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 glycated hemoglobin (HbA1c) level was a strong risk factor for HMB [BP: OR, 19.39 (95%CI 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,
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; Barnet, 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; Solé et al., 2017; Bekhbat 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). 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; 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 | 40.9 ± 9.0 |
| Pre-treatment BMI | 20.8 ± 2.5 | 21.9 ± 2.2 | 22.5 ± 2.8 | 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 ± 0.5 | 2.0 ± 0.4 | 2.2 ± 0.4 | 2.1 ± 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, % | 4.8 ± 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 | 2.3 ± 1.1 | 2.1 ± 0.5 | 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 | 1,220.9 ± 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/L | 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 ± 1.0 | 2.9 ± 0.8 |
| Prolactin, ng/ml | 2,158.6 ± 797.2 | 1,754.4 ± 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 | 758 (88.4) | 1,001 (96.4) | 1,145 (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 |

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.

*mo*, 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 ± 88,115.2 | 324,041.0 ± 94,638.3 | 275,796.7 ± 123,914.7 |
| Fluoxetine equivalent, mg | 2,046.78 ± 6,813.3 | 2,161.7 ± 5,430.8 | 18,660.8 ± 6,006.9 | 20,328.2 ± 534.0 |
| Valproate equivalent, mg | 973,003.5 ± 613,026 | 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                  | 634 (74.19) | 852 (81.22) | 1,027 (86.3) | 2,513 (71.22) |
| Yes                  | 221 (25.81) | 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         | 530 (62.0) | 364 (85.2) | 592 (49.7) | 1,806 (58.4) |
| No. ECT sessions     | 43 (38.01) | 55 (65.8) | 98 (50.3) | 1,288 (41.6) |
| HMB-related anemia treatment | 137 (61.99) | 154 (78.17) | 135 (68.83) | 426 (67.15) |
| Yes                  | 84 (38.01) | 43 (21.83) | 28 (17.17) | 155 (32.85) |
| Nutrition change only for HMB-related anemia | No | 137 (100) | 154 (100) | 135 (100) | 426 (100) |
| Yes                  | 842 (94.85) | 1,035 (98.7) | 1,176 (98.8) | 3,053 (98.7) |
| Patient knows HMB is a side effect of drugs | 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) |
| Doctor said HMB is a side effect of drugs | 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) |
| Pharmacotherapy for menstrual dysfunction | No | 810 (94.74) | 977 (93.14) | 245 (20.59) | 2,032 (68.77) |
| Yes                  | 45 (5.26) | 72 (6.86) | 945 (79.41) | 1,062 (3.23) |
| 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 | <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 (18.79) | 25 (15.15) | 103 (16.59) |
| ≥50%                 | 118 (53.39) | 98 (49.74) | 86 (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
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.

Table 3: Comparison of MCCB scores before treatment, after 3 months treatment, and at study enrollment.

| Time of assessment | MCCB dimension | BP       | MDD      | SCZ       | Inter-group ANOVA p |
|--------------------|----------------|----------|----------|-----------|---------------------|
| Before treatment   | Speed procession | 35.30 ± 4.55 | 35.14 ± 4.25 | 34.07 ± 3.20 | 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 ± 2.67 | 0.735 |
|                    | Visual learning    | 36.56 ± 6.23 | 36.09 ± 3.12 | 37.03 ± 1.88 | 0.702 |
|                    | Reasoning          | 37.28 ± 2.58 | 39.24 ± 3.98 | 39.91 ± 3.89 | 0.825 |
|                    | Social recognition | 38.98 ± 5.84 | 37.15 ± 3.69 | 32.93 ± 7.78 | 0.920 |
|                    | Composite          | 30.03 ± 2.70 | 31.26 ± 3.09 | 30.99 ± 3.76 | 0.911 |
| 2 ~ 3 months from accepting 1st 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 ± 1.86 | 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 ± 0.43 | 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

| Time of assessment | MCCB dimension | BP       | MDD      | SCZ       | ANOVA p |
|--------------------|----------------|----------|----------|-----------|---------|
| 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

| Time of assessment | MCCB dimension | BP       | MDD      | SCZ       | —         |
|--------------------|----------------|----------|----------|-----------|-----------|
| 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.

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                                | BP              | MDD             | SCZ             | All              |
|---------------------------------------|-----------------|-----------------|-----------------|------------------|
| **Diagnosis**                         | SCZ             | MDD             | SCZ             | SCZ              |
| Age <30 years                         | 5.93 (3.89–9.44)| 3.45 (2.17–7.88)| 3.45 (2.17–7.88)| 1.96 (1.15–2.40)| 3.33 (1.10–4.07) |
| Illness duration, mos                 | 1.01 (0.99–1.03)| 1.01 (0.99–1.03)| 1.01 (0.98–1.02)| 1.01 (1.00–1.02)| 1.06 (0.36–1.10) |
| 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)| 3.33 (1.10–4.07) |
| Before accepting 1st treatment        | 5.93 (3.89–9.44)| 3.45 (2.17–7.88)| 1.96 (1.15–2.40)| 3.33 (1.10–4.07)| 1.96 (1.15–2.40)| 3.33 (1.10–4.07)| 4.10 (3.43–4.91) |
| 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 (4.93–11.96)| 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 (0.96–1.08)| 0.98 (0.93–1.04)| 1.02 (0.99–1.06) |
| MD in year before this study          | Yes             | 1.0             | 1.0             | 1.0              |
| No                                    | 1.78 (0.96–4.08)| 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              |
| No                                    | 1.18 (0.16–2.54)| 0.82 (0.74–4.33)| 1.04 (0.29–4.36)| 1.00 (0.88–1.60) |
| ECT treatment 18mPreEn                 | Yes             | 1.0             | 1.0             | 1.0              |
| No                                    | 3.33 (2.22–5.01)| 2.08 (1.47–2.63)| 5.03 (3.35–7.54)| 3.35 (2.69–4.18) |
| Cumulative dosage 18mPreEn            | 2.66 (1.12–6.33)| 1.85 (1.26–8.21)| 1.77 (1.45–3.31)| 2.22 (1.96–3.56) |
| Antipsychotica                        | 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                         | 2.71 (1.70–5.75)| 4.13 (2.70–8.81)| 3.21 (1.90–5.40)| 1.95 (1.76–5.19) |
| Anti-mania agent                       | 0.20 (0.12–0.49)| 0.29 (0.17–0.48)| 0.49 (0.20–0.97)| 0.60 (0.31–0.99) |
| Mood stabilizer                        | 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                             | 1.46 (0.19–11.31)| 0.27 (0.17–0.50)| 2.65 (0.13–52.45)| 1.18 (0.25–5.67) |
| Spasmolytic                            | 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                       | 2.52 (0.65–4.80)| 1.60 (0.85–2.46)| 1.97 (0.67–4.05)| 2.28 (0.73–5.25) |
| Antipsychiatric                        | 1.27 (0.56–4.99)| 0.89 (0.75–1.37)| 1.44 (0.93–2.66)| 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) |

*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 in the total sample.

| Factor | BP (95% CI) | SCZ (95% CI) | MDD (95% CI) | All (95% CI) |
|--------|-------------|--------------|--------------|--------------|
| Age <30 years | 4.89 (2.21–8.59) | 1.87 (1.10–3.56) | 3.12 (2.19–7.87) | 2.87 (1.09–7.97) |
| HbA1c | 19.39 (16.60–23.01) | 2.33 (1.76–3.09) | 12.69 (4.59–37.8) | 2.89 (1.55–5.37) |
| FBS* | 18.57 (11.85–119.81) | 9.59 (6.14–12.43) | 9.97 (7.52–13.49) | 40.87 (16.50–65.23) |
| PBG-2h* | 9.22 (6.48–12.35) | 8.53 (6.15–12.61) | 8.44 (4.63–13.44) | 1.75 (1.33–2.29) |
| Visual learning* | 14.12 (11.15–15.99) | 13.19 (7.80–15.08) | 10.00 (10.37–14.08) | 6.58 (2.17–10.81) |
| ECT treatment | 3.11 (1.19–5.00) | 9.03 (7.15–12.30) | 5.55 (2.94–12.87) | 1.92 (1.13–3.28) |

Cumulative dose

| Antipsychotic | 5.51 (3.89–11.52) | 2.22 (1.23–4.55) | 1.87 (1.30–4.10) | 3.52 (1.58–12.15) |
| Antidepressant | 1.14 (1.02–2.88) | 1.87 (1.27–6.00) | 9.03 (7.23–12.48) | 2.28 (1.22–11.00) |
| Valproate | 16.00 (12.74–20.22) | 4.12 (2.66–9.50) | 4.88 (1.24–7.03) | 4.59 (2.85–9.60) |
| Lithium | 0.22 (0.14–0.40) | 11.99 (6.74–14.44) | 0.30 (0.20–0.62) | 0.50 (0.09–0.99) |

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.

**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 (Nikolouloupoulos, 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% (197/1,049); 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 changed 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 HMB 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. 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/publication material, further inquiries can be directed to the corresponding authors.

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**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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