilst requiring replication, there is some experimental evidence (23) to support suggestions that IR may be less distressing than techniques using exposure and preferable to positive imagery alone, which may represent another form of avoidance (24).

PROTOCOL DEVELOPMENT

IR follows three steps, recalling the image in a different way in each step (see **Figure 1**). The protocol was co-designed with adolescents based on previous adult literature (11, 25). IR took place in a single 90-min session, with preparation work completed in the previous session. Co-design included consulting YP and adults with lived experience, parents of YP with lived experience, teachers, and clinicians. Overall, more than 60 people with lived experience were involved. This includes two service user consultants who provided consistent oversight throughout the project. Consultation and developmental adaptations have included:

- Discussions informing early development of ideas with YP with lived experience and their parents (attending Child and Adolescent Mental Health Services) and a workshop run by a national YP's mental health charity. This highlighted having the inclusion criteria as YP with symptoms of depression (rather than diagnosis, this also reflects current practice in UK services) and delivering the intervention in schools (rather than NHS clinics).
- Individual feedback on intervention content during discussions in clinical and research settings with YP and adults with lived experience, parents, and clinicians. Feedback highlighted that targeting distressing negative memories was acceptable and therapeutically valuable. Adaptations to aid engagement in IR included, firstly, psychoeducation on the impact that memories have on our mood, behavior and sense of self and how this interacts with the meaning that we ascribe to memories; secondly, an extensive practice with a positive image to familiarize YP with imaginal reliving (e.g., the level of multi-sensory detail required).
- Advisory groups gave feedback on rationale and methodology. The Biomedical Research Centre Service User Advisory Group (SURE, King's College London) provided feedback and the project was presented at three meetings with the Young Person's Mental Health Advisory Group. This included reviewing summaries, methods and ethical considerations and recommendations for enhancing recruitment. Whilst they emphasized the importance of school-delivery, adaptations for this were discussed. For example, the therapy space may feel less safe than a clinical setting and the memory is likely to be more recent for a YP (including reminders being more likely). Discussions identified the importance of rescripting a non-traumatic image, to take regular mood ratings, and to actively encourage YP to be compassionate toward themselves (e.g., having time to process the session and not to return straight to class).
- Discussion with teachers on current practice for pupils with depression and implementation feasibility. This highlighted considerations for intervention length and practicalities around school-delivery.

Context: Imagine Methodology

IMAGINE was developed with inner-city schools with high diversity. In the participating schools, on average, 29.2% of the pupils were eligible for free school meals (UK average 12.4%) and 59.9% of pupil's first language was not English (UK average 16.6%). Thirty-eight participants were enrolled to complete IMAGINE across the case series and RCT (age $\bar{x} = 17.06$, $SD = 0.56$; 63% female; 74% Black, Asian, and Minority Ethnic individuals). One participant did not begin and one participant discontinued the intervention. The feasibility randomized controlled trial (RCT) was prospectively registered (https://www.isrctn.com/; ISRCTN85369879). Ethical approval was obtained from the Psychiatry, Nursing and Midwifery Research Ethics Committee at Kings College London (ref: HR-16/17-3548). All participants provided written and informed consent. Inclusion criteria were: aged 16–18; being able to provide informed consent; being willing to engage in psychological therapy and complete assessments; and scoring above cut-off for depression (score of 20) on

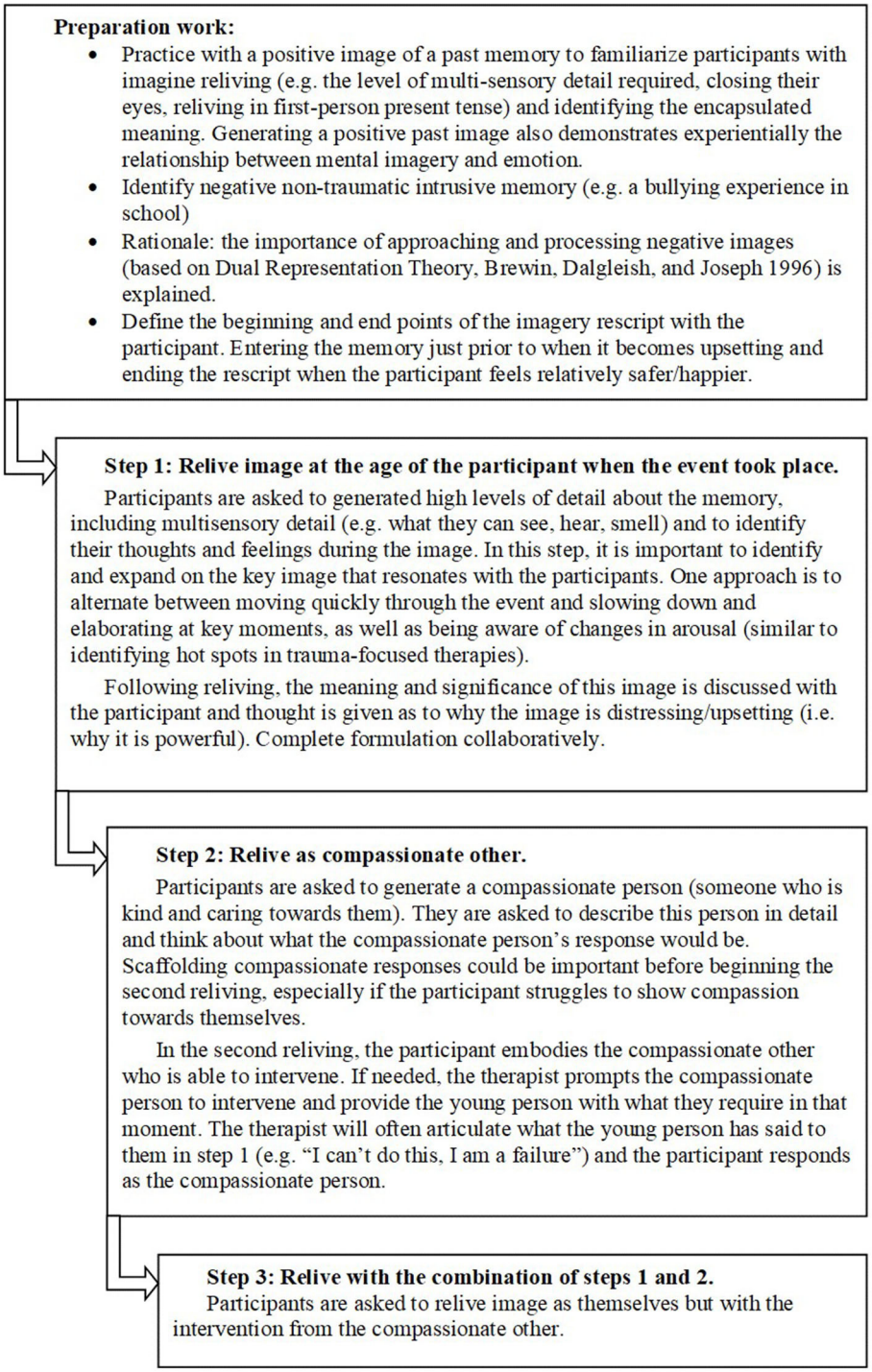

FIGURE 1 | Protocol for imagery rescripting.

the Mood and Feelings questionnaire [MFQ; (26)] at two time points. Exclusion criteria were: diagnosis of intellectual disability or significant head injury, neurological disorder or epilepsy; unable to fluently communicate in spoken English; unable to give informed consent; factors contra-indicating imagery rescripting (e.g., high levels of current risk); currently receiving another psychological intervention (including school counseling); experiencing distressing psychotic symptoms or depressed in the postnatal period (participants with comorbid physical illness or non-psychotic disorders, such as anxiety,

were not excluded). A clinical interview was completed at first interview to check inclusion/exclusion criteria, assess risk, and previous diagnoses. Four participants reported mental health diagnoses (2 major depressive disorder, 1 bulimia nervosa, 1 post-traumatic stress disorder) and one a diagnosis of autism. Eight participants reported other diagnoses including asthma ($n = 5$); learning difficulties ($n = 1$); Turner syndrome ($n = 1$); irritable bowel syndrome ($n = 1$).

There were three assessment timepoints (pre-intervention, post intervention, and 3-month follow-up) with depression measured using the MFQ. The therapist completed an individual case report form each session, including a description of the session and a summary of the generated images. Please see trial protocol for full methodology (13).

THEMES OF NEGATIVE IMAGES

Thematic analysis identified three themes (from the 37 images). These were *failure, interpersonal adversity*, and *family conflict or disruption.* First, two researchers familiarized themselves with the descriptions of the negative images and generated themes. Themes were reviewed and then images independently categorized with high agreement (95%). One image was categorized separately as representing a personal health issue (although there was overlap with the failure theme as key cognitions included "I'll miss out on life"). In addition, there were three images that (whilst coded within these themes) could have represented a separate category of loss/bereavement.

Failure

Eight participants identified images of failure, most often failing an exam. For example, one participant (age 16, female, Asian/Asian British) described getting a B grade in in her science GCSE. She described science as her passion and wanting to become a General Practitioner. This image was having a significantly negative impact on her mood, motivation, and behavior. She spoke about attempting to revise for multiple hours after school and often instead staring blankly into space. During IR, she described the image in great detail (with the key moment being standing crying against a wall, staring at her results sheet). Key cognitions around this image were "I'm a failure" and "I'm not good enough." She reported cognitively avoiding this image and needing to study at every opportunity to ensure it did not repeat itself. Please see **Figure 2** for the formulation. She was able to clearly generate a compassionate other to intervene in the image. In this case, she chose her mother who saw her crying, approached and hugged her, and warmly assured her she has other options available and would get support from school to understand her next steps. Following rescripting, she spoke about the image no longer being "zoomed in" on the B grade and that she could now see it in context. She spoke about being more able to take a compassionate perspective toward herself, and to approach her academic work alongside her other values. Her depression scores reduced (MFQ score: Pre = 35; Post = 12; Follow-up = 4).

Interpersonal Adversity

Fifteen participants identified images of interpersonal adversity, most commonly incidents of bullying, and rejection. For example, one young person (age 16, female, White British) spoke about being bullied and spoke about one particularly powerful intrusive image. This was of the group laughing at her in the classroom, and she left and closed the door (which shut loudly). When she returned, the group were impersonating her. She described feeling angry, being unsure of what to do or say. She described a sensation of rising heat. She was able to identify key cognitions as "I'm not as good as them" and "I'm so stupid to let them treat me like this." She spoke about frequently ruminating about the event, e.g., "Why did this happen to me," "What did I do wrong?." She had since changed school and spoke about these experiences driving unhelpful behavior, such as avoiding friendships, not disclosing personal information and isolating herself. She acknowledged this was preventing her forming friendships at her new school. She generated her older cousin as a compassionate other, who intervened by checking she was OK and then responding to the group. The compassionate other removed her from the situation and then spent time thinking about what had happened, as well as highlighting her positive friendships and qualities. Following the intervention, she reported seeking out new friendships; no longer constantly questioning why the bullying had happened; significantly reducing her worry about future bullying; and standing up for herself more. Depression scores decreased (MFQ score: Pre = 42; Post = 18; Follow-up = 14).

Family Conflict or Disruption

Thirteen participants identified images of family conflict or where family relationships had been disrupted. Examples include arguments between parents, parents leaving the family home or upsetting family events. One participant (age 17, male, White British) described having images of their mother being admitted to hospital. His mother was restrained and shouted some upsetting phrases at him. He described feeling angry, upset, and helpless. He described regularly having intrusive images about the event and "pushing" these out of his mind. Key cognitions included "how can she do this to me" and "it is my fault." He had not previously spoken about this event and believes his mother does not remember her words. This was impacting on his relationship with his mother and his friends. He identified his father as a compassionate other who intervened, comforted him and took responsibility for the event. When providing feedback, he spoke about needing time after the session to process the event but now rarely experiencing intrusions. He spoke about the perspective-taking element (step 2) of the rescripting being "eye-opening," as it had allowed him to acknowledge the impact the event had on him and that the event would have been difficult for anyone to cope with. Following IR, he was able to speak with his parents about what had happened and this had significantly improved their relationship. He also spoke about now being able to have their friends around to his house. Symptoms of depression decreased (MFQ score: Pre = 23; Post = 16; Follow-up = 6).

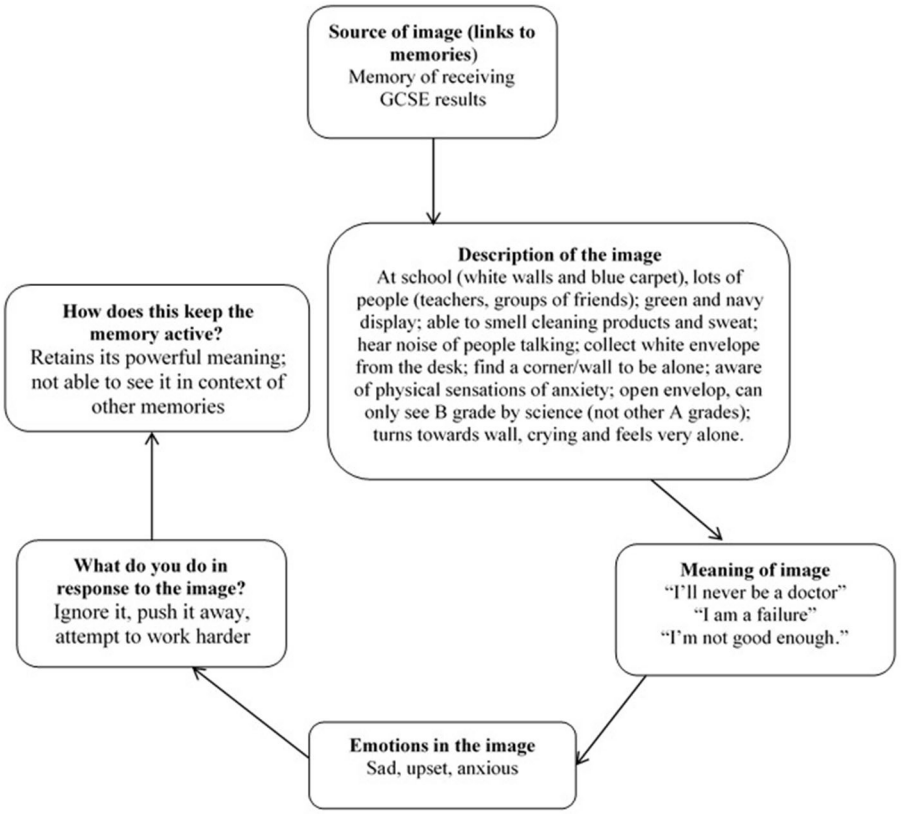

FIGURE 2 | Example formulation of a negative non-traumatic image. The formulation is collaboratively completed in the IR session, during step 1.

NEGATIVE CONSEQUENCES OF IR

No adverse events were reported that were associated with the therapy. There were some adverse events reported during the RCT but these all had begun before the young person began therapy.

It seems likely that elevation in emotional arousal is important for emotional processing of the image. Almost all participants showed an increase in emotional arousal during step 1. Mood ratings were taken regularly throughout the session and, by the end of the session, ratings had almost always returned to near baseline levels. Participants frequently reported that they found the session emotionally challenging and it had a short-term negative impact (less than a day) on their mood but identified that, in the longer term, IR had been helpful for their mood and behavior. Finally, working clinically with distressing imagery can be emotionally challenging for the therapist. It is important to have supervision structures in place, including time to debrief on difficult sessions.

DISCUSSION

We have aimed to provide a comprehensive account of IR for adolescent depression. We have described the dearth of literature in young people, the developmental adaptations and stages in co-designing our protocol, three key themes of negative images with case examples, and that there were no reported negative consequences of IR. IR was a helpful tool to engage YP, explore and process negative recurrent memories, access key cognitions and decrease symptoms of depression.

No YP struggled to generate and manipulate a negative image. Negative images were accessible and frequent. This is important as the participants were selected for symptoms of depression, not for intrusive images. A trusting relationship is clearly important in allowing YP to engage with and manipulate imagery. There were concerns (before beginning) that the intervention might not be long enough to establish this relationship, this was not found to be the case. Session 1, including careful explanation and preparation work, is likely to have been important in forming this relationship. One advantage of IR is remaining flexible to what arises in step 1, as there were occasions where an unexpected, key cognition emerged. For example, for an image of being hit over the head by a peer, the key cognition was identified as "being weak" rather than the "world is dangerous" as first appeared.

The themes identified within the images (*failure, interpersonal adversity, family conflict, or disruption)* were consistent with the broader literature. For example, a qualitative study exploring what factors adolescents believe led to their depression (27),

identified one key theme (of three) as being "depression as a result of rejection, victimization, and stress." Another qualitative study identified five themes concerning the experience of adolescent depression (28), including "impact on education"; "isolation and cutting off from the world"; and "anger and violence toward self and others." Research that could map the relationships between the content of intrusive images and the subjective experience of depression, as well as how this may vary across different cultures, would be valuable.

There were no examples of the young person being unable to identify a compassionate other. Most participants used a parent rather than an older self for this role. One therapeutic dilemma is whether to allow the compassionate other to prevent the event from taking place (rather than to intervene after the event). This is usually permitted in adult work. Whilst we did not give explicit instructions/guidelines about what the compassionate other could and couldn't do, none of the participants prevented the event taking place. In our view, it was helpful for the compassionate other to respond to the event (and for the participant to experience another perspective) rather than prevent the event from taking place. Further research could explore the relative benefits of preventing vs. intervening in the event.

Imagery rescripting appears to be an appropriate, acceptable and helpful intervention for YP with depression. A fully-powered trial could further test this approach and establish efficacy when delivered by non-specialist practitioners (to improve access). Although highly manualized and designed for non-specialist practitioners, the therapy was delivered by a clinical psychologist. Furthermore, whilst clinical judgement and feedback from YP (by questionnaires and qualitative interviews) suggests that IR was a key active ingredient in reducing depression, it would be helpful to establish the relative effects of the treatment components. Understanding developmental influences through experimental and/or longitudinal studies on the mechanisms of IR are important to translate effects to different age groups.

DATA AVAILABILITY STATEMENT

Data for this study are available in Mendeley Data. Pile (14), IMAGINE trial data, Mendeley Data V2. doi: 10.17632/7w3fwx7y2y.2.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Psychiatry, Nursing and Midwifery Research Ethics Committee at Kings College London (ref: HR-16/17-3548). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VP: conceptualization, methodology, investigation, resources, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition. PS: conceptualization, methodology, writing—review and editing, and supervision. JL: conceptualization, methodology, resources, writing—review and editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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Automatically Generated Smartphone Data in Young Patients With Newly Diagnosed Bipolar Disorder and Healthy Controls

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Background: Smartphones may facilitate continuous and fine-grained monitoring of behavioral activities *via* automatically generated data and could prove to be especially valuable in monitoring illness activity in young patients with bipolar disorder (BD), who often present with rapid changes in mood and related symptoms. The present pilot study in young patients with newly diagnosed BD and healthy controls (HC) aimed to (1) validate automatically generated smartphone data reflecting physical and social activity and phone usage against validated clinical rating scales and questionnaires; (2) investigate differences in automatically generated smartphone data between young patients with newly diagnosed BD and HC; and (3) investigate associations between automatically generated smartphone data and smartphone-based self-monitored mood and activity in young patients with newly diagnosed BD.

Methods: A total of 40 young patients with newly diagnosed BD and 21 HC aged 15–25 years provided daily automatically generated smartphone data for 3–779 days [median (IQR) = 140 (11.5–268.5)], in addition to daily smartphone-based self-monitoring of activity and mood. All participants were assessed with clinical rating scales.

Results: (1) The number of outgoing phone calls was positively associated with scores on the Young Mania Rating Scale and subitems concerning activity and speech. The number of missed calls ($p = 0.015$) and the number of outgoing text messages ($p = 0.017$) were positively associated with the level of psychomotor agitation according to the Hamilton Depression Rating scale subitem 9. (2) Young patients with newly diagnosed BD had a higher number of incoming calls compared with HC (BD: mean = 1.419, 95% CI: 1.162, 1.677; HC: mean = 0.972, 95% CI: 0.637, 1.308; $p = 0.043$) and lower self-monitored mood and activity (p's < 0.001). (3) Smartphone-based self-monitored mood and activity were positively associated with step counts and the number of outgoing calls, respectively (p's < 0.001).

Conclusion: Automatically generated data on physical and social activity and phone usage seem to reflect symptoms. These data differ between young patients with newly

diagnosed BD and HC and reflect changes in illness activity in young patients with BD. Automatically generated smartphone-based data could be a useful clinical tool in diagnosing and monitoring illness activity in young patients with BD.

Keywords: bipolar disorder, smartphones, sensor data, child and adolescent psychiatry, activity, social activity

INTRODUCTION

Bipolar disorder (BD) is a serious, recurrent, and disabling disorder often with an onset of symptoms during a young age (1). In addition to fluctuations in mood, BD is characterized by fluctuations in behavioral, social, and physical activity with alterations both during affective episodes and between episodes (2). As of today, there are no blood tests, radiologic findings, or other biomarkers to assist clinical decision making in symptom monitoring and diagnostic evaluations; hence, early interventions rely on clinical evaluations often made with large intervals between outpatient visits, making monitoring of symptoms vulnerable to potential recall bias (3).

Diagnostic work in children and adolescents with psychiatric disorders is especially challenging as it is often characterized by unspecific prodromal symptoms (4). Correct diagnosis and interventions are crucial in the early stages of BD (5). The clinical presentation of children and adolescents with BD is characterized by a more continuous course of affective dysregulation, with episodes of depression and (hypo)mania lasting for hours rather than days or weeks, as in adult-onset BD (6). Also, (hypo)mania is characterized by irritability more than elation (7).

Smartphones, equipped with sensors, such as accelerometers, are widely used all over the world, with 45% of people in the world owning a smartphone (8). This allows for smartphones to make potentially meaningful clinical data out of behavioral activity. Prior research has shown automatically generated smartphone data to give an accurate reflection of behavioral activity associated with fluctuations in BD in adults (9–13).

For many young people, smartphone interaction is a significant part of their everyday life and important for social interaction (14). Thus, smartphones would be widely available to many young people as a diagnostic and monitoring tool.

However, for a diagnostic tool to be useful, it needs foremost to be able to differentiate between patients and healthy controls (HC). Recent studies have shown that smartphone-based self-monitored data represent symptom burden according to clinical ratings and are also able to differentiate between adult patients with newly diagnosed BD and HC (9, 10, 12, 15). Nonetheless, self-monitoring demands that users be devoted to daily self-monitoring of their mood, activity, etc. Dedication to perform the monitoring is vulnerable to attrition, and adherence often decreases over time (16). This issue is avoidable using automatically generated smartphone data, which do not depend on daily self-monitoring. If automatically generated smartphone data are associated with self-monitored data, it can somewhat compensate for the decrease of adherence in self-monitored data, in addition to supplementing it with more fine-grained information.

Prior research has found automatically generated smartphone data to be useful, feasible, and valid for adult patients with BD (9, 10, 12, 15, 17–20). In a recent systematic review conducted by the authors investigating the use of smartphones in self-monitoring and treatment of adolescents and young adult patients with psychiatric disorders (21), we identified two studies collecting automatically generated smartphone data only (in patients with depression and early psychosis), but none of these studies included automatically generated smartphone data in their analyses (22, 23). To conclude, to date, no studies on automatically generated smartphone data on young patients with BD and HC have been published.

OBJECTIVES

The present pilot study aimed to (1) validate automatically generated smartphone data reflecting physical and social activity and phone usage against validated clinical ratings and questionnaires in young patients with newly diagnosed BD and HC; (2) investigate differences in automatically generated smartphone data reflecting physical and social activity and phone usage between young patients with newly diagnosed BD and HC; and (3) investigate associations between automatically generated smartphone data reflecting physical and social activity and phone usage and smartphone-based self-monitored activity and mood in young patients with newly diagnosed BD.

Based on prior research on adults with BD, we hypothesized that (1) automatically generated smartphone data reflecting physical and social activity and phone usage would be associated with validated clinical ratings and questionnaires, among young patients with newly diagnosed BD and HC; (2) automatically generated smartphone data reflecting physical and social activity and phone usage differ between young patients with newly diagnosed BD and HC with lower scores in physical and social activity in BD than in the HC group; (3) automatically generated smartphone data reflecting physical and social activity and phone usage would be associated with smartphone-based self-monitored activity and mood, with positive associations between smartphone-based self-monitored activity and mood, and automatically generated smartphone data on physical and social activity, respectively, in young patients with newly diagnosed BD.

MATERIALS AND METHODS

The participants included in the present study were recruited as part of the Bipolar Illness Onset study (the BIO study) (24), a longitudinal observational study including patients with newly diagnosed BD, their unaffected relatives, and HC (25, 26). In

the BIO study, all participants underwent a clinical assessment, combined with blood tests, MRI scan, and cognitive tests at baseline in addition to annual visits.

Study Design, Settings, and Participants

Among the participants in the BIO study, we recruited individuals newly diagnosed with BD and control persons without a personal or psychiatric family history, aged 25 years or younger at the time of inclusion (HC). Participants newly diagnosed with BD were recruited from the Copenhagen Affective Disorder Clinic at Rigshospitalet in Copenhagen, Denmark. The Copenhagen Affective Disorders Clinic is a specialized clinic that offers a 2-year course of treatment to everyone newly diagnosed with BD in the larger region of Copenhagen over the age of 18. We also included young patients with newly diagnosed BD under the age of 18, from the Child and Adolescent Mental Health Center in Copenhagen. We recruited HC among blood donors from the Blood Bank at Rigshospitalet. The exclusion criterion for the latter was a history of a psychiatric disorder requiring treatment, personally or in a first-degree relative.

Diagnostic Assessment

All participants underwent a diagnostic interview using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (27), during the baseline interview, to ensure that participants fulfilled the inclusion criteria for the respective groups. Trained researchers performed the SCAN interviews. For young patients with newly diagnosed BD, baseline interviews were performed by PhD students in medicine or psychology; for HC, some of the SCAN interviews were performed by medical or psychology students.

Baseline Interview and Follow-Up

The baseline interview consisted of a collection of general information about educational and work status in addition to diagnostic and clinical assessments. Information about time for onset of symptoms, diagnosis, start of treatment, and number and duration of affective episodes was collected among the young patients with newly diagnosed BD. All participants also completed a questionnaire addressing physical activity. After baseline, participants attended an annual follow-up interview as well as interviews every time they had a change from one affective episode to another, from an affective episode to euthymic stage, or from a euthymic stage to an affective episode.

Clinical Ratings

At baseline and follow-up interviews, the following rating scales were used: the severity of depressive symptoms was assessed using the 17-item Hamilton Depression Rating Scale (HAMD) (28, 29); the severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS) (30); and the level of functioning was assessed using the Functioning Assessment Short Test (FAST) (31), which is a test developed explicitly for BD and addresses six areas of functioning (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationship, and leisure time). All 24 items are rated from 0 (no difficulties) to 3 (severe difficulties) and assess the last 2 weeks up to the rating. FAST has been validated against the Global Assessment of Functioning scale (GAF) and has a high test–retest reliability (31).

Questionnaire

The participants completed the International Physical Activity Questionnaire Short Form (IPAQ) at each visit with the researchers. In the IPAQ, participants report how many minutes of physical activity in different intensities (vigorous, moderate, and walking) they had the prior week; these are then converted to metabolic equivalent task (MET) minutes per week, which then add up to a total MET score (32). MET is equivalent to kilocalories for a 60-kg person; we adjusted for weight for each participant to express the last week's activity in kcal/week (33).

Smartphone-Based Monitoring

The Monsenso system is a smartphone-based monitoring system with a collection of automatically generated smartphone data as mobility, activity, and phone usage using the telephones sensors, in addition to daily self-monitoring of, e.g., mood, sleep, and activity (34, 35). The system is available for both Android and iOS; however, the collection of automatically generated smartphone data is only available on smartphones using the Android operating system; thus, in this article, only participants using Android phones were included. Every participant was registered in the Monsenso system before the time of inclusion and instructed to start using the system 3 days before the baseline interview. The participants installed the app in their private phone, or we offered to loan an Android smartphone (LG Nexus 5) to participants not owning a phone. In this study, only one participant utilized a borrowed phone. We asked the young patients with newly diagnosed BD to use the system for at least 3 months, and the HC were asked to use it for at least 1 month. Participants were reminded to start using the system again when they were booked for follow-up interviews. As HAMD and YMRS capture symptoms from 3 days prior to the interview, we chose to include only participants who provided at least 3 days of smartphone data.

The automatically generated smartphone data collected daily by the Monsenso system were step counts; the total number of steps during a 24-h period detected by the accelerometer in the phone, reflecting the physical activity; the number of incoming and outgoing text messages during a 24-h period, reflecting social activity; duration and number of incoming and outgoing calls and the number of missed calls during a 24-h period, reflecting social activity; and the number of seconds the screen was on (screen time) and the number of times the screen was turned on, reflecting the smartphone usage.

For self-monitoring, all participants scored their daily level of activity and their mood, reflecting how good or how bad their day had been on a 7-point scale (−3, −2, −1, 0, 1, 2, 3). Additionally, young patients with newly diagnosed BD scored their affective state on a 9-point scale with scores from depressive to manic, which is a more fine-grained scale (−3, −2, −1, −0.5, 0, 0.5, 1, 2, 3) (34).

Statistical Analyses

Hypotheses and statistical analyses for the present study were defined *a priori*. For continuous variables, we used linear mixed effect models to investigate between-group differences in the mean regarding background characteristics. We used chi-square tests for between-group differences of categorical data. For analyses concerning aims 1–3, for each measure of interest, we employed a linear mixed effect model, which accommodates both the variation of the variables of interest within young patients with newly diagnosed BD (intra-individual variation) and between individuals (inter-individual variation). For participants with data available from both baseline and up to nine follow-up visits, a linear mixed effect model analysis to account for repeated measurements within each participant was employed. All participants were identified with a unique ID number. For aim 1, we used a linear mixed effect model to analyze the association between automatically generated smartphone data, as the dependent variable, and scores from clinical rating scales and questionnaires. For these analyses, averages of automatically generated smartphone data for the current day and 3 days before ratings with the HAMD and the YMRS, 7 days prior for the IPAQ, and 14 days prior for the FAST were calculated. For aim 2, we used a linear mixed effect model to investigate the between-group difference in daily automatically generated smartphone data between young patients with newly diagnosed BD and HC, from every observation available. For aim 3, we used a linear mixed effect model to analyze the associations between smartphone-based self-monitored mood and activity, as the dependent variable, and automatically generated smartphone data on physical and social activity and phone usage, respectively. Individual ID number was added as a random factor for all analyses. For aim 1, we included pooled data available from all participants. For aim 3, we included data available from young patients with newly diagnosed BD only. Analyses were conducted first in an unadjusted model and secondly in models adjusted for age and sex, by adding sex and age (as a numeric covariate) as fixed factors.

As no prior studies have investigated differences in automatically generated smartphone data between young patients with newly diagnosed BD and HC, we were not able to perform statistical power analyses prior to the study. Since data were collected as part of a larger longitudinal observational study, the sample size was defined according to this. As this is the first study on automatically generated smartphone data in young patients with BD and, in this way, the study is explorative by nature, we did not correct for multiple analyses. We checked model assumptions by visually utilizing residuals and QQ plots for each of the statistical analyses. SPSS version 25 (Statistical Package for the Social Sciences) was used for all analyses. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The present pilot study included a total of 40 young patients with newly diagnosed BD and 21 HC aged 25 years or younger by the time of inclusion and who provided automatically generated smartphone data. The HC group was statistically significantly older than the BD group (BD: mean = 21.6, 95% CI: 20.9, 22.3; HC: mean = 23.1, 95% CI: 22.2, 24.0; $p = 0.012$), the groups did not differ on other background characteristics (**Table 1**). Furthermore, all models were adjusted for age, and age was an insignificant covariate in all the analyses comparing BD with HC. The number of days where participants performed smartphone-based self-monitoring varied from 3 to 779 days [median (IQR) = 140 (11.5–268.5)] and added up to a total of 12,827 days. A total of 80% of the young patients with newly diagnosed BD and 71% of the HC had automatically generated data available for more than 1 month (**Figures 1, 2**). The number of visits for each participant varied from one to nine visits. A total of 27 participants had more than one visit. There were a total number of 77 visits with clinical assessment and automatically generated smartphone data from the 3 days prior to the visit (52 in the BD group and 25 in the HC group). Among the 52 in the BD group, 28 were during remission, 14 during a depressive episode, 6 during a hypomania, and 2 during a manic or mixed episode.

TABLE 1 | Demographics and background characteristics of young patients with newly diagnosed BD and HC, at baseline, $N = 61$.

	BD	HC	BD vs. HC *p*
Participants	40	21	
Age, years	21.6 (20.9, 22.3)	23.1 (22.2, 24.0)	**0.012**
Female, % (*n*)	72.5 (29)	61.9 (13)	0.40
Education, years	10.4 (5.8, 15.0)	15.0 (8.6, 21.3)	0.25
Full-time employment, % (*n*)	5.0 (2)	9.5 (2)	0.51
Student, % (*n*)	65.0 (26)	76.2 (16)	0.37
HAMD-17[a]	10.9 (8.7, 13.1)	1.2 (−1.8, 4.2)	**<0.001**
YMRS[b]	3.88 (2.65, 5.10)	0.48 (−1.21, 2.16)	**0.002**
FAST, total score[c]	19.83 (16.12, 23.53)	1.48 (−3.64, 6.60)	**<0.001**
IPAQ total, kcal/week[d]	2,489.10	2,437.92	0.90
Bipolar disorder II, % (*n*)	72.5 (29)	–	–
Age of onset, years	15 (12.87–17.13)	–	–
Illness duration, years[e]	5.5 (2.0–9.0)	–	–
Years of untreated BD[f]	1 (0.0–2.0)	–	–
No. of depressive episodes	4 (0.00–8.75)	–	–
No. of hypomanic episodes	3 (0.50–5.50)	–	–
No. of manic episodes	0 (0.00–0.75)	–	–
No. of mixed episodes	0 (0.00–1.00)	–	–
No. of total episodes	9.50 (4.13–14.88)	–	–

Continuous variables are presented as mean (SD) or median [interquartile range], and p-values are calculated based on differences in the mean between the two groups using linear mixed effect models. Categorical data are presented as % (n), and p-values are calculated using chi-square tests.

[a] HAMD-17, 17-item Hamilton Depression Rating Scale.

[b] YMRS, Young Mania Rating Scale.

[c] FAST, Functional Assessment Short Test.

[d] IPAQ, International Physical Activity Questionnaire adjusted for weight and converted to kcal/week.

[e] Illness duration was defined as the time from the first episode to the time of inclusion.

[f] Years of untreated BD was defined as the time from the first mania, hypomania, or mixed episode to time of diagnosis.

Bold values indicate statistical significance (p-value ≤ 0.05).

Validity of Automatically Generated Smartphone Data Against Clinical Ratings and Questionnaires

These results can be seen in **Table 2**.

As can be seen in **Table 2**, the number of incoming calls was statistically significantly positively associated with the HAMD total score ($B = 0.040$; 95% CI: 0.005, 0.074; $p = 0.024$), the HAMD subitem 8 ($B = 0.36$; 95% CI: 0.025, 0.70; $p = 0.036$), and the HAMD subitem 9 ($B = 0.79$; 95% CI: 0.30, 1.27; $p = 0.002$). Thus, for every increase of 1 point in the HAMD total score, there was a 0.04 increase in the number of incoming calls.

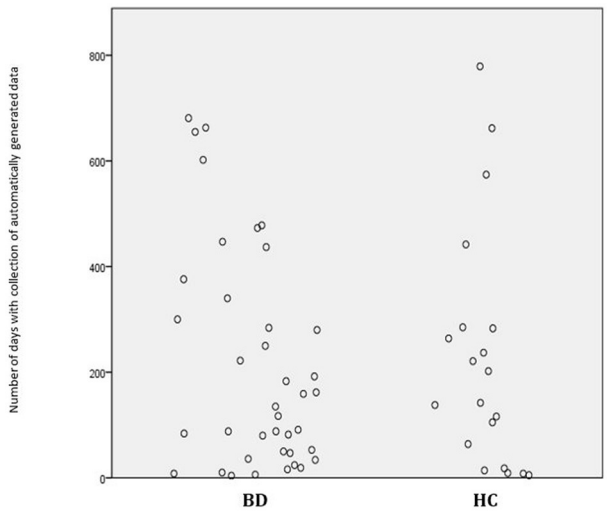

FIGURE 1 | The number of days with collection of automatically generated smartphone data in young patients with newly diagnosed bipolar disorder (BD) and healthy control individuals (HC). Each circle represents a participant.

As can be seen in **Table 2**, the number of outgoing calls was statistically significantly positively associated with YMRS total score ($B = 0.18$; 95% CI: 0.092, 0.26; $p < 0.001$), the YMRS subitem 2 ($B = 1.11$; 95% CI: 0.43, 1.78; $p = 0.003$), the YMRS subitem 6 ($B = 0.79$; 95% CI: 0.48, 1.10; $p < 0.001$), and the HAMD subitem 9 ($B = 1.024$, 95% CI: 0.21, 1.84; $p = 0.015$). Thus, for every increase of 1 point in the YMRS total score, there was a 0.18 increase in the number of incoming calls.

The number of missed calls was statistically significantly positively associated with the HAMD subitem 9 ($B = 0.41$; 95% CI: 0.083, 0.73; $p = 0.015$). Thus, for every increase of 1 point in the HAMD subitem 9 score, there was a 0.41-point increase in the number of missing calls. The number of incoming text messages was statistically significantly positively associated with the HAMD subitem 9 ($B = 3.26$; 95% CI: 0.88, 5.64; $p = 0.008$), and the same was the case between the number of outgoing text messages and the HAMD subitem 9 ($B = 2.88$; 95% CI: 0.53, 5.23; $p = 0.017$). Thus, for every increase of 1 point in the HAMD subitem 9 score, there was a 3.26-point increase in the number of incoming text messages and a 2.88-point increase in the number of outgoing text messages. For the associations between the number of incoming text messages and scores on the clinical rating scales, age was also a significant covariate. We found no associations between screen time, the number of step counts, the number of times the screen was turned on, total screen time, and scores on clinical ratings or questionnaires.

Differences in Smartphone Data Between Young Patients With Newly Diagnosed BD and HC

These results can be seen in **Table 3**.

As can be seen, there was a statistically significant difference in the number of incoming calls between young patients with newly diagnosed BD and HC (BD: mean = 1.42, 95% CI: 1.16,

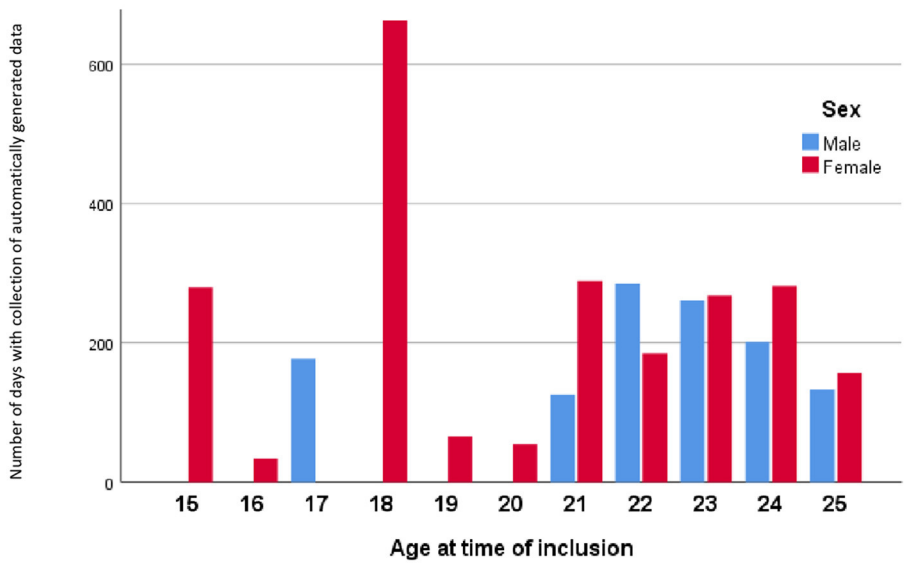

FIGURE 2 | The mean number of days with collection of automatically generated smart phone data grouped by age and sex, for all participants pooled ($n = 61$).

TABLE 2 | Associations between automatically generated smartphone data reflecting physical activity, social activity, and phone usage and clinical ratings and questionnaires in young patients with newly diagnosed BD and HC, from 77 clinical interviews (52 with BD and 25 with HC)[a].

	Number of observations	*B*	95% CI	*p*
Step count (number/day)[b]				
HAMD 17-item total score[c]	43	−4.26	(−154.90, 146.39)	0.96
HAMD subitem 8[d]	43	−201.36	(−1,791.15, 1,388.44)	0.81
HAMD subitem 9[e]	43	817.71	(−1,313.08, 2,948.50)	0.44
YMRS total[f]	43	21.92	(−301.81, 345.65)	0.89
YMRS subitem 2[g]	43	371.92	(−1,768.61, 2,512.45)	0.73
YMRS subitem 6[h]	43	−38.41	(−1,482.68, 1,405.87)	0.96
FAST[i]	49	−26.76	(−82.50, 28.97)	0.34
IPAQ[j]	37	0.037	(−0.42, 0.49)	0.87
Screen time (min/day)[b]				
HAMD 17-item total score[c]	76	−0.44	(−4.72, 3.84)	0.84
HAMD subitem 8[d]	76	0.77	(−41.07, 42.61)	0.97
HAMD subitem 9[e]	76	−10.05	(−71.13, 51.02)	0.74
YMRS total[f]	76	−2.82	(−9.98, 4.35)	0.43
YMRS subitem 2[g]	76	−39.08	(−94.08, 15.91)	0.16
YMRS subitem 6[h]	76	−14.98	(−49.62, 19.67)	0.39
FAST[i]	77	0.99	(−0.51, 2.50)	0.19
IPAQ[j]	60	−0.009	(−0.022, 0.003)	0.12
Screen on (number/day)[b]				
HAMD 17-item total score[c]	77	−0.57	(−1.98, 0.84)	0.42
HAMD subitem 8[d]	77	−11.33	(−24.62, 1.97)	0.093
HAMD subitem 9[e]	77	−9.18	(−29.41, 11.05)	0.37
YMRS total[f]	77	0.61	(−1.97, 3.19)	0.64
YMRS subitem 2[g]	77	6.14	(−12.73, 24.99)	0.52
YMRS subitem 6[h]	77	0.39	(−11.28, 12.05)	0.95
FAST[i]	77	−0.12	(−0.73, 0.50)	0.70
IPAQ[j]	61	0.001	(−0.003, 0.005)	0.47
Incoming calls (number/day)[b]				
HAMD 17-item total score[c]	63	0.040	(0.005, 0.074)	**0.024**
HAMD subitem 8[d]	63	0.36	(0.025, 0.70)	**0.036**
HAMD subitem 9[e]	63	0.79	(0.30, 1.27)	**0.002**
YMRS total[f]	63	0.062	(−0.012, 0.14)	0.095
YMRS subitem 2[g]	63	0.38	(−0.15, 0.91)	0.16
YMRS subitem 6[h]	63	0.23	(−0.064, 0.53)	0.12
FAST[i]	65	0.014	(−0.002, 0.029)	0.077
IPAQ[j]	52	−3.307e−5	(−0.0001, 9.977e−5)	0.62
Outgoing calls (number/day)[b]				
HAMD 17-item total score[c]	63	0.031	(−0.029, 0.091)	0.30
HAMD subitem 8[d]	63	0.25	(−0.33, 0.83)	0.39
HAMD subitem 9[e]	63	1.024	(0.21, 1.84)	**0.015**
YMRS total[f]	63	0.18	(0.092, 0.26)	**<0.001**
YMRS subitem 2[g]	63	1.11	(0.43, 1.78)	**0.003**
YMRS subitem 6[h]	63	0.79	(0.48, 1.10)	**<0.001**
FAST[i]	65	0.007	(−0.026, 0.039)	0.69
IPAQ[j]	52	0.0001	(−5.488e−5, 0.0003)	0.14
Missed calls (number/day)[b]				
HAMD 17-item total score[c]	63	0.014	(−0.009, 0.038)	0.22
HAMD subitem 8[d]	63	0.11	(−0.12, 0.34)	0.33
HAMD subitem 9[e]	63	0.41	(0.083, 0.73)	**0.015**
YMRS total[f]	63	0.031	(−0.019; 0.080)	0.21

(Continued)

TABLE 2 | Continued

	Number of observations	*B*	95% CI	*p*
YMRS sub-item 2[g]	63	−0.012	(−0.36; 0.34)	0.95
YMRS sub-item 6[h]	63	0.16	(−0.038; 0.367)	0.11
FAST[i]	65	0.003	(−0.008; 0.014)	0.58
IPAQ[j]	52	8.844e-6	(−8.658e-5; 0.0001)	0.85
Duration of phone calls (minutes/day)[b]				
HAMD 17-item total score[c]	63	0.22	(−0.20; 0.63)	0.30
HAMD sub-item 8[d]	63	2.71	(−1.18; 6.59)	0.17
HAMD sub-item 9[e]	63	2.56	(−3.48; 8.61)	0.40
YMRS total[f]	63	0.009	(−0.78; 0.80)	0.98
YMRS sub-item 2[g]	63	−0.15	(−5.72; 5.42)	0.96
YMRS sub-item 6[h]	63	−0.58	(−3.76; 2.60)	0.71
FAST[i]	65	0.12	(−0.087; 0.32)	0.25
IPAQ[j]	52	0.0008	(−0.003; 0.001)	0.39
Incoming text messages (number/day)[b]				
HAMD 17-item total score[c]	62	0.13	(−0.036; 0.29)	0.12
HAMD sub-item 8[d]	62	1.49	(−0.15; 3.12)	0.075
HAMD sub-item 9[e]	62	3.26	(0.88; 5.64)	**0.008**
YMRS total[f]	62	0.20	(−0.57; 0.17)	0.29
YMRS sub-item 2[g]	62	−1.53	(−4.41; 1.34)	0.29
YMRS sub-item 6[h]	62	−0.73	(−2.30; 0.84)	0.35
FAST[i]	64	0.031	(−0.017; 0.078)	0.20
IPAQ[j]	50	8.056e-5	(−0.0004; 0.0006)	0.75
Outgoing text messages (number/day)[b]				
HAMD 17-item total score[c]	62	0.10	(−0.061; 0.26)	0.22
HAMD sub-item 8[d]	62	1.21	(−0.40; 2.82)	0.14
HAMD sub-item 9[e]	62	2.88	(0.53; 5.23)	**0.017**
YMRS total[f]	62	−0.19	(−0.56; 0.17)	0.29
YMRS sub-item 2[g]	62	−1.61	(−4.41; 1.19)	0.25
YMRS sub-item 6[h]	62	−0.75	(−2.29; 0.78)	0.33
FAST[i]	64	0.021	(−0.032; 0.075)	0.42
IPAQ[j]	50	5.224e-5	(−0.0005; 0.0006)	0.85

[a] *Models adjusted for age and gender.*
[b] *Averages of automatically generated smartphone data were calculated for the current day and 3 days before ratings with the HAMD and the YMRS, 14 days prior for the FAST rating, and 7 days prior for the IPAQ.*
[c] *Hamilton Depression Rating Scale (HAMD) 17-item version total score.*
[d] *HAMD sub-item 8—level of psychomotor retardation for the past 3 days.*
[e] *HAMD sub-item 9—level of psychomotor agitation for the past 3 days.*
[f] *Young Mania Rating Scale (YMRS) total score.*
[g] *YMRS sub-item 2—level of increased motor activity for the past 2 days.*
[h] *YMRS sub-item 6—increased talkativeness for the past 2 days.*
[i] *FAST, The Functional Assessment Short Test total score.*
[j] *IPAQ, The Physical Activity Questionnaire—short form total score calculated to be expressed in kcal/week.*
Bold values indicate statistical significance (p-value ≤ 0.05).

1.68; HC: mean = 0.97, 95% CI: 0.64, 1.31; $p = 0.043$). There were no other statistically significant differences in automatically generated smartphone data between young patients with newly diagnosed BD and HC. Furthermore, there was a statistically significant difference in smartphone-based self-monitored mood as well as activity between young patients with newly diagnosed BD and HC (mood: BD mean = 0.21, 95% CI: −0.42, 0.46; HC mean = 1.60, 95% CI: 1.28, 1.92; $p < 0.001$).

As can be seen, young patients with newly diagnosed BD had a statistically significant higher score on the HAMD, YMRS, and FAST compared with HC (results can be found in **Table 3**).

Associations Between Automatically Generated Smartphone Data and Smartphone-Based Self-Monitoring

These results can be seen in **Table 4**.

As can be seen in **Table 4**, there was a statistically significant positive association between smartphone-based self-monitored activity and automatically generated data on step count ($B =$

TABLE 3 | Differences in automatically generated smartphone data reflecting mobility, social activities and phone usage between young patients with newly diagnosed BD ($n = 40$), and healthy controls ($n = 21$), ($N = 61$).

	BD			HC			BD/HC
	Number of observations	Mean	95% CI	Number of observations	Mean	95% CI	*P*
Automatically generated smartphone data							
Step count (steps/day)	6,649	4,561.99	(3,206.22; 5,917.77)	2,977	5,459.78	(3,628.93; 7,290.64)	0.44
Screen time (minutes/day)	8,137	220.14	(175.10; 265.19)	4,547	157.63	(99.89; 215.38)	0.096
Screen on (number/day)	8,256	77.94	(58.40; 97.48)	4,568	64.45	(39.39; 89.51)	0.40
Call duration (minutes/day)	6,521	16.12	(11.58; 20.67)	3,188	8.70	(2.77; 14.63)	0.056
Incoming calls (number/day)	6,521	1.42	(1.16; 1.68)	3,188	0.97	(0.64; 1.31)	**0.043**
Outgoing calls (number/day)	6,521	2.32	(1.87; 2.77)	3,188	1.81	(1.23; 2.40)	0.18
Missed calls (number/day)	6,521	0.90	(0.73; 1.06)	3,188	0.72	(0.51; 0.93)	0.19
Incoming text-messages (number/day)	6,447	4.65	(3.44; 5.87)	3,729	4.60	(3.02; 6.20)	0.96
Outgoing text-messages (number/day)	6,447	3.52	(1.99; 5.03)	3,729	3.68	(1.70; 5.66)	0.90
Smartphone-based self-monitored data							
Activity score	4,742	−0.007	(−0.22; 0.21)	2,764	0.64	(0.38; 0.91)	**<0.001**
Mood	4,796	0.21	(−0.042; 0.46)	2,779	1.60	(1.28; 1.92)	**<0.001**
Clinical ratings							
HAMD 17-item total score[a]	76	8.51	(6.94; 10.09)	39	0.84	(−1.23; 2.91)	**<0.001**
HAMD sub-item 8[b]	76	0.37	(0.20; 0.53)	39	0.003	(−0.21; 0.22)	**0.009**
HAMD sub-item 9[c]	76	0.29	(0.17; 0.41)	39	0.034	(−0.12; 0.19)	**0.010**
YMRS total score[d]	76	4.11	(2.99; 5.24)	39	0.38	(−1.09; 1.85)	**<0.001**
YMRS sub-item 2[e]	76	0.39	(0.17; 0.61)	39	0.042	(−0.24; 0.33)	0.057
YMRS sub-item 6[f]	76	0.72	(0.47; 0.96)	39	−0.026	(−0.35; 0.30)	**<0.001**
FAST total score[g]	76	17.37	(14.39; 20.35)	39	0.33	(−3.57; 4.24)	**<0.001**
Questionnaire							
IPAQ total score[h]	72	3476.58	(2645.07; 4308.10)	36	2787.90	(1761.84; 3813.97)	0.31

In total 12,827 days with collection of automatically generated smartphone data (BD: 8,258 days, HC: 4,569 days)[i].
[a]Hamilton Depression Rating Scale (HAMD) 17-item total score.
[b]HAMD Sub-item 8—level of psychomotor retardation.
[c]HAMD Sub-item 9—level of psychomotor agitation.
[d]Young Mania Rating Scale total score.
[e]YMRS Sub-item 2—level of increased motor activity.
[f]YMRS Sub-item 6—increased talkativeness.
[g]FAST, The Functional Assessment Short Test total score.
[h]IPAQ, The Physical Activity Questionnaire—short form total score calculated to be expressed in kcal/week.
[i]Adjusted for age and sex.
Bold values indicate statistical significance (p-value ≤ 0.05).

347.41; 95% CI: 233.06, 461.77; $p < 0.001$), the number of time the screen was turned on ($B = 7.62$; 95% CI: 6.37, 8.87; $p < 0.001$), number of outgoing calls ($B = 0.21$; 95% CI: 0.12, 0.29; $p < 0.001$), and the number of incoming text messages ($B = 0.24$; 95% CI: 0.033, 0.44; $p = 0.023$). Furthermore, there was a statistically significantly negative association between smartphone-based self-monitored activity and automatically generated data on screen time ($B = -12.05$; 95% CI: −16.70, −7.41; $p < 0.001$) and call duration ($B = -1.52$; 95% CI: −2.42, −0.62; $p = 0.001$). Thus, for every increase of 347 increase in step count, there was 1-point increase in smartphone self-monitored activity.

There was a statistically significant positive association between smartphone-based self-monitored mood and automatically generated data on step count ($B = 367.48$; 95% CI: 119.61, 615.35; $p = 0.004$) and numbers of time the screen was turned on ($B = 10.49$; 95% CI: 8.07, 12.90; $p < 0.001$). There was a statistically significant negative association between smartphone-based self-monitored mood and automatically generated data on screen time ($B = -15.87$; 95% CI: −24.79, −6.94, $p < 0.001$). Thus, for every increase of 367 in step count, there is a 1-point increase in smartphone-based self-monitored mood.

DISCUSSION

For the first time, the present pilot study investigated the use of automatically generated smartphone data collected in young patients with newly diagnosed BD and HC. Intriguingly, as hypothesized, automatically generated smartphone data on social activity was associated with clinically evaluated depressive and

TABLE 4 | Associations between automatically generated smartphone data reflecting physical and social activity, and smartphone-based self-monitored activity and mood in young patients with newly diagnosed BD, ($N = 40$), from a total of 3,804 days with collection of both automatically generated smartphone data and smartphone-based self-monitored data[a].

	Number of observations	*B*	95% CI	*p*
Step count (number/day)				
Smartphone-based self-monitored activity[b]	2,762	347.41	(233.06; 461.77)	**<0.001**
Smartphone-based self-monitored mood[c]	2,786	367.48	(119.61; 615.35)	**0.004**
Screen time (min/day)				
Smartphone-based self-monitored activity[b]	3,678	−12.05	(−16.70; −7.41)	**<0.001**
Smartphone-based self-monitored mood[c]	3,705	−15.87	(−24.79; −6.94)	**<0.001**
Screen on (number/day)				
Smartphone-based self-monitored activity[b]	3,756	7.62	(6.37; 8.87)	**<0.001**
Smartphone-based self-monitored mood[c]	3,782	10.49	(8.07; 12.90)	**<0.001**
Call duration (min/day)				
Smartphone-based self-monitored activity[b]	2,469	−1.52	(−2.42; −0.62)	**0.001**
Smartphone-based self-monitored mood[c]	2,482	−0.14	(−1.86; 1.57)	0.87
Incoming calls (number/day)				
Smartphone-based self-monitored activity[b]	2,469	−0.022	(−0.070; 0.027)	0.38
Smartphone-based self-monitored mood[c]	2,482	−0.017	(−0.11; 0.075)	0.72
Outgoing calls (number/day)				
Smartphone-based self-monitored activity[b]	2,469	0.21	(0.12; 0.29)	**<0.001**
Smartphone-based self-monitored mood[c]	2,482	−0.032	(−0.19; 0.13)	0.70
Missed calls (number/day)				
Smartphone-based self-monitored activity[b]	2,469	−0.021	(−0.064; 0.022)	0.33
Smartphone-based self-monitored mood[c]	2,482	−0.11	(−0.19; −0.032)	**0.006**
Incoming text-messages (number/day)				
Smartphone-based self-monitored activity[b]	2,468	0.24	(0.033; 0.44)	**0.023**
Smartphone-based self-monitored mood[c]	2,486	−0.089	(−0.46; 0.28)	0.64
Outgoing text-messages (number/day)				
Smartphone-based self-monitored activity[b]	2,469	0.20	(−0.018; 0.41)	0.072
Smartphone-based self-monitored mood[c]	2,482	0.017	(−0.38; 0.42)	0.93

[a] *Adjusted for age and gender.*
[b] *Smartphone-based self-monitored activity rated on a scale from −3 to +3.*
[c] *Smartphone-based self-monitored mood rated on a 9-point scale from −3 to +3.*
Bold values indicate statistical significance (p-value ≤ 0.05).

manic symptoms. Furthermore, as hypothesized, smartphone-based self-monitored mood, activity, automatically generated smartphone data on social activity (number of incoming calls/day), and clinically evaluated symptoms differed between young patients with newly diagnosed BD and HC. However, in contrast with our hypotheses, there were no other differences in automatically generated smartphone data between young patients with newly diagnosed BD and HC. In addition, as hypothesized, automatically generated smartphone data on physical activity and phone usage were associated with smartphone-based self-monitored mood and activity in young patients with newly diagnosed BD.

Validity of Automatically Generated Smartphone Data Against Clinical Ratings and Questionnaires

The findings that automatically generated smartphone data on social activity were associated with clinically evaluated depressive and manic symptoms are in line with prior studies on adult patients with BD (9–13).

However, in the present study, we only found this association between social activity, reflected by the number of calls and text messages, and total scores and subitem scores on the HAMD and the YMRS. A possible reason for this could be that the participants included in the present study did not present with severe symptoms during the clinical evaluations, and thus, the associations may differ during more severe states. Also, a possible explanation could be that young patients with newly diagnosed BD may present with more complex clinical presentation with unspecific prodromal symptoms (4) or a more continuous course of affective dysregulation, with episodes of depression and (hypo)mania lasting for hours rather than days or weeks, as in adult-onset BD (7). Further, in contrast to prior studies including adult patients with BD, the participants included in the present study were rather young, and it may be that this particular population may use smartphones for communication in different ways than older populations do, and thus, changes may not be captured with the automatically generated smartphone data included in the present study (36). We found no statistically significant associations between scores on FAST and automatically generated smartphone

data. This may be a type II error due to few high scores on FAST.

Differences in Smartphone Data Between Young Patients With Newly Diagnosed BD and HC

The findings that smartphone-based self-monitored mood, activity, and automatically generated smartphone data on social activity (number of incoming calls/day) differed between young patients with newly diagnosed BD and HC are in line with prior studies on adult patients with BD (10) and may reflect activation of the social network in young patients with newly diagnosed BD. Potentially automatically generated smartphone data on social activity could facilitate identification of BD in young people. Future studies including unaffected first-degree relatives could provide interesting knowledge on early changes in communicative activities and potentially be a useful supplementary diagnostic tool and facilitate early intervention, as it potentially allows for identification of prodromal symptoms which sometimes patients with BD during early stages of illness have difficulties identifying themselves (37).

Associations Between Automatically Generated Smartphone Data and Smartphone-Based Self-Monitoring

The findings that automatically generated smartphone data on physical activity and phone usage was associated with smartphone-based self-monitored mood and activity in young patients with newly diagnosed BD are also in line with prior studies on adult patients with BD (9–13, 20). In the present study, we found no association between automatically generated smartphone data on social activity and smartphone-based self-monitored mood. This could be due to the fact that young people tend to use alternative smartphone-based applications for social communication over the traditional call and text messages that were collected in the present study (36). However, we included information on the amount of time on the smartphone (screen time), which would include time spent on other messaging applications.

In the present study, we chose a naturalistic approach where the participants used their own smartphones as they would naturally; hence, there are missing data from when participants, i.e., turned off their phone, left it at home, or deactivated the app. Due to the nature of automatically generated smartphone-based data, we cannot say anything about the time periods where data were not available (missing data). However, since most people carry their smartphone with them during most of the day and use it in most of their online communications, we find that the results from the present study are valid. Overall, results from the present study confirm that automatically generated smartphone data may be used to monitor illness activity in young patients with BD unobtrusively during naturalistic settings between outpatient visits in a fine-grained and valid manner.

Limitations

Firstly, due to a large portion of iPhone users among the participants included in the BIO study, the number of participants using Android phones and thus being eligible for the present study was relatively limited. Therefore, the results from the present study should be interpreted with caution, as negative findings may be due to type II errors. It is possible that inclusion of a larger sample size and inclusion of a larger control group would have revealed other associations and differences. However, the present study is the first of its kind and therefore hypotheses generating.

Secondly, few young patients with newly diagnosed BD were clinically evaluated during severe depressive and manic episodes; this will lower the probability of finding associations between automatically generated smartphone data and clinically evaluated symptoms reflected by clinical rating scales. Future studies, with a higher number of established affective episodes, could do classification modeling investigating differences in smartphone data during euthymic and affective episodes. Thirdly, as the participants used their own smartphone, there was no standardized platform for data collection, possibly leading to heterogeneity in the data collected. Fourthly, several of the young patients with newly diagnosed BD were using psychotropic medicine; this was not accounted for in the analyses. Fifthly, the HC in the present study were recruited among blood donors, possibly representing a "super healthy" population (38, 39). Nevertheless, the blood donors included in this study were recruited from the same catchment area as patients with BD; they did not differ in educational or work status form patients, and they were not granted economic compensation for participating. Alternative methods for recruiting control groups include using advertisements and the Danish Civil Registration System. However, both methods have relatively low participation response rates and a high risk of selection bias. Taken together, we find that our control group represents the most reasonable and assessable control group for this study. Lastly, as the present study was not a randomized controlled trial, we were not able to investigate potential adverse effects or harms of the smartphone-based monitoring. Future randomized controlled trials could investigate this important aspect further.

Advantages

All young patients with newly diagnosed BD in the present study were diagnosed at a specialized mood disorder clinic, and the diagnosis or lack of diagnoses was verified for all participants with a SCAN interview conducted by trained PhD students in medicine or psychology. Additionally, all participants were assessed using clinically validated observer-based rating scales with the HAMD, the YMRS, and the FAST. The smartphone-based system used in the present study is well-validated, is useful, and fulfills the safety of data storage and privacy requirements. Although the collection of automatically generated data works on Android led to a smaller population in this study, it is an advantage regarding global generalizability, as Android is the most used OS worldwide.

Perspectives

Prior research has shown smartphone-based monitoring in young patients with psychiatric disorders to be feasible and acceptable (40), and as shown by us in a recent study,

smartphone-based self-monitoring gives a valid reflection of clinical symptoms in young patients with newly diagnosed BD (41). However, self-monitoring is susceptible to attrition regardless of whether being paper based or electronic, and unless it is monitored many times a day, it cannot identify shorter fluctuations in symptoms during the day, which is found to be more common in young patients with BD (7, 42). Thus, automatically generated data could be a valuable supplement to smartphone-based self-assessment, which together gives a basis for a valid fine-grained tool for diagnosing and illness monitoring in young patients with newly diagnosed BD, delivering both subjective and more objective information.

CONCLUSIONS

The present innovative pilot study investigated the use of automatically generated smartphone data collected daily during a long-term period in young patients with newly diagnosed BD and HC. Automatically generated smartphone data on social activity reflected clinically evaluated depressive and manic symptoms, differed between young patients with newly diagnosed BD and HC, and reflected self-reported changes in mood and activity in young patients with newly diagnosed BD. Although a rather low number of participants with a rather low level of affective symptoms during the study were included, our results suggest that automatically generated data on physical and social activity and phone usage could represent a potentially useful tool in diagnosing and monitoring young patients with newly diagnosed BD.

Future studies including young patients with newly diagnosed BD during more severe affective states, unaffected first-degree relatives, and different psychiatric disorders could provide interesting knowledge on early changes in communicative activities.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the study is ongoing; and therefore, the research data are not shared. Requests to access the datasets should be directed to https://www.psykiatri-regionh.dk/forskning/forskningsomraader/Neuropsykiatri/cadic/Sider/default.aspx.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Bipolar Illness Onset (BIO) study has been approved by the Ethics Committee in the Capital Region, Copenhagen, Denmark (Ref. Nr. H-7-2014-007) and the Danish Data Protection Agency, Capital Region of Copenhagen (Protocol No.: RHP-2015-023). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LK, MF-J, and MV conceived the study and were in charge of overall direction and planning. JB and MF were in charge of the development of the technology, which was further adjusted for clinical use in by LK, MF-J, MV, MF, and JB. SM and SS were in charge of recruiting and clinical data collections. SM, SS, and MF-J conducted the statistical analysis. SM, MF-J, and LK were in charge of the manuscript. All authors have contributed in the final configuration of the manuscript.

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Right Care, First Time: Developing a Theory-Based Automated Protocol to Help Clinically Stage Young People Based on Severity and Persistence of Mental Illness

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Most mental disorders emerge before the age of 25 years and, if left untreated, have the potential to lead to considerable lifetime burden of disease. Many services struggle to manage high demand and have difficulty matching individuals to timely interventions due to the heterogeneity of disorders. The technological implementation of clinical staging for youth mental health may assist the early detection and treatment of mental disorders. We describe the development of a theory-based automated protocol to facilitate the initial clinical staging process, its intended use, and strategies for protocol validation and refinement. The automated clinical staging protocol leverages the clinical validation and evidence base of the staging model to improve its standardization, scalability, and utility by deploying it using Health Information Technologies (HIT). Its use has the potential to enhance clinical decision-making and transform existing care pathways, but further validation and evaluation of the tool in real-world settings is needed.

Keywords: mental health, eHealth, health informatics, clinical decision support, health information technologies

INTRODUCTION

Most mental disorders emerge before the age of 25 years and result in considerable burden of disease (1, 2). The early onset of disorders often has lifelong impacts even if the disorder is subthreshold or has remitted, so effective mental health care during this period is critical to reduce their burden (3, 4). While youth mental health services have improved access to care (5–8), many services struggle to manage high demand and have difficulty matching individuals to timely interventions due to the heterogeneity of disorders. Together these challenges perpetuate a vicious cycle between health service inefficiencies and poor treatment outcomes at high costs to the health system and society (9–12).

The increased adoption and development of HITs in mental health emphasize their growing importance in the mental health services landscape (13–15). Using HITs for assessment, triage and referral is an area of particular interest due to the scalability and standardization of technologies (16). Though, the utility of triage protocols depends on having a heuristic for allocating care appropriately, which accounts for the complexities of emerging mood and psychotic disorders among youth (17). For this the clinical staging model for youth

TABLE 1 | Clinical stages for youth mental health (18).

Clinical stage	Definition
Stage 1a	Non-specific symptoms, mild to moderate symptom severity and only recent or mild impacts on social, educational, or occupational functioning
Stage 1b	Attenuated syndromes, with more specific anxiety, depression, mania, or psychosis symptoms of a moderate to severe severity and moderate to severe impacts on social, educational, or occupational functioning
Stage 2	Relatively more "discrete" disorders, with clear depressive, manic, psychotic, or mixed syndromes that persist over time, and clear, major impacts on social, educational, or occupational functioning
Stage 3	Discrete disorders that have persisted for at least 12 months following reasonable course of treatment or recurred after a complete recovery period of at least 3 months, with associated deterioration in social, educational, or occupational functioning
Stage 4	Chronic, severe, and unremitting illness that has persisted without remission for at least 2 years, with associated marked deterioration in social, educational, or occupational functioning

mental health may be particularly useful as a validated and transdiagnostic framework that aims to deal with the heterogeneity of disorders based on the persistence and severity of their symptoms and syndromes (18). The application of the clinical staging model using HITs could improve its scalability and serve as a useful guiding tool for clinicians making treatment decisions and service managers deciding how to allocate resources to provide the most effective care pathways. The objective of this paper is to describe the translation of the clinical staging model into a decision support tool using HITs.

Clinical Staging for Youth Mental Health

Young people experiencing mental illness vary along a continuum by factors including severity, duration of symptoms, and illness course (e.g., first episode vs. recurrent illness). Clinical staging is a framework which deals with clinical heterogeneity by using these factors to distinguish between young people in the early subthreshold phases of illness from those who have reached full threshold for major, discrete, and persistent or recurrent disorders. The clinical staging model is summarized in **Table 1**, and a detailed description of its development, validity and utility can be found in previous publications (18–22).

The clinical staging model is supported by a range of clinical and neurobiological validation studies. The construct validity of the model is supported by the high rates of agreement for classifying clinical stage across independent expert raters (18), and longitudinal work supports the differential rates of progression from earlier to later stages of anxiety, mood, psychotic, or comorbid disorders (23)—a key assumption of the model. Clinical stage has also been associated with neurobiological change [e.g., white brain matter; (24), differences in neuropsychological performance (25), and sleep disruption (26)]. These objective features characterize major demarcation points in adolescent-onset mood and psychotic syndromes, which are consistent with the clinical staging models assumptions about illness progression and severity (**Figure 1**).

The clinical staging model lends itself to allocating different levels of care and providing early intervention to slow or prevent the emergence and recurrence of these syndromes (27). Young people at later clinical stages will typically (though not always) require more intensive mental health care (19). While stages 1a and 1b represent subthreshold syndromes, and if left untreated, they have the potential to progress to more debilitating and persistent mental illness. Stage 1b in particular describes a relatively more severe state of attenuated syndrome that is associated with a higher risk of progressing to the development of more persistent and crystallized symptom clusters characteristic of discrete disorders (23). Young people at stage 1b are therefore recommended for more frequent clinical follow-up compared to those at stage 1a, as well as lengthier monitoring. This translates to a more intensive allocation of service resources (17). Therefore, identifying whether young people presenting to mental health services are at stage 1a, stage 1b, or beyond (Stage 2+) is of paramount importance for effective early intervention and secondary prevention.

Importantly, and as is the case with other clinical staging models (e.g., cancer), once placed on the mental illness continuum and assigned a clinical stage, young people cannot move back to an earlier stage, even in case of remission. As guidelines and standards of care are developed around the various clinical stages, this may provide a more accessible frame of reference for mental health consumers to quickly develop a shared understanding of their mental health with their clinician as well as an idea of what to expect in treatment. Ultimately, this framework has the potential to assist mental health services in resource (particularly human resource) management and in ensuring that all young people presenting to mental health services receive the most appropriate care for their personal circumstances that minimizes their risk of illness progression: "right care, first time."

DEVELOPING AN AUTOMATED CLINICAL STAGING PROTOCOL FOR HITs

This paper extends previous work on developing a clinical decision-making protocol based on the clinical staging framework (18, 23), by presenting the basic structure of an automated version of this protocol (Algorithms 1 and 2). This automated protocol was developed as a feature of a HIT that aimed to support mental health services by (among other things) automating intake processes, including conducting a multidimensional initial assessment by collecting demographic data, administering psychometric scales, and providing real-time feedback about results. This HIT is currently used in multiple youth mental health services across Australia (28).

The multidimensional initial assessment is the first step of a proposed model for youth mental health service delivery that aims to deliver highly personalized and measurement-based care (19, 29). In this step, a comprehensive assessment spanning a

wide variety of biopsychosocial health domains is conducted in order to gather enough information to allocate the appropriate intensity and type (e.g., online CBT, clinician-delivered CBT, "non-mental health" interventions focusing on returning to school) of care (27, 29). By using clinical staging principles to distill a young person's scores on key domains into a suggested clinical stage, this automated protocol aims to provide another source of information for clinicians to consider when making key treatment decisions (including shared decision-making with the young person).

We present this automated protocol in algorithm format (in pseudocode) for ease of understanding and to illustrate how the clinical staging model has been translated. The translation of this model was led by FI, SC, and IH. The process involved collating all previously published works on clinical staging criteria and supporting evidence and identifying the critical differentiating features from these publications. These differentiating features were best matched to the self-report items available in the HIT. This process involved wider consultation with youth mental health clinicians practicing in the application of clinical staging for young people, until the algorithm could be refined to maximize face validity.

We focused on distinguishing between young people at stages 1a, 1b, and 2+ at this initial phase of development as these clinical stages are the most relevant for early intervention and prevention. The protocol aims to automate two critical decision points associated with clinical staging (19, 23) and is presented in **Table 2**. The first is to determine whether there is any clear evidence of at least one full-threshold, major, discrete, and persistent or recurrent syndrome. This decision aims to distinguish between stage 2+ disorders and stage 1 (1a or 1b) disorders. The second is to then determine, of those among the stage 1 group, whether the syndrome is non-specific or attenuated. This decision aims to separate stage 1a and stage 1b syndromes.

Each of the evaluation criterion (text in italics) found in the algorithm 1 are underpinned by a secondary algorithm which evaluates the raw data to ascertain a result. **Table 3** presents an example of a secondary algorithm used to evaluate a young person's depression results to determine the appropriate flag for algorithm 1. The examples in this table were chosen to show the versatility with which these secondary algorithms can feed into algorithm 1, and how the clinical staging model has been operationalized using scale thresholds, individual items and symptom severity in other mental health domains (e.g., mania-like experiences and psychotic-like experiences).

Multiple scales measuring the same construct, such as the Quick Inventory of Depressive Symptomatology [QIDS; (30)], or the Patient Health Questionnaire-9 [PHQ-9; (31)], which measure depressive symptoms can be added as conditions. This increases the versatility of the protocol (and the HIT) since it can be simultaneously used by multiple services employing different psychometric scales. Should they fit clinical staging criteria, responses to individual scale items can also be added to the secondary algorithms. For example, the QIDS items "*Feeling slowed down*" and "*Feeling restless*" (30) are conceptually similar to the PHQ-9 item "*Moving or speaking so slowly that other people could have noticed. Or, the opposite—being so fidgety or restless that you have been moving around a lot more than usual*" (31). As endorsements of these items can indicate specific functional or circadian disruptions differentially associated with clinical staging (compared to other QIDS and PHQ-9 items or total scores), adding these as flag conditions can allow more targeted identification of young people at higher risk of worsening mental health outcomes. Specifying the exact degree of endorsement (e.g., a response of "2" or "3" on a 4-point Likert scale ranging from "0" to "3" where "0" indicates no impairment) could further increase precision.

While the secondary algorithm allows for the incorporation of multiple scales measuring the same construct, they cannot be assumed to be psychometrically equivalent to each other. For example, someone who scores "Severe" on the QIDS may not score "Severe" on the PHQ-9. This problem could perhaps be solved by using Item Response Theory to identify how scores for frequently used scales measuring each biopsychosocial domain would map onto a common metric (32). This would enable the conversion of scores between psychometric scales, yet would require further validation.

TABLE 2 | Pseudocode for the translation of clinical staging decisions into an algorithm.

Algorithm 1: clinical staging algorithm

```
//Apply formula to determine if young person meets conditions of being
rated stage 2+
IF
Social and occupational function rating indicates
ongoing and major impact on functioning
AND
    (
    Clear manic syndrome (not just symptoms) OR
    Clear psychotic syndrome (not just symptoms) OR
    Clear severe depressive syndrome OR
    Clear severe anxiety syndrome OR
    Previous Hospitalization for mental ill-health OR
    Significant and ongoing comorbid syndromes (e.g., substance
    misuse, eating disorders, personality)
    )
THEN assign 'Stage 2+'

//Apply formula to determine if young person meets conditions of being
rated stage 1b syndrome
ELSE IF
Social and occupational function rating indicates moderate to severe
impact on functioning
    AND
    (
    Specific and more severe anxiety syndrome (e.g., avoidance) OR
    Moderate depression syndrome without features indicative of stage
    2+ OR
    Hypomanic or attenuated psychotic symptoms as part of mood or
    anxiety syndrome OR
    Significant comorbid syndromes (e.g., substance, eating disorders,
    personality disorders)
    )
THEN assign 'Stage 1b'

//Young person does not meet criteria for stage 2+ or stage 1b,
therefore assign stage 1a
ELSE assign 'Stage 1a'
```

TABLE 3 | Detailed example for the translation of self-report data into clinical staging decisions.

Algorithm 2: specific clinical staging algorithm for depressive syndromes
//Apply formula to determine if young person meets conditions of a stage 2+ depressive syndrome
IF
//Evaluate cut-offs for 'Severe' depressive symptoms
(QIDS ≥ 21 **OR** PHQ-9 ≥ 20)
AND
//Evaluate features indicative of more severe syndromes
A: Two or more symptoms indicative of a severe syndrome
(
QIDS – either of the slow/restless items ≥ 3 **OR** *//psychomotor retardation/agitation*
PHQ-9 – slow/restless item ≥ 3 **OR** *//psychomotor retardation/agitation*
QIDS – highest score on sleep items = 3 **OR** *//severe circadian dysfunction*
PHQ-9 – sleep item = 3 **OR** *//severe circadian dysfunction*
QIDS – concentration/decision making item ≥ 3 **OR** *//major cognitive impairment*
PHQ-9 – trouble concentrating item ≥ 3 **OR** *//major cognitive impairment*
QIDS – Energy level item ≥3 **OR** *//severe energy disruption*
PHQ-9 – tired or little energy item ≥3 //severe energy disruption
)
AND
B: At least one other specific feature indicative of a severe syndrome
(
Probable hypomanic episodes **OR**
Probable psychotic symptoms **OR**
Severe suicidality **OR**
Probable comorbidity (e.g., anxiety disorder, personality disorder, eating disorder) **OR**
Probable substance misuse **OR**
Flag for early onset, previous severe episode, treatment resistance or recurring illness
)
THEN assign 'Stage 2+ - Clear severe depressive syndrome'

//Apply formula to determine if young person meets conditions of a stage 1b depressive syndrome
ELSE IF
//Evaluate cut-offs for 'Moderate' depressive syndrome
(QIDS ≥ 11 **OR** PHQ-9 ≥ 10)
AND
//Evaluate features indicative of more moderate syndromes
A: Two or more symptoms indicative of a moderate syndrome
(
QIDS – either of the slow/restless items ≥ 2 **OR**
PHQ-9 – slow/restless item ≥ 2 **OR**
QIDS – highest score on sleep items = 2 **OR**
PHQ-9 – sleep item = 2 **OR**
QIDS – concentration/decision making item ≥ 2 **OR**
PHQ-9 – trouble concentrating item ≥ 2 **OR**
QIDS – Energy level item ≥2 **OR**
PHQ-9 – tired or little energy item ≥2
)
AND
B: At least one other specific feature indicative of a moderate syndrome
(
Possible hypomanic episodes **OR**
Possible psychotic symptoms **OR**
Severe suicidality **OR**
Possible comorbidity (e.g., anxiety disorder, personality disorder, eating disorder) **OR**
Possible substance misuse
)
THEN assign 'Stage 1b—Moderate depression syndrome;
ELSE assign 'Stage 1a—Non-specific, mild depressive syndrome'

USING THE AUTOMATED CLINICAL STAGING PROTOCOL AS A DECISION SUPPORT TOOL

Clinical staging is not meant to replace diagnosis but instead act as an adjunct to it. This means that the automated clinical staging protocol presented here, should not (and is not intended to) be taken as the sole indicator of a young person's mental health. Instead, the application of the clinical staging model using HITs provides the opportunity for it to be used as a standardized and scalable decision support tool in services. In tandem with the multidimensional intake assessment administered by the HIT, the automated clinical staging protocol provides a useful heuristic for distilling the complex assessment results into a clinical stage that can be used to help clinicians decide about the best care plan and pathway for a young person.

The ability to assess and process this information prior to the first appointment could expedite the intake process and improve service efficiencies, such as wait times for assessment and treatment, by shifting initial assessment to HITs. Thus, the first application of this tool may be to help differentiate between those who would be suitable for self-directed or low intensity services (stage 1a) from those who require higher intensity services (stage 1b and 2+). Young people at stage 1b or stage 2+ typically require more complex interventions (17) and further assessment (including neuropsychological and circadian), however young people at stage 1a, typically experience milder symptoms and have a lower risk of progressing to a discrete disorder (23). This provides services with an opportunity to direct these young people to suitable care faster by leveraging HITs and the widespread availability of brief online mental health interventions such as Internet-delivered cognitive behavioral therapy (CBT) and other app-based programs (17, 29). This has the dual benefit of ensuring that limited mental health specialist resources directly assist those most at need while also ensuring that those with a relatively lower risk of illness progression receive the appropriate supports for recovery. Importantly, these young people (stage 1a) would not be sent away from the service, but rather HITs are used here to keep the young people in contact with the service so that their progress can be monitored, and if required, they can be directed to higher intensity interventions if they do not respond to the initial treatment options.

As clinical staging operates on a consensus model, a clinical stage suggested by this protocol represents one source of information that the clinician could use when considering a young person's case. For those at higher clinical stages or not accessing self-directed or low intensity services, their cases would ideally be reviewed at a full multidisciplinary team meeting or by a highly skilled clinician to determine the right care plan and pathway (29). To facilitate this staging process, the HIT was designed to collate much of the relevant information in one place and provide an overview of the factors driving the clinical staging decision. With this information, decisions can be made about the need for further assessment, the care team required to address their needs and the overall intensity of services (i.e., type

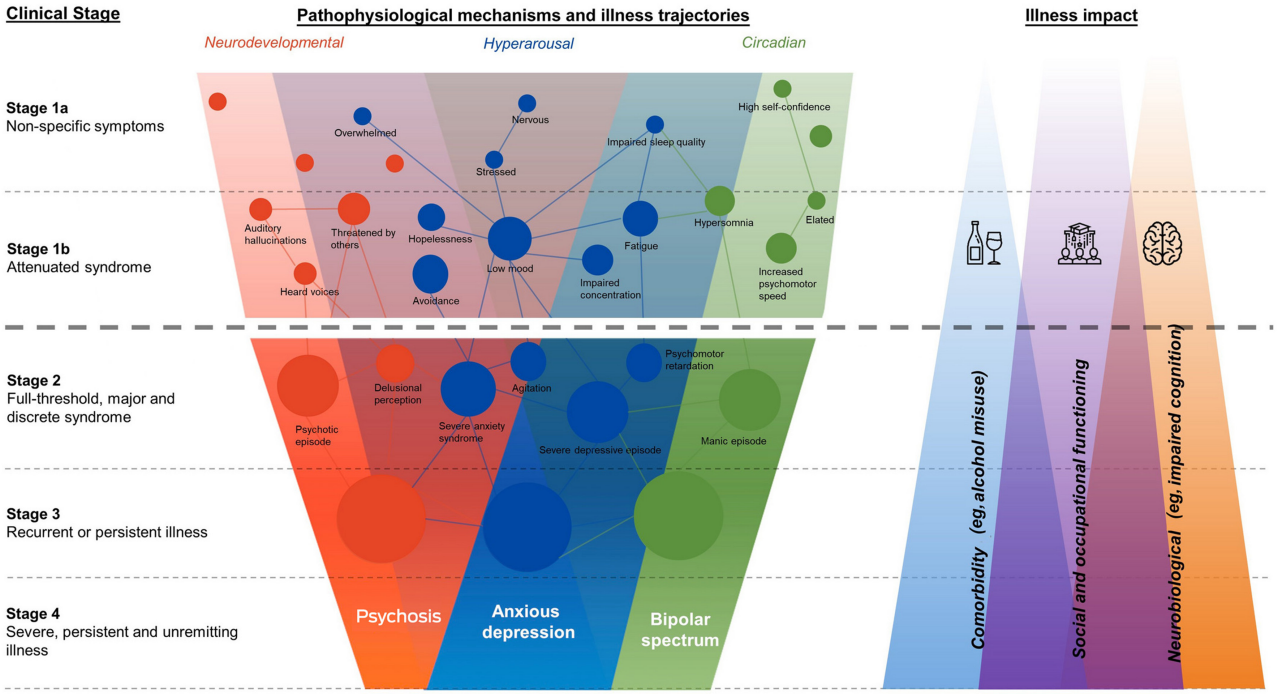

FIGURE 1 | Transdiagnostic framework of clinical stages overlapping pathophysiological domains, and theorized magnitude of illness impacts (19).

of service and treatments, minimum duration of care required, treatment frequency). This ensures that young people receive the right level of care for an appropriate amount of time to optimize treatment and prevention outcomes (27).

Ideally, in all cases, after the young person completes the multidimensional assessment a clinician would review their full intake data [including demographic information, assessment responses via a "dashboard" (28), and other contextual information collected during intake] alongside the suggested clinical stage, and record whether they agree with the automated protocols' recommendation (**Figure 2**). Any cases of disagreement should be referred to a multidisciplinary team for review and care allocation.

In practice, the application of this protocol extends beyond the initial care allocation process and can be applied dynamically over the course of a person's care. A young person's clinical stage should be reviewed periodically over time and HITs can be used to automatically schedule these according to a young person's clinical stage (i.e., stage 1b after 1 month). These reviews integrate further information, including continual multidimensional data from the young person (which would provide clinically valuable information on longitudinal trends) and results from further assessment (e.g., neuropsychological or circadian) if required. These results can then be used to increase confidence in the clinical stage result or identify what pieces of information are required to reduce uncertainty in the result. The dynamic use of this protocol ensures that an individual's care plan is adjusted over time to match any changes in their clinical stage or care needs.

DISCUSSION AND FUTURE DIRECTIONS

The demand and need for youth mental health care continues to increase, which puts pressure on an under resourced system, and impacts the overall quality of care a young person receives (33). Innovations to the way services assess, treat and monitor youth mental health problems are critical to improve service efficiencies and clinical outcomes.

Young people presenting for youth mental health care typically vary in terms of the type, severity, and complexity of illness. This makes the initial assessment and care allocation process difficult (34), particularly when greater demand forces services to place individuals on waitlists before initial and standard consultations (35). The use of HITs facilitates the initial assessment of a young person's needs prior to face-to-face contact, yet a current limitation of these HITs is being able to distill a comprehensive assessment into useful information for clinical decision making. Current solutions typically heavily rely on scoring of validated measures to identify a young person's symptom severity or need for care; however these approaches do not properly account for the complexity of youth mental health.

In contrast, the automated clinical staging protocol developed and presented here extracts critical clinical information from the multidimensional assessment to provide clinically meaningful evaluation and interpretation of a young person's current mental health illness trajectory. Its proposed use to identify young people in the very early stages of illness (stage 1a) and direct them to the relevant online services for treatment, has the potential to improve current wait times in services for all young people.

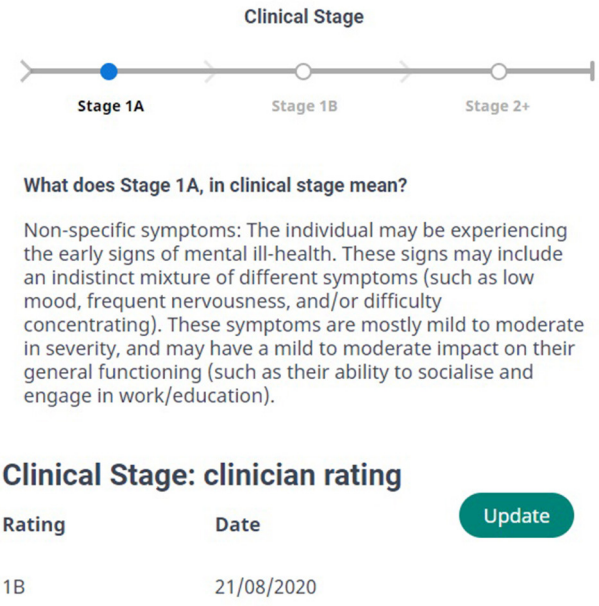

FIGURE 2 | A (fictional) young person's suggested clinical stage from our automated protocol, and the clinician's initial assessment of clinical stage (in this case disagreeing with the protocol).

In addition to improving care pathways, the allocation of care plans according to clinical stage has the potential to guide the type, intensity and duration of treatments according to a young person's illness trajectory.

While, clinical staging has been validated (24–26, 36), the automated clinical staging protocol has yet to be validated within a clinical setting (i.e., does the application of these concepts result in an improved delivery of mental health care and improved mental health outcomes for young people). Hence, an important next step will be to conduct this clinical validation to determine the actual predictive power in the sample of young people attending the mental health services that use the HIT (28). Further work will need to also evaluate the applicability of this automated protocol across different culturally and linguistically diverse populations to determine its generalizability.

As health systems embrace digital health, the medicolegal, and ethical guidelines for the legal and ethical use of health data, algorithms, and clinical decision support tools more generally is critical. It is important that all young people, clinicians, and service managers have a clear understanding of what personal and health information is being collected and how this data will be shared and used. This ensures transparency about how the decision support tool works and generates an output, which will be critical to managing any biases in any algorithm or tool using data to make recommendations about treatment. For this, engaging young people and clinicians in the further design, implementation and roll out of this tool is important for its real-world applicability.

Finally, one of the challenges in the broad implementation of this work (and the wider clinical staging framework to deliver technology-enabled mental health care) is the sector's relative lack of integration with technology, such as HITs. While a consequence of COVID-19 has been the rapid digitization of mental health service provision (12), this needs to continue in order to provide a base from which to execute the described service delivery model in a sustainable and scalable manner. It is important that this continual integration [for example implementing the capability for long term monitoring; (37)] always keeps mental health consumers at the center of their care and promotes their best interests.

Here, we have presented the translation of the clinical staging model into a decision support tool using HITs and its potential use in youth mental health services. The automated clinical staging protocol leverages the clinical validation and evidence base of the staging model to improve its standardization, scalability, and utility by deploying it using HITs. Its use has the potential to enhance clinical decision-making and transform existing care pathways, but further validation and evaluation of the tool in real-world settings is needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FI and VC wrote the manuscript. FI, SC, VC, and HY developed the automated staging protocol. TD, ES, and IH supervised the work and provided scientific leadership. All authors assisted with manuscript drafting and approved the final manuscript.

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Conflict of Interest: IH was an inaugural Commissioner on Australia's National Mental Health Commission (2012–2018). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017–2020; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. ES is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Principal Research Fellow, Brain and Mind Centre, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

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.

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