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Prevalence of Heavy Menstrual Bleeding and Its Associated Cognitive Risks and Predictive Factors in Women With Severe Mental Disorders

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There has been limited studies examining treatment-induced heavy menstrual bleeding (HMB) in women with severe mental illnesses. The aim of this study was to examine HMB prevalence and HMB-associated factors in young women (18–34 years old) diagnosed with bipolar disorder (BP), major depressive disorder (MDD), or schizophrenia (SCZ) who have full insight and normal intelligence. Eighteen-month menstruation histories were recorded with pictorial blood loss assessment chart assessments of HMB. Multivariate analyses were conducted to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Drug effects on cognition were assessed with the MATRICS Consensus Cognitive Battery (MCCB). HMB prevalence were: BP, 25.85%; MDD, 18.78%; and SCH, 13.7%. High glycosylated hemoglobin (HbA1c) level was a strong risk factor for HMB [BP OR, 19.39 (16.60–23.01); MDD OR, 2.69 (4.59–13.78); and SCZ OR, 9.59 (6.14–12.43)]. Additional risk factors included fasting blood sugar, 2-h postprandial blood glucose, and use of the medication valproate [BP: OR, 16.00 (95%CI 12.74–20.22); MDD: OR, 13.88 (95%CI 11.24–17.03); and SCZ OR, 11.35 (95%CI 8.84–19.20)]. Antipsychotic, antidepressant, and electroconvulsive therapy use were minor risk factors. Pharmacotherapy-induced visual learning impairment was associated with HMB [BP: OR, 9.01 (95%CI 3.15–13.44); MDD: OR, 5.99 (95%CI 3.11–9.00); and SCZ: OR, 7.09 (95%CI 2.99–9.20)]. Lithium emerged as a protective factor against HMB [BP: OR, 0.22 (95%CI 0.14–0.40); MDD: OR,

0.30 (95%CI 0.20–0.62); and SCZ: OR, 0.65 (95%CI 0.33–0.90)]. In SCZ patients, hyperlipidemia and high total cholesterol were HMB-associated factors (ORs, 1.87–2.22). Psychiatrist awareness of HMB risk is concerningly low (12/257, 2.28%). In conclusion, prescription of VPA should be cautioned for women with mental illness, especially BP, and lithium may be protective against HMB.

Keywords: bipolar disorder, major depressive disorder, schizophrenia, heavy menstrual bleeding, visual learning, lithium

INTRODUCTION

There is a relatively high prevalence of serious mental disorders, namely bipolar disorder (BP; lifetime prevalence, 2.4%), major depressive disorder (MDD; lifetime prevalence, 9.9%), and schizophrenia (SCZ, lifetime prevalence, 1%) in young women 18–34 years old (Kennedy et al., 2014; Tondo et al., 2014; Hui Poon et al., 2015; APA, 2016; Barnett, 2018; McIntyre et al., 2020; Howes et al., 2021; Papp et al., 2021; Rybak et al., 2021). Currently, they are treated primarily with antipsychotic agents, mood stabilizers (not a true pharmacological category; Stahl, 2021), antidepressants (Sienaert et al., 2013; Sinclair et al., 2019; Baandrup, 2020; Elias et al., 2021; Seppälä et al., 2021; Borbély et al., 2022), and electroconvulsive therapy (ECT) (Sinclair et al., 2019; Elias et al., 2021; Trifu et al., 2021).

Most antipsychotics inhibit serotonin reuptake, which can alter functioning of the hypothalamic-pituitary-gonadal (HPG) axis and thus may alter prolactin secretion and thereby cause menstrual disturbances (Huhn et al., 2019; Solmi et al., 2020), including heavy menstrual bleeding (HMB), hypomenorrhea, or amenorrhea (Haddad and Wieck, 2004; Kumar et al., 2013; Besag et al., 2021). Furthermore, HPG axis dysfunction can also cause glucose and lipid metabolism disorders that can lead to excessive weight gain and obesity (An et al., 2018; Tian et al., 2021; Piatoikina et al., 2022). Obesity is associated with dysregulation of adipose tissue functions and aberrations in adipokine secretion that can alter inflammatory responses, endothelial cell functions, and coagulation pathways.

Antipsychotic agents, antidepressant agents, and mood stabilizers have been reported to increase risk of hemorrhage and bleeding (Aranth and Lindberg, 1992; Joffe et al., 2006a; Paavola et al., 2019; Thomas et al., 2020). In women with severe mental illness, hemorrhage/bleeding presents mainly as HMB (El-Nashar et al., 2010; Stahl, 2021). HMB, which is defined as excessive regular or irregular menstrual bleeding (>80 ml per cycle) (Reavey et al., 2021b), affects 4% of women without organic pathology (Lethaby et al., 2009; Davies and Kadir, 2017). In mentally ill women, HMB has been reported to be associated with further psychiatric deterioration (Iles and Gath, 1989; Shannon, 1993; Pramodh, 2020; Arias-de la Torre et al., 2021; Padda et al., 2021). HMB in overweight women specifically has been related to metabolic disorders of blood glucose, lipids, and reproductive hormones (Iles and Gath, 1989; Shannon, 1993; Noerpramana, 1997; Pottegård et al., 2018; Pramodh, 2020; Schlaff et al., 2020; Arias-de la Torre et al., 2021; Padda et al., 2021; Pavlidi et al., 2021), all of which can be induced or exacerbated by psychiatric drugs (Iles and Gath, 1989; APA, 1994; Noerpramana, 1997; Meyer, 2002; Reynolds et al., 2007; Muir et al., 2008; Bradley and Gueye, 2016; Bora et al., 2017; Culpepper et al., 2017; Solé et al., 2017; Bekhbat et al., 2018; Pottegård et al., 2018; Calaf et al., 2020; Pramodh, 2020; Schlaff et al., 2020; Jang et al., 2021; Padda et al., 2021; Pavlidi et al., 2021).

Moreover, HMB can impair cognitive ability (Iles and Gath, 1989; Shannon, 1993; APA, 1994; Noerpramana, 1997; Meyer, 2002; Reynolds et al., 2007; Muir et al., 2008; El-Nashar et al., 2010; Bradley and Gueye, 2016; Bora et al., 2017; Culpepper et al., 2017; Solé et al., 2017; Bekhbat et al., 2018; Pottegård et al., 2018; Calaf et al., 2020; Pramodh, 2020; Schlaff et al., 2020; Arias-de la Torre et al., 2021; Jang et al., 2021; Padda et al., 2021; Pavlidi et al., 2021; Stahl, 2021), which may also be directly affected by mental illness and mental illness treatments (Iles and Gath, 1989; Shannon, 1993; APA, 1994; First et al., 1996; Noerpramana, 1997; Meyer, 2002; Reynolds et al., 2007; Muir et al., 2008; El-Nashar et al., 2010; Bradley and Gueye, 2016; Bora et al., 2017; Culpepper et al., 2017; Solé et al., 2017; Bekhbat et al., 2018; Pottegård et al., 2018; Calaf et al., 2020; Pramodh, 2020; Schlaff et al., 2020; Arias-de la Torre et al., 2021; Jang et al., 2021; Padda et al., 2021; Pavlidi et al., 2021; Stahl, 2021). Additionally, HMB may compromise patients' reproductive potential (Iles and Gath, 1989; Shannon, 1993; APA, 1994; First et al., 1996; Noerpramana, 1997; Meyer, 2002; Reynolds et al., 2007; Muir et al., 2008; Bradley and Gueye, 2016; Bora et al., 2017; Culpepper et al., 2017; Solé et al., 2017; Bekhbat et al., 2018; Pottegård et al., 2018; Calaf et al., 2020; Pramodh, 2020; Schlaff et al., 2020; Arias-de la Torre et al., 2021; Jang et al., 2021; Padda et al., 2021; Pavlidi et al., 2021; Stahl, 2021). Hence, there is a multitude of negatively interacting factors related to HMB that can worsen the prognosis of young women suffering from serious mental disorders.

In the present study, we examined HMB occurrence and HMB-associated factors in young women diagnosed with BP, MDD, or SCZ who were being treated with antipsychotic medications. We conducted a retrospective multi-hospital study across 10 provinces in China. Data acquired for an 18-months target period were subjected to multiple regression analysis to investigate HMB-associated risk and protective factors in patients using therapeutic agents. The main aims of this work were to determine HMB prevalence, to identify HMB-associated associated factors in young women with severe mental illness, and to assess how aware psychiatrists are of HMB risk in this patient population.

MATERIALS AND METHODS

Study Design and Participants

In this retrospective cohort study, we used convenience sampling to recruit participants being treated by 514 psychiatrists (257

TABLE 1 | Characteristics of the total sample (*N* = 3,094) and the bipolar disorder (BP; *N* = 855), major depressive disorder (MDD; *N* = 2,049), and schizophrenia (SCZ; *N* = 1,190) groups.

Variable		BP	MDD	SCZ	All
Education y, >12		557 (65.1)	556 (53.0)	664 (55.8)	1,777 (57.4)
Age, y		27.9 ± 3.7	27.6 ± 3.9	27.7 ± 3.8	27.7 ± 3.8
Total illness duration, mos		39.5 ± 9.0	41.1 ± 8.8	41.4 ± 9.0	40.8 ± 9.0
Pre-treatment BMI		20.8 ± 2.5	21.9 ± 2.2	22.5 ± 2.6	21.8 ± 2.5
First seeking treatment	HbA1c, %	4.2 ± 0.1	4.3 ± 0.2	4.1 ± 0.5	4.2 ± 0.6
	FBS, mmol/L	4.7 ± 0.4	4.9 ± 0.1	4.8 ± 0.2	4.8 ± 0.7
	PBG-2h, mmol/L	6.2 ± 1.1	6.9 ± 0.7	7.1 ± 1.5	6.9 ± 0.2
	TC, mmol/L	2.3 ± 0.3	2.0 ± 0.4	2.2 ± 0.4	2.2 ± 0.2
	TG, mmol/L	1.2 ± 0.1	1.4 ± 0.2	1.5 ± 0.3	1.3 ± 0.3
	Prolactin, ng/ml	8.1 ± 2.9	6.6 ± 2.3	9.9 ± 2.9	8.3 ± 3.0
	Estradiol, pg/ml	788.7 ± 370.2	695.9 ± 299.3	680 ± 303.9	700.5 ± 317.3
	Prog, ng/ml	13.8 ± 5.7	14.5 ± 6.0	13.8 ± 25.2	13.2 ± 4.6
	Testos, nmol/L	0.8 ± 0.3	1.0 ± 0.4	1.9 ± 0.9	1.5 ± 0.7
1–2 mos after accepting treatment	HbA1c, %	4.6 ± 0.5	4.4 ± 0.6	4.7 ± 0.5	4.6 ± 0.5
	FBS, mmol/L	5.5 ± 0.2	5.3 ± 0.4	5.7 ± 0.3	5.5 ± 0.5
	PBG-2h, mmol/L	6.1 ± 1.0	6.0 ± 0.7	6.2 ± 0.9	6.1 ± 0.5
	TC, mmol/L	3.7 ± 0.5	3.2 ± 0.4	3.9 ± 0.8	3.6 ± 0.1
	TG, mmol/L	1.7 ± 0.3	1.4 ± 0.2	1.9 ± 0.5	1.8 ± 0.1
	Prolactin, ng/ml	513.6 ± 230.9	355.6 ± 145.5	694.8 ± 241	529.7 ± 255.1
	Estradiol, pg/ml	696.5 ± 88.7	438.7 ± 110.2	490.6 ± 138.8	390.5 ± 117.3
	Prog, ng/ml	18.9 ± 2.2	25.4 ± 4.9	22.7 ± 6.5	21.8 ± 3.9
	Testos, nmol/L	1.5 ± 0.4	1.9 ± 0.7	2.3 ± 1.1	2.0 ± 0.5
2–3 mos after accepting treatment	HbA1c, %	5.6 ± 0.4	5.1 ± 0.3	5.6 ± 0.3	5.2 ± 0.5
	FBS, mmol/L	6.0 ± 0.2	5.6 ± 0.3	6.1 ± 0.4	5.9 ± 0.5
	PBG-2h, mmol/L	9.2 ± 0.2	8.5 ± 0.1	9.5 ± 0.4	9.4 ± 0.5
	TC, mmol/L	4.2 ± 0.4	3.9 ± 0.5	4.1 ± 0.9	4.0 ± 0.1
	TG, mmol/L	2.8 ± 0.2	2.1 ± 0.1	2.9 ± 0.5	2.6 ± 0.3
	Prolactin, ng/ml	1,528.0 ± 289.8	1,230.9 ± 251.6	1,883.0 ± 293.7	1,607.4 ± 318.6
	Estradiol, pg/ml	662.3 ± 202.4	398.3 ± 118.9	369.7 ± 220.0	525.40 ± 125.5
	Prog, ng/ml	26.0 ± 9.7	28.6 ± 6.9	30.4 ± 5.2	29.5 ± 10.2
	Testos, nmol/LL	2.2 ± 0.2	2.3 ± 0.3	2.7 ± 0.5	2.6 ± 0.8
Study enrollment	HbA1c, %	5.7 ± 0.3	5.4 ± 0.1	5.8 ± 0.2	5.5 ± 0.4
	FBS, mmol/L	6.3 ± 0.2	6.0 ± 0.1	6.4 ± 0.2	6.3 ± 0.3
	PBG-2h, mmol/L	9.1 ± 0.5	8.8 ± 0.5	9.3 ± 0.6	9.1 ± 0.9
	TC, mmol/L	5.3 ± 0.6	5.2 ± 0.3	5.8 ± 0.2	5.5 ± 0.5
	TG, mmol/L	2.9 ± 0.4	2.3 ± 0.5	3.1 ± 0.5	2.9 ± 0.8
	Prolactin, ng/ml	2,158.6 ± 797.2	1754.4 ± 627.7	2,628.3 ± 1101.7	2,200.5 ± 957.1
	Estradiol, pg/ml	541.8 ± 155.7	349.8 ± 158.6	362.8 ± 244.4	444.71 ± 97.85
	Prog, ng/ml	29.5 ± 12.3	33.2 ± 15	36.6 ± 20.4	28.9 ± 11.5
	Testos, nmol/L	2.9 ± 1.0	3.5 ± 0.9	3.4 ± 1.5	3.0 ± 1.7
MD ≤ 1 year pre-illness onset	No	441 (51.6)	901 (85.9)	1052 (88.4)	2,394 (77.4)
	Yes	414 (48.4)	148 (14.1)	138 (11.6)	700 (22.6)
HMB ≤1 year pre-illness onset	No	756 (88.4)	1,001 (95.4)	1145 (96.2)	2,902 (93.8)
	Yes	99 (11.6)	48 (4.6)	45 (3.8)	192 (6.2)
No. HMB periods in the year		1.8 ± 1.3	2.0 ± 1.3	1.6 ± 1.3	1.8 ± 1.3
Pre-treatment MCCB		BP	MDD	SCZ	ANOVA *p*
Speed procession		35.30 ± 5.45	35.14 ± 4.25	34.07 ± 2.30	0.667
Attention vigilance		36.47 ± 6.25	36.55 ± 3.12	37.53 ± 3.02	0.577
Working memory		36.65 ± 4.30	36.57 ± 2.39	38.22 ± 3.20	0.690
Verbal learning		37.20 ± 2.77	37.68 ± 2.24	38.45 ± 2.87	0.735
Visual learning		36.56 ± 6.23	36.09 ± 3.12	37.03 ± 1.88	0.702
Reasoning		37.25 ± 2.58	39.24 ± 3.38	39.97 ± 3.69	0.825
Social recognition		38.99 ± 5.84	37.15 ± 3.69	32.93 ± 1.78	0.920
Composite		30.03 ± 2.70	31.26 ± 3.09	30.99 ± 3.76	0.911

Mos, months; BMI, body mass index; HbA1c, hemoglobin A1C; FBS, fasting blood glucose; PBG-2h, 2-h postprandial blood glucose; TC, total cholesterol; TG, triglycerides; Prog, progesterone; Testos, testosterone; MD, menstrual dysfunction; HMB, heavy menstrual bleeding; MCCB, MATRICS, consensus cognitive battery; ANOVA, analysis of variance.

TABLE 2 | Treatment information within the 18 months before enrolling in the study.

Variable		BP	MDD	SCZ	All
Chlorpromazine equivalent, mg		116,983.4 ± 61,504.3	124,359.1 ± 68,115.2	324,041.0 ± 94,638.3	275,796.7 ± 123,914.7
Fluoxetine equivalent, mg		2,046.78 ± 6,813.3	21,161.7 ± 3,540.89	18,560.8 ± 6,006.9	20,328.2 ± 534.0
Valproate equivalent, mg		973,003.5 ± 613,025	274,344.0 ± 210,271.5	448,888.5 ± 280,239.7	563,127.9 ± 232,708.7
Total lithium, mg		406,189.2 ± 4,808.5	364,447.4 ± 2,756.3	102,222.5 ± 1,200.8	275,402.3 ± 2,735.4
Diazepam equivalent, mg		8,836.8 ± 2,648.2	8,627.7 ± 2,691.4	8,240.8 ± 2,727.9	8,539.5 ± 2,701.9
Benzhexol total dosage, mg		2,776.1 ± 544.7	2,861.3 ± 539	2,729.7 ± 547.4	2,763.8 ± 544.6
Promethazine total dosage, mg		49,050.0 ± 28,059.5	24,080.4 ± 12,350.7	55,233.0 ± 33,039.9	53,473.9 ± 31,767.9
Cumulative aripiprazole dose (hyperprolactinemia treatment)		2,907.4 ± 681.4	2,918.4 ± 700.2	2,996.6 ± 816.6	2,946.3 ± 744.5
HMB self-report scale responses, mean ± standard deviation or N (%)					
No. menstrual cycles		6.6 ± 2.3	5.3 ± 2.6	6.5 ± 1.9	6.1 ± 2.3
HMB	No	634 (74.15)	852 (81.22)	1,027 (86.3)	2,513 (71.22)
	Yes	221 (25.85)	197 (18.78)	163 (13.70)	581 (18.78)
HMB frequency	4.1 ± 1.1	2.4 ± 0.5	1.5 ± 0.3	2.2 ± 0.6	
Accepted ECT	No	530 (62.0)	684 (65.2)	592 (49.7)	1,806 (58.4)
	Yes	325 (38.0)	365 (34.8)	598 (50.3)	1,288 (41.6)
No. ECT sessions		36.0 ± 11.8	35.0 ± 11.9	35.5 ± 12.5	35.5 ± 12.1
HMB-related anemia treatment	No	137 (61.99)	154 (78.17)	135 (82.83)	426 (67.15)
	Yes	84 (38.01)	43 (21.83)	28 (17.17)	155 (32.85)
Nutrition change only for HMB-related anemia	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	yes	137 (100)	154 (100)	135 (100)	426 (100)
Patient knows HMB is a side effect of drugs	No	842 (98.5)	1,035 (98.7)	1,176 (98.8)	3,053 (98.7)
	Yes	13 (1.5)	14 (1.3)	14 (1.2)	41 (1.3)
Doctor said HMB is a side effect of drugs	No	853 (99.76)	1046 (98.7)	1,183 (98.8)	3,041 (98.7)
	Yes	2 (0.24)	3 (0.29)	7 (0.60)	12 (0.39)
Pharmacotherapy for menstrual dysfunction	No	810 (94.74)	977 (93.14)	245 (20.59)	2,032 (98.7)
	Yes	45 (5.26)	72 (6.86)	945 (79.41)	1062 (2.3)
TCM for menstrual dysfunction	No	199 (23.27)	260 (24.79)	340 (29.40)	799 (26.72)
	Yes	656 (76.73)	789 (75.21)	850 (71.60)	2,295 (74.18)
Doctor asks about HMB and adjusts treatment to alleviate it	No	853 (99.76)	1,046 (98.7)	1,183 (98.8)	3,041 (98.7)
	Yes	2 (0.24)	3 (0.29)	7 (0.60)	12 (0.39)
Illness deteriorated due to HMB; if yes, degree rating	No	0 (0)	0 (0)	0 (0)	0 (0)
	<15%	25 (11.31)	33 (16.75)	35 (21.47)	93 (14.98)
	15%–30%	37 (16.74)	29 (14.72)	37 (22.70)	103 (16.59)
	30%–50%	41 (18.55)	37 (18.78)	25 (15.15)	103 (16.59)
	≥50%	118 (53.39)	98 (49.74)	66 (40.49)	282 (45.41)
Told doctor about HMB-related anemia treatment	No	204 (92.31)	175 (88.32)	155 (95.09)	534 (91.91)
	Yes	17 (7.69)	22 (11.68)	8 (4.91)	47 (8.09)
After telling, doctor adjusted meds or advised protection	No	204 (92.31)	175 (88.32)	155 (95.09)	534 (91.91)
	Yes	17 (7.69)	22 (11.68)	8 (4.91)	47 (8.09)

Questionnaire responses are presented as N(%). HMB, heavy menstrual bleeding; ECT, electroconvulsive therapy; TCM, traditional chinese medicine.

senior psychiatrists, i.e., >10 years' experience with annual research methods training) in outpatient departments at 10 hospitals located in the north, south, east, and west regions of China (across 10 provinces). A group of 10 gynecologists was invited to help assess HMB. The physician recruitment period lasted 2 months (July 1st to 31 August 2021). Recruited doctors furnished detailed information of the samples, including sociodemographic characteristics, diagnosis, menstrual cycle timing history from 1 January 2020 through 31 August 2021, HMB incidence, and cumulative therapeutic agent dosages. Informed consent forms were signed by patients and their guardians prior to data collection. Ethics approval was granted from the ethic committee of Tianjin Fourth Center Hospital of Tianjin Medical University (No. ZC-R-0001).

The patient inclusion criteria were as follows: 1) 18–34-year-old female patient with treatment-resistant BP, treatment-resistant MDD, or treatment-resistant SCZ; 2) first episode; 3) full insight about one's own mental illness and treatment methods; 4) normal memory ability (to ensure recall of periods in the past 18 months); 5) medical record available to assure the absence of neurological or physical disease comorbidity, any history of menstrual dysfunction, and pharmacotherapies administrated in the prior 18 months; 6) willingness to volunteer participation in this study and provide detailed personal sociodemographic information. The exclusion

TABLE 3 | Comparison of MCCB scores before treatment, after 3 months treatment, and at study enrollment.

Time of assessment MCCB dimension	Diagnosis group			Inter-group ANOVA *p*
	BP	MDD	SCZ	
Before treatment				
Speed procession	35.30 ± 5.45	35.14 ± 4.25	34.07 ± 2.30	0.667
Attention vigilance	36.47 ± 6.25	36.55 ± 3.12	37.53 ± 3.02	0.577
Working memory	36.65 ± 4.30	36.57 ± 2.39	38.22 ± 3.20	0.690
Verbal learning	37.20 ± 2.77	37.68 ± 2.24	38.45 ± 2.87	0.735
Visual learning	36.56 ± 6.23	36.09 ± 3.12	37.03 ± 1.88	0.702
Reasoning	37.25 ± 2.58	39.24 ± 3.38	39.97 ± 3.69	0.825
Social recognition	38.99 ± 5.84	37.15 ± 3.69	32.93 ± 1.78	0.920
Composite	30.03 ± 2.70	31.26 ± 3.09	30.99 ± 3.76	0.911
*2 ~ 3 months from accepting 1*st *treatment*				
Speed procession	30.28 ± 3.69	29.87 ± 7.35	26.02 ± 1.82	0.051
Attention vigilance	30.66 ± 2.56	31.99 ± 1.75	30.36 ± 1.82	0.361
Working memory	30.33 ± 4.75	32.11 ± 1.87	30.25 ± 1.52	0.123
Verbal learning	32.55 ± 2.55	30.99 ± 1.98	32.00 ± 1.25	0.317
Visual learning	20.21 ± 1.22	20.00 ± 1.45	20.03 ± 1.07	0.675
Reasoning	32.15 ± 2.99	34.05 ± 1.39	30.04 ± 1.85	0.049
Social recognition	31.22 ± 1.79	28.88. ± 3.23	25.44 ± 3.45	0.037
Composite	29.44 ± 1.52	30.21 ± 1.44	28.52 ± 2.13	0.063
Study enrollment				
Speed procession	24.77 ± 1.13	26.47 ± 1.05	24.78 ± 10.86	0.049
Attention vigilance	28.35 ± 0.85	28.23. ± 0.45	27.66 ± 1.10	0.024
Working memory	30.02 ± 0.45	30.51 ± 0.69	29.17 ± 1.23	0.335
Verbal learning	29.56 ± 1.17	28.96 ± 0.59	27.59 ± 1.37	0.046
Visual learning	16.44 ± 0.85	15.28 ± 0.78	13.25 ± 0.85	0.017
Reasoning	30.00 ± 0.77	31.25 ± 0.80	25.14 ± 1.11	0.022
Social recognition	30.57 ± 1.74	32.55 ± 0.98	28.00 ± 0.97	0.047
Composite	24.88 ± 1.25	28.00. ± 1.52	20.44 ± 0.35	0.010
Intra-group rmANOVA				
Speed procession	0.0297	0.0219	0.0401	—
Attention vigilance	0.0378	0.0347	0.0234	—
Working memory	0.0481	0.0301	0.0377	—
Verbal learning	0.0394	0.0285	0.0390	—
Visual learning	<0.0001	<0.0001	0.0001	—
Reasoning	0.0493	0.0313	0.0010	—
Social recognition	0.0019	0.0477	0.0473	—
Composite	0.0010	0.0599	0.211	—
Score reduction				
Speed procession	34.60%	34.69%	27.27%	—
Attention vigilance	22.26%	22.76%	36.79%	—
Working memory	18.59%	16.57%	37.46%	—
Verbal learning	20.73%	23.14%	28.44%	—
Visual learning	56.42%	57.66%	64.22%	—
Reasoning	17.58%	20.34%	39.34	—
Social recognition	37.5%	13.35%	14.97%	—
Composite	39.20%	10.43%	33.72%	—

MCCB, MATRICS, consensus cognitive battery; BP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; ANOVA, analysis of variance; rmANOVA, repeated measures ANOVA.

criteria were as follows: 1) did not volunteer to participate; 2) cannot recall menstrual history of the past 18 months; 3) history of pregnancy and/or abortion in the past 18 months; 4) neurological illness, physical disease, or substance abuse history in the past 18 months; 5) diagnosis with any other mental disorder (including comorbid anxiety, depression, or personality disorder); 6) no majorly stressful life events in the past 18 months; and 7) no female family member/guardian available to assist with collecting information about the patient's illness, menstrual status, HMB status, and other needed information. Typically, in Chinese culture, even if a woman has a close relationship with her husband, her mother will continue to manage her care from childhood into adulthood, which worked well for information acquisition in this study.

Procedures

Data Collection

We collected clinical information from one insurance settlement period in China (3 months). Each participating physician collated the following patient information: category of mental illness; total

TABLE 4 | Univariate analysis results.

Factor		Or (95%CI)			
		BP	**MDD**	**SCZ**	**All**
Diagnosis	SCZ	—	—	—	1.0
	MDD	—	—	—	1.04 (0.83–1.30)
	BP	—	—	—	1.66 (1.31–2.09)
Education	≤12 years	1.0	1.0	1.0	1.0
	>12 years	1.00 (0.71–1.41)	0.74 (0.54–1.00)	1.00 (0.72–1.39)	0.88 (0.73–1.06)
Age <30 years		5.93 (3.89–9.44)	3.45 (2.17–7.88)	1.96 (1.15–4.20)	3.33 (1.10–4.07)
Illness duration, mos		1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.00 (0.98–1.02)	1.01 (1.00–1.02)
Pretreatment BMI		1.80 (0.95–4.41)	1.33 (0.78–3.39)	2.74 (2.33–3.21)	1.06 (0.36–1.10)
Before accepting 1st treatment		5.93 (3.89–9.44)	3.45 (2.17–7.88)	1.96 (1.15–4.20)	3.33 (1.10–4.07)
HbA1c, %		6.82 (4.80–9.68)	5.38 (3.85–7.51)	4.14 (2.94–5.84)	4.10 (3.43–4.91)
FBS, mmol/L		16.77 (10.81–26.02)	9.91 (6.67–14.71)	7.68 (4.93–11.95)	8.75 (6.94–11.02)
PBG-2h, mmol/L		4.71 (3.70–6.01)	1.86 (1.47–2.08)	2.66 (2.27–3.12)	2.50 (2.30–2.72)
TC, mmol/L		1.05 (0.83–1.33)	1.28 (1.03–1.59)	0.95 (0.75–1.21)	1.10 (0.96–1.25)
TG, mmol/L		0.76 (0.48–1.20)	0.69 (0.45–1.04)	0.75 (0.47–1.19)	0.74 (0.57–0.95)
Prolactin, ng/ml		0.99 (0.93–1.05)	1.02 (0.95–1.08)	0.98 (0.93–1.04)	1.02 (0.99–1.06)
Within 1–2 mos of accepting 1st treatment		6.82 (4.80–9.68)	5.38 (3.85–7.51)	4.14 (2.94–5.84)	4.10 (3.43–4.91)
HbA1c, %		29.66 (18.48–47.62)	5.83 (4.26–7.99)	6.17 (4.19–9.09)	7.20 (5.88–8.82)
FBS, mmol/L		22.21 (13.86–35.59)	11.18 (7.48–16.70)	6.17 (4.17–9.13)	10.13 (8.02–12.80)
PBG-2h, mmol/L		4.13 (3.32–5.14)	1.85 (1.66–2.07)	2.52 (2.18–2.92)	2.43 (2.25–2.63)
TC, mmol/L		0.88 (0.69–1.12)	0.97 (0.78–1.20)	1.07 (1.00–2.36)	0.98 (0.86–1.12)
TG, mmol/L		0.98 (0.62–1.56)	1.07 (0.71–1.62)	1.59 (1.64–7.57)	1.02 (0.79–1.32)
Prolactin, ng/ml		1.78 (0.95–4.20)	1.79 (0.98–6.82)	6.48 (2.08–10.70)	2.30 (0.85–5.35)
Within 2–3 months of accepting 1st treatment		29.66 (18.48–47.62)	5.83 (4.26–7.99)	6.17 (4.19–9.09)	7.20 (5.88–8.82)
HbA1c, %		5.17 (3.01–9.57)	8.96 (6.13–13.10)	7.90 (4.00–10.13)	5.92 (2.35–10.53)
FBS, mmol/L		5.42 (4.22–9.9)	9.08 (5.98–14.55)	4.59 (2.47–9.88)	3.59 (1.88–7.00)
PBG-2h, mmol/L		9.59 (6.91–13.30)	2.08 (1.82–2.38)	6.82 (5.22–8.92)	3.80 (3.41–4.24)
TC, mmol/L		1.24 (0.97–1.57)	0.86 (0.69–1.07)	4.10 (1.09–7.15)	1.01 (0.89–1.15)
TG, mmol/L		0.98 (0.62–1.56)	0.89 (0.58–1.36)	3.87 (1.98–9.75)	0.97 (0.75–1.26)
MD in year before this study	Yes	1.0	1.0	1.0	1.0
	No	1.78 (0.56–4.08)	1.16 (1.11–2.23)	1.34 (0.76–2.36)	1.49 (0.88–5.60)
HMB in year before this study	Yes	1.0	1.0	1.0	1.0
	No	1.18 (0.16–2.54)	0.82 (0.74–6.33)	1.04 (0.29–1.36)	1.00 (0.88–1.60)
ECT treatment 18mPreEn	Yes	1.0	1.0	1.0	1.0
	No	3.33 (2.22–5.01)	2.08 (1.47–2.96)	5.03 (3.35–7.54)	3.35 (2.69–4.18)
Cumulative dosage 18mPreEnr		2.66 (1.12–6.33)	1.85 (1.26–2.81)	1.77 (1.45–3.31)	2.22 (1.96–3.56)
Antipsychotic[a]		2.37 (1.48–3.78)	2.69 (1.06–6.83)	3.22 (1.18–8.19)	1.96 (1.34–2.86)
Antidepressant[a]		2.71 (1.10–7.35)	4.13 (2.70–8.81)	3.21 (1.90–5.40)	1.95 (1.76–5.19)
Anti-mania agent[a]		0.20 (0.12–0.49)	0.29 (0.17–0.48)	0.49 (0.20–0.87)	0.60 (0.31–0.99)
Mood stabilizer[a]		0.93 (0.39–2.20)	0.93 (0.44–1.98)	0.25 (0.10–0.64)	0.60 (0.37–0.97)
Anxiolytic[a]		1.46 (0.19–11.31)	0.27 (0.17–5.00)	2.65 (0.13–52.45)	1.18 (0.25–5.67)
Spasmolytic[a]		1.45 (0.75–2.79)	0.85 (0.42–1.59)	1.23 (0.83–1.83)	1.29 (0.92–1.80)
Anti-nausea/pain[a]		2.52 (0.65–4.80)	1.60 (0.85–2.46)	1.97 (0.67–4.05)	2.28 (0.73–5.25)
Antipsychotic[a]		1.27 (0.56–4.99)	0.89 (0.75–1.37)	1.44 (0.93–3.66)	1.11 (0.49–1.75)
TCM for MD		9.37 (3.18–14.56)	6.24 (4.18–9.43)	8.56 (7.14–13.25)	7.80 (3.13–29.99)
Visual learning, 2~3mTx		1.57 (1.01–3.45)	1.07 (1.00–3.11)	2.00 (1.00–6.02)	1.47 (1.00–6.59)
Composite, 2~3mTx		2.66 (1.12–6.33)	1.85 (1.26–2.81)	1.77 (1.45–3.31)	2.22 (1.96–3.56)

[a]Logarithms used in analysis and reported as follows: antipsychotic, chlorpromazine equivalent (eq); antidepressant, fluoxetine eq; anti-mania agent, valproate eq; mood stabilizer, lithium eq; anxiolytic, diazepam eq; spasmolytic, trihexyphenidyl eq; anti-nausea/pain, promethazine eq; antipsychotic, aripiprazole eq. OR, odds ratio; CI, confidence interval; BP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; HbA1c, hemoglobin A1C; FBS, fasting blood glucose; PBG-2h, 2-h postprandial blood glucose; TC, total cholesterol; TG, triglycerides; MD, menstrual dysfunction; HMB, heavy menstrual bleeding; ECT, electroconvulsive therapy; 18mPreEn, within the 18 months before enrolling to participate in the study; TCM, traditional Chinese medicine; 2~3mTx, within first 2–3 months of treatment.

menstrual cycles in the past 18 months; HMB incidence in the past 18 months; total cumulative medication dosage in the past 18 months; glycosylated hemoglobin A1c (HbA1c) level; steroid hormone levels; blood sugar levels; blood total cholesterol (TC) levels; blood lipid levels; and body mass index (BMI). BP, MDD, and SCZ definitions were adopted from the Diagnostic and

TABLE 5 | Multivariate analysis of HMB risk factors in each diagnosis group and in the total sample.

Factor	BP		SCZ		MDD		All	
	Or (95% CI)	*p*	Or (95% CI)	*p*	Or (95% CI)	*p*	Or (95% CI)	*p*
Age <30 years	4.89 (2.21–8.59)	<0.0001	1.87 (1.10–3.56)	<0.0001	3.12 (2.19–7.874)	<0.0001	2.87 (1.09–3.97)	<0.0001
HbA1c[a]	19.39 (16.60–23.01)	0.0012	2.33 (1.76–3.09)	<0.0001	12.69 (4.59–13.78)	<0.0001	2.89 (1.55–5.37)	0.0008
FBS[a]	15.87 (11.85–119.81)	<0.0001	9.59 (6.14–12.43)	<0.0001	9.97 (7.52–13.49)	<0.0001	40.87 (16.50–65.23)	<0.0001
PBG-2h[a]	9.22 (6.48–12.35)	0.0001	8.53 (6.15–12.61)	<0.0001	8.44 (4.63–13.44)	<0.0001	1.75 (1.33–2.29)	<0.0001
Visual learning[a]	14.12 (11.15–15.99)	<0.0001	13.19 (7.80–15.08)	<0.0001	10.00 (10.03–14.08)	<0.0001	6.58 (2.17–10.81)	0.0004
ECT treatment	3.11 (1.19–5.00)	0.0298	9.03 (7.15–12.30)	<0.0001	5.55 (2.94–12.87)	<0.0001	1.92 (1.13–3.26)	0.0167
Cumulative dose								
Antipsychotic	5.51 (3.89–11.52)	<0.0001	2.22 (1.23–4.55)	<0.0001	1.87 (1.30–4.10)	<0.0001	3.52 (1.58–12.15)	<0.0001
Antidepressant	1.14 (1.02–2.88)	<0.0001	1.87 (1.27–6.00)	<0.0001	9.03 (7.23–12.48)	<0.0001	2.28 (1.22–11.00)	<0.0001
Valproate	16.00 (12.74–20.22)	<0.0001	4.12 (2.66–9.50)	<0.0001	4.88 (1.24–7.03)	<0.0001	4.59 (2.85–9.60)	<0.0001
Lithium	0.22 (0.14–0.40)	<0.0001	11.99 (6.74–14.44)	<0.0001	0.30 (0.20–0.62)	<0.0001	0.50 (0.09–0.99)	<0.0001

Group comparisons BP vs. SCH: 2.52 (1.50–3.13), $p < 0.0001$ MDD vs. SCH: 1.21 (1.12–2.01), $p = 0.0002$

[a]*Within 2–3 months of accepting the first treatment. BP, bipolar disorder; SCZ, schizophrenia; MDD, major depressive disorder; OR, odds ratio; CI, confidence interval.*

Statistical Manual of Mental Disorders–Edition IV (First et al., 1996) and Structured Clinical Interview for DSM-IV Axis I Disorders (Birchwood et al., 1994). Mental illness etiology was described based on core symptoms. Blood constituent level data determined closest to the start of the study were used. Each patient's medical record was consulted for confirming medication dosage accuracy and an absence of neurological and physical disease history in the past 18 months.

Instruments

Patient insight was confirmed with the Birchwood Insight Scale (Beck et al., 2004) and Beck Cognitive Insight Scale (Wang et al., 2015). Normal memory function was confirmed with the Chinese version of the Wechsler memory scale-Fourth edition (Ko et al., 2021).

Total numbers of menstrual times in the past 18 months were recorded and the Pictorial Blood-loss Assessment Chart (PBAC) (Leucht et al., 2003) was used to assess HMB (although PBAC is used extensively to assess HMB at the moment, its validity regarding previous HMB status remains to be verified). Because this study was conducted retrospectively, we brought in gynecologists to show patients and their female guardians HMB on PBAC and guide information collection, including the presence of blood clots on sanitary napkins, how many sanitary napkins were used in one menstrual period, and how to calculate menstrual bleeding. Although previous studies have used more accurate HMB diagnostic criteria, the large sample included in this study precluded the use of such a highly complex procedure. Although our retrospective use of the PBAC represents a limitation, it provided useful information for this study. Eighteen-month cumulative antipsychotic, antidepressant, mood stabilizer, and anxiolytic/sleep aide use were converted to chlorpromazine equivalent (Hayasaka et al., 2015), fluoxetine equivalent (Rossetti and Alvarez, 2021), sodium valproate equivalent (García-Carmona et al., 2021), and diazepam equivalent (Paulzen et al., 2016), respectively.

Obesity was determined based on BMI (Mizuno et al., 2014). Prolactin, estradiol, progesterone, testosterone levels were determined with double-antibody radio-immunoassays. The cut-offs for hyperprolactinemia, high progesterone, and high testosterone were ≥40.0 μg/L (Nikolac Gabaj et al., 2018), ≥97.6 nmol/L, and ≥3.1 nmol/L (Lee et al., 2013), respectively. Fasting and 2-h postprandial blood glucose analyses (Gu et al., 2016) were conducted by a Cobas 6,000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Glycosylated hemoglobin (HbA1c), TC, and blood lipid levels (Nick and Campbell, 2007) were determined with an H-7600 automated biochemical analyzer (Hitachi High-Technologies, Tokyo, Japan).

Pregnancy tests were conducted to exclude pregnant patients from the study (Wang et al., 2015). An HMB self-report scale was used to assess patients' views of the influence of HMB on their mental illness status. It included the following items and answer point values: 1) did you feel your mental illness symptoms deteriorated from HMB? (yes, 1; no, 0); 2) did the total deteriorated time exceed a month? (yes, 1; no, 0 AND if severe, +3, if moderate +2, if mild +1); 3) did you feel that you were suffering when experiencing HMB? (yes, 1; no, 0); 4) did you feel the total time of your suffering from HMB exceeded a month? (yes, 1; no, 0; severe suffering, +3; moderate suffering, +2; mild suffering, +1); 5) did you feel your life quality in the past 18 months was influenced by your HMB? (severe influence, four; moderate influence, three; mild influence, two; no influence, 0).

Cognition was assessed with the MATRICS Consensus Cognitive Battery (MCCB), which has a three-domain structure (McCleery et al., 2015; Lo et al., 2016). Specifically, MCCB assessments of processing speed (Trail Making Test, Part A; Symbol Coding; and Category Fluency: Animal Naming), working memory (Letter-Number Span); and verbal learning (Hopkins Verbal Learning Test-Revised; HVLT-R) were conducted. Verbal learning was assessed with the Rey Auditory Verbal Learning Test (Schmidt, 1996; Bowie et al., 2018) instead of the HVLT-R in one participant.

Statistical Analysis

Statistical analyses were completed in SAS statistical software (version 9.3, SAS Institute, Cary, NC). Continuous-variable data are expressed as means ± standard deviations (normally distributed

data). Data are compared across groups and within groups over time with analyses of variance (ANOVAs) and repeated measures ANOVAs, respectively. Categorical-variable data are expressed as numbers and percentages. Associations of clinical-demographic characteristics with HMB incidence were evaluated with univariate and multivariate logistic regression models and expressed as odds ratios (ORs) and 95% confidence intervals (CIs) in the overall sample and by diagnosis group. Multivariate logistic models were first developed by adjusting for factors found to be significant in univariate analyses ($p < 0.02$); final multivariate models were limited to risk factors or confounders that were statistically significant (Nikoloulopoulos, 2012; Hidalgo and Goodman, 2013; Vuong et al., 2014; Fu et al., 2020).

RESULTS

Sample

Complete information was obtained 3,094 of 3,500 participants (88.4%) who were recruited to enroll in this study. The final study sample of 3,094 participants, included 855 patients with BP, 1,049 patients with MDD, and 1,190 patients with SCZ. The BP, MDD, and SCZ groups were similar with respect to age, education level, and illness duration. The sample characteristics (as a whole and of each diagnosis group) are summarized in **Table 1**.

The patients' treatment histories, including their interactions with their physicians in relation to HMB awareness as indicated on the HMB self-report scale, are summarized in **Table 2**, respectively. Although the patients indicated that HMB had negative effects on their illness progression and quality of life, few patients had been informed that HMB was a potential secondary adverse reaction to psychiatric medications. Furthermore, when queried, only 12 of the 257 psychiatrists servicing these patients (awareness rate, 2.28%) were aware of the risk.

HMB Prevalence

It was determined that 581/3,094 participants (18.78%) had HMB. Their average frequency of HMB in the past 18 months was 2.2 ± 0.6 menstrual cycles. The HMB prevalence rates by diagnosis group were: BP, 28.85% (221/855); MDD, 18.78% (197/1.49); and SCZ, 13.70% (163/1190). The prevalence rates of HMB in patients with BP and patients with MDD were 2.52-fold and 1.21-fold that in patients with SCZ.

Evolution of Cognitive Functioning

Mean (±standard deviations) of MCCB scores over time are reported in **Table 3**. Note that no MCCB domain scores differed between the diagnosis groups prior to the patients starting pharmacological treatment, though differences emerged over time, with diagnosis group having a main effect on all MCCB domain scores, except working memory, by the time of the study enrollment assessment. Visual learning was the most heavily impacted domain (see **Table 3**). Repeated measures ANOVAs showed that all MCCB domain scores changes over time for all groups, though the composite scores changed significantly over time for only the BP group.

HMB-Associated Factors

As reported in detail in **Table 4**, univariate analyses indicated that the following variables were associated with HMB (ORs, 1.86–16.77): <30 years old; HbA1c; fasting blood sugar (FBS); and 2-h postprandial blood glucose (PBG-2h). As reported in detail in **Table 5**, multivariate analysis demonstrated that HMB in BP patients was associated with being younger than 30 years old as well as with visual learning scores, HbA1c levels, FBS, and PBG-2h within 2–3 months after commencing pharmacological treatment. In patients with SCZ, hyperlipidemia and high TC were associated with HMB. Reproductive hormone concentrations did not fluctuate in association with HMB. Notably, HMB was found to be strongly significantly associated with cumulative antidepressant, valproate, and lithium use in the patient sample as a whole and in each diagnosis group (**Table 5**), with the former two being a risk association (use predicts higher HMB risk) and the latter one being a protective association (use predicts lower HMB risk).

DISCUSSION

This study was the first to our knowledge to examine HMB risk factors in patients with severe mental illness. We found that nearly one in five of the women in our study experienced HMB. Treatment-related HMB was associated with mental illness symptom deterioration in a majority of those patients, with the symptom deterioration being severe for more than half of those affected and 17.17%–38.01% of patients with HMB needing a professional gynecological medical intervention. The destructive influence of HMB in these patients was most prevalent in women diagnosed with BP. Our analyses revealed additional valuable information in multiple areas important for quality of care as elaborated below.

In the present study sample, HMB was more prevalent in patients with BP than in patients with MDD or SCZ. The reasons for this differentiation are not known and worthy of exploring in future studies. We found that high blood sugar levels were associated with HMB risk in patients with BP. Patients with BP had higher rates of menstrual dysfunction in our sample than in several previous studies (Rasgon et al., 2005a; Rasgon et al., 2005b; Konicki et al., 2021). Half of the BP patients with HMB in our sample were diagnosed with menstrual dysfunction before being diagnosed with BP. Meanwhile 38% developed menstrual dysfunction only after starting psychiatric pharmacotherapy, ~80% of whom experienced menstrual flow increases, including HMB or prolonged bleeding. HMB was particularly prevalent among patients with BP who were taking valproate (Vuong et al., 2014; Fu et al., 2020; Konicki et al., 2021). Serum testosterone increases induced by valproate may contribute to the development of HMB (Bilo and Meo, 2008; Flores-Ramos et al., 2020; Kenna et al., 2009; McAllister-Williams, 2006; O'Donovan et al., 2002; Rasgon et al., 2005b; Zhang et al., 2016). Notably, in 2018, Elboga et al. reported the case of a boy who had manic episode after being given testosterone replacement therapy for hypogonadotropic hypogonadism (Elboga and Sayiner, 2018).

The frequency of HMB periods experienced was found to be influenced by blood sugar levels, cumulative medication dosages, and HbA1c changes emerging within 2–3 months after accepting treatment. Indeed, HbA1c and age (<30 years) were found to be persistent risk factors for treatment-associated HMB across the diagnostic groups. Among patients with SCZ, hyper-prolactin, high TC, high triglyceride levels, and an overweight BMI before treatment were all found to be risk factors for subsequent HMB. It remains to be determined in prospective cohort studies whether blood sugar disturbances are causative of or consequential to HMB. Notwithstanding, these findings indicate that physicians managing the cases of young women with mental illnesses should be attentive to changes in HbA1c and blood sugar, particularly in relation to monitoring cumulative medication dosage and medication phases.

Although patients with menstrual dysfunction of any kind in our study were found to have elevated levels of prolactin, estrogen, progesterone, and testosterone, those with HMB per se did not have significantly elevated levels, and the frequency of HMB periods did not correlate with prolactin levels, consistent with previous studies (Lethaby et al., 2015). The need for a gynecological intervention was also not found to be related to prolactin level, neither was it related to estrogen, progesterone, or testosterone levels.

Medication-induced menstrual dysfunction could be due to drug-induced disruption of the hypothalamic-pituitary-ovarian (H-P-O) axis, thus altering the estrogen and progesterone cycles that regulate menstruation (Kadir and Davies, 2013; Bradley and Gueye, 2016; James, 2016; Ryan, 2017; Thomas et al., 2020; Ramalho et al., 2021). HMB may follow several months of amenorrhea/oligomenorrhea during which the endometrium could not fall off normally, which can cause endometrial hyperplasia (Kadir and Davies, 2013; Bradley and Gueye, 2016; James, 2016; Thomas et al., 2020; Ramalho et al., 2021). According to this view, HMB may reflect a disorder of estrogen and progesterone secretion, independent of hyper-prolactin. In women with BP, valproate has been reported to induce hyperandrogenism, which leads to oligomenorrhea, consistent with an H-P-O disturbance (Death et al., 2005; Joffe et al., 2006a; Bilo and Meo, 2008; Sidhu et al., 2018). Notwithstanding, pharmacotherapeutic-induced hyper-prolactin reflects a cryptorrhea phenomenon, the effects of which should be elucidated in a prospective cohort study. Psychiatric medications have secondary effects on the hemic system (Dahl, 1986; Krieger et al., 2004; Dietrich-Muszalska and Wachowicz, 2017; Pavlidi et al., 2021), and thus can cause or exacerbate coagulation disorders and abnormal bleeding, which can lead to HMB in women (Yasui-Furukori et al., 2012; Kranz et al., 2021). Although the precise mechanisms underlying these drug effects are unknown, physicians should be screening for HMB in the course of female psychiatric patient monitoring.

Surprisingly, among the cognitive functions followed, impaired visual learning performance emerged as being strongly associated with HMB. The reasons for this association are difficult to speculate about, but certainly worthy of future examination.

Lithium was unique among the analyzed medications in that it seemed to be a protective factor against HMB. Interestingly, lithium has also been shown to be a protective factor against cognitive impairment (Matsunaga et al., 2015; Ochoa, 2022). However, to the best of our knowledge, lithium effects on cognitive performance cannot explain its protective influence on HMB in women with severe mental illnesses.

HMB awareness among psychiatrists was found to be abysmal at 2.28%, particularly given the substantial prevalence of HMB in the patient population served by the surveyed psychiatrists. Common remedies for menstrual dysfunction, including aripiprazole and traditional Chinese medicines, were ineffective for alleviating HMB in our patient sample. Thus, there is an urgent need to alert psychiatrists of this epidemiological information, especially those who treat women with BP.

This study had a number of limitations that warrant discussion. First, it was a retrospective study employing the PABC to assess HMB history. The validity of the PBAC for assessing menstrual bleeding in prior months needs to be confirmed. The patients in this sample were confirmed to have a good memory according to the Wechsler memory scale and used the last menstrual bleeding status as a reference standard.

Second, although our data pointed to blood sugar variables, including HbA1c, as risk factors for HMB. Even HbA1c, which can only reflect blood sugar alterations over the preceding 3 months, cannot reflect 18 months of physiological history. Although our data support the view that HbA1c alterations may trigger HMB (Sharawy et al., 2016; van Baar et al., 2022), the mechanisms of such an effect, if true, remain to be clarified.

Third, although valproate use, theoretically, might explain the observed higher incidence of HMD in BP patients than in the MDD and SCZ groups due to valproate disruption of the H-P-O axis, nearly half of the patients in the MDD and SCZ groups were using valproate as a synergist. In a prior study of patients with SCZ, antipsychotic agents were not significantly related to testosterone or estradiol levels (O'Donovan et al., 2002). Although antidepressants cannot induce testosterone upregulation, testosterone has been reported to have an antidepressive effect by way of its reducing influence on monoamine oxidase A levels [88]. Related to this concern, as discussed above, our data do not enable us to disentangle how high blood sugar levels and hyperprolactinemia may influence HMB risk via effects on the H-P-O-axis. Thus, there are as yet to be clarified sophisticated relationships among therapeutic agents and H-P-O axis pathways.

Although obesity has been previously associated with HMB risk (Seif et al., 2015), the present data cannot confirm this putative relationship because antipsychotic medication use itself was associated with increasing BMI in women with SCZ. Additionally, we did not assess HMB prior to mental illness onset. Although we did not find an association between ECT and HMB, a minor portion of our sample received ECT and thus we are not confident in ruling out a possible association.

Notably, the remedies recommended to our patients for menstrual dysfunction, primarily aripiprazole and traditional Chinese medicines did not normalize menstrual function. Indeed, remarkably, every individual in our sample (N = 3,094) reported having irregular menstrual periods. Finally, the results obtained in the present treatment-resistant patient sample may not generalize to treatment response patients; only ~30% of

patients with BP, MDD, or SCZ (beyond this study) are treatment resistant.

CONCLUSION

The present study yielded five pivotal pieces of clinical reference information. 1) The risk for HMB in young adult women is substantial. 2) Psychiatric medications may induce hyperglycemia and poor visual learning performance within three treatment months, and medication dosage is related to HMB risk. Thus, healthcare providers should be screening for the emergence of HMB and adjust treatment plans accordingly. 3) Women with BP who are treated with valproate are at heightened risk of HMB, suggesting that perhaps valproate therapy should be prescribed less frequently for BP, at least in young women. 4) Lithium is a protective factor against HMB. Finally, 5) psychiatrists' awareness of HMB risk in women with severe mental illness is extremely low. Hence, there is a need to inform psychiatric clinicians of the need to pay attention to HMB risk.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethic committee of Tianjin Fourth Center Hospital of Tianjin Medical University (No. ZC-R-0001). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CJZ, HT, WL, WY, and CZ conceived and designed this study. JS, CZ, XS, and HW contributed to data analysis and interpretation, wrote and revised the manuscript. XM, RL, HY, GC, JS, JZ, ZC, CL, LC, GC, YX, SL, CZ, QL, YZ, SJ, CXL, QZ, LL, LY, JC, and QL contributed to data collection, analysis and interpretation.

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