The problem of medicating women like the men: conceptual discussion of menstrual cycle-dependent psychopharmacology

Sun Kyoung Yum[1] iD, Sun Young Yum[2] iD and Tak Kim[1]* iD

[1]Department Obstetrics and Gynecology, Korea University Anam Hospital, Seoul 02841, Korea
[2]Department Psychiatry, New Jersey Medical School, UMDNJ, NJ, USA
*Correspondence: T. Kim; Tel: +82-2-920-6842, E-mail: tkim@kumc.or.kr
This paper was presented in part at the American Medical Association as a poster, Las Vegas, Nov 10, 2006.

Check for updates

While hormonal changes during the ovulatory cycles affect multiple body systems, medical management, including medication dosing remains largely uniform between the sexes. Little is known about sex-specific pharmacology in women. Although hormonal fluctuations of the normal menstruating process alters women's physiology and brain biochemistry, medication dosing does not consider such cyclical changes. Using schizophrenia as an example, this paper illustrates how a woman's clinical symptoms can change throughout the ovulatory cycle, leading to fluctuations in medication responses. Effects of sex steroids on the brain, clinical pharmacology are discussed. Effective medication dose may be different at different phases of the menstrual cycle. Further research is needed to better understand optimal treatment strategies in reproductive women; we present a potential clinical trial design for examining optimal medication dosing strategies for conditions that have menstruation related clinical fluctuations.

Should women receive the same medication dose throughout the menstrual cycle?

Women's hormonal milieu changes throughout her menstrual cycle. Neuromodulatory actions of ovarian steroids range from neurogenesis to neuronal death, and such effects occur in complex interaction with the brain environment, further complicated by the introduction of psychotropic medications. So, should women patients receive the same dose of medication throughout their menstrual cycle?

In the clinic, authors have observed that blood pressures, fingersticks, heart rates also have cyclical patterns. So, should antihypertensives, antidiabetics also be dosed differently throughout the menstrual cycle?

This paper intends to stimulate discussions that we may need to reconsider current medication dosing strategies in reproductive women. We will use schizophrenia with catamenial presentations as an example to illustrate the problem.

Catamenial presentation of schizophrenia in women

Experienced nurses in psychiatric inpatient units know that certain women will have periods soon after they are admitted, and that these women are likely to be ready for discharge when their period ends. Psychiatric literature has extensively described psychosis related to menstruation, including hyperestrogenic cyclical psychosis,[1] recurrent menstrual psychosis,[2] atypical endogenous psychosis,[3] and periodic psychosis.[4] Patients with schizophrenia are more likely to have hospitalizations and recurrence of psychotic episodes during the premenstrual and menstrual periods.[5,6] In a ten-year follow-up of seven patients in whom psychotic episodes occurred regularly, symptom exacerbations occurred 5–10 days premenstrually and resolved by the end of menstruation. In this paper, the authors describe a patient who required psychiatric admission during menstruation with restlessness, irritability, hallucinations, and delusions of reference, but as soon as her menstruation came

Reviewer
This article was invited and reviewed by the editors of TCP.

REVIEW

to an end, complete remission seemed to have taken place, but with menses, severe psychomotor excitement returned.[3]

In psychiatric practice, women patients are often viewed as having more complaints, complex symptoms, erratic clinical courses, wanting more attention, perhaps less reliable historians, more sensitive, imaginative, and fragile. In clinical settings, it is not uncommon for a woman patient with schizophrenia to have multiple diagnoses, and frequent disagreements among psychiatrists about the main diagnosis. As described in couple century-old literature as well as anecdotal cases cited in the preceding paragraph, women patients who were thought to be stabilized may suddenly present with symptom worsening despite no discernible precipitant while reporting medication compliance. They may also present with an adverse reaction to a medication they have been responding well to. Such unexpected visits are often unwelcomed and many of these women end up with multiple additional labels on their charts, including personality disorders. Perhaps the answer lies in continuous changes in the hormonal milieu.

There is abundant literature on population level epidemiologic look at women vs. men in disease expression, comorbidities, role of life events, treatment outcome, disability, and mortality. There is remarkable paucity of literature on what happens to individual women throughout the menstrual cycle.

Clinical example of a woman who needed menstrual cycle-dependent medication dosing

A 33-year-old woman received numerous antipsychotic medications since age 19 for treatment refractory schizophrenia. Volatility in her psychopathology was reflected in numerous comorbid psychiatric diagnoses over the years.

The patient is an educated, intelligent woman with good premorbid function. However, since the onset of illness, her social function had significantly declined, and she has not been able to maintain work for more than a month at most. Past clinical history noted multiple episodes of rapid psychotic decompensations, often within a week of starting a new job. She became neglectful of personal hygiene, with incomprehensible thought processes accompanied by uncontrollable outbursts of rage.

During initial evaluations, the patient demonstrated unremarkable gross psychopathology. Subsequently, she was noted to have periods of unprecipitated intolerable anger accompanied by auditory hallucinations, paranoia, gross conceptual disorganization, inability to resist intrusive thoughts, bizarre rituals, and affective lability despite being compliant with the treatment regimen.

For a period of approximately seven months following initial evaluations, she remained fairly stable during her visits, but made occasional cancellations with phone messages stating her inability to leave the house due to being "too fat," fears of hitting babies if she were to drive and dangerous accidents if she were to use public transportations, and of "demons." After each odd message, she would return the following week pleasant, intelli-

gible, and reasonable, with no overt symptom. She had two unexpected crisis visits, one with a suicide note in hand following a physical altercation with her brother, the other after making several confrontational visits with other doctors and a patient advocate to report abusive doctors from several years ago. During the latter visit, she presented with a disheveled appearance and well-formed bizarre persecutory delusions about her psychiatrist, neighbors, and friends.

While increase in antipsychotic dosage invariably led to better symptom control, it also eventually caused adverse effects, including complaints of stiffness and tremors, constipation, dry mouth, excessive somnolence, and inability to feel full and constant hunger. Reduction in dose resulted in relapses, triggering a vicious cycle. Review of the extended clinical record indicated that previous psychiatrists had also noted wide fluctuations in psychopathology. Cancellations, decompensations, and crisis situations seemed to have occurred at approximately monthly intervals. The patient associated some of her symptoms with the premenstrual period, such as anger, sleep problems, and reported that the world around her seemed louder. Derogatory and sometimes commanding auditory hallucinations were intermittent, but no associations were made. The patient was able to predict upcoming menses with breast enlargement, bloating, "water retention"; for one or two days before her period, she reported an uncontrollable appetite and sweet cravings.

The patient was given a mood diary to log daily mood, anxiety, hallucinations, hours of sleep, and menstruation. She was prescribed as-needed doses of antipsychotic medication for self-titration based on symptoms in addition to a continuous standing dose. Psychotherapy frequency and session duration remained approximately the same as for the nine prior years.

A serial psychopathological evaluation was performed at each visit with the Positive and Negative Symptom Scale (PANSS). The scores ranged from 13–26 for positive symptoms, 14–26 for negative symptoms, 32–60 for general symptoms, and 59–110 total scores during the follow-up period, reflecting wide fluctuations in psychopathology from minimal symptoms to moderately severe psychosis.

A basal hormone assay during the early follicular phase was performed including thyroid stimulating hormone, prolactin, fasting glucose, estradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and dehydroepiandrosterone (DHEA) was within the normal range for the cycle day. LH/FSH ratio was 3.55 (patient's body mass index = 23.8). Total testosterone was marginally elevated at 71 ng/dL (reference range 15–70 ng/dL) with 1.7% free testosterone (reference range 0.5–1.8%). She had never been sexually active, and had never taken oral contraceptives or other hormone supplements. Menstruation intervals were thirty-one to thirty-five days, four to five days in duration, and reportedly included unbearably large amounts of bleeding, often wetting seats and beds. She had not noted any change in her menstruation quality and amount since menarche except two periods of amenorrhea associated with

hyperprolactinemia while on perphenazine and risperidone, both of which resolved with a change of medication.

The patient had multiple dose changes in olanzapine orally disintegrating tablet (ODT) from 2.5 mg to 20 mg, with periods of non-compliance over the past year prior to starting self-dosing. Review of extended medical chart over approximately 10 years showed multiple antipsychotic medication and dose changes. The patient was prescribed olanzapine ODT 5 mg q pm, plus 5–10 mg q hs prn.

Subjective and objective measures of symptom worsening were observed to occur premenstrually (Fig. 1). Medication side effects occurred during periods clinically assessed to be follicu-
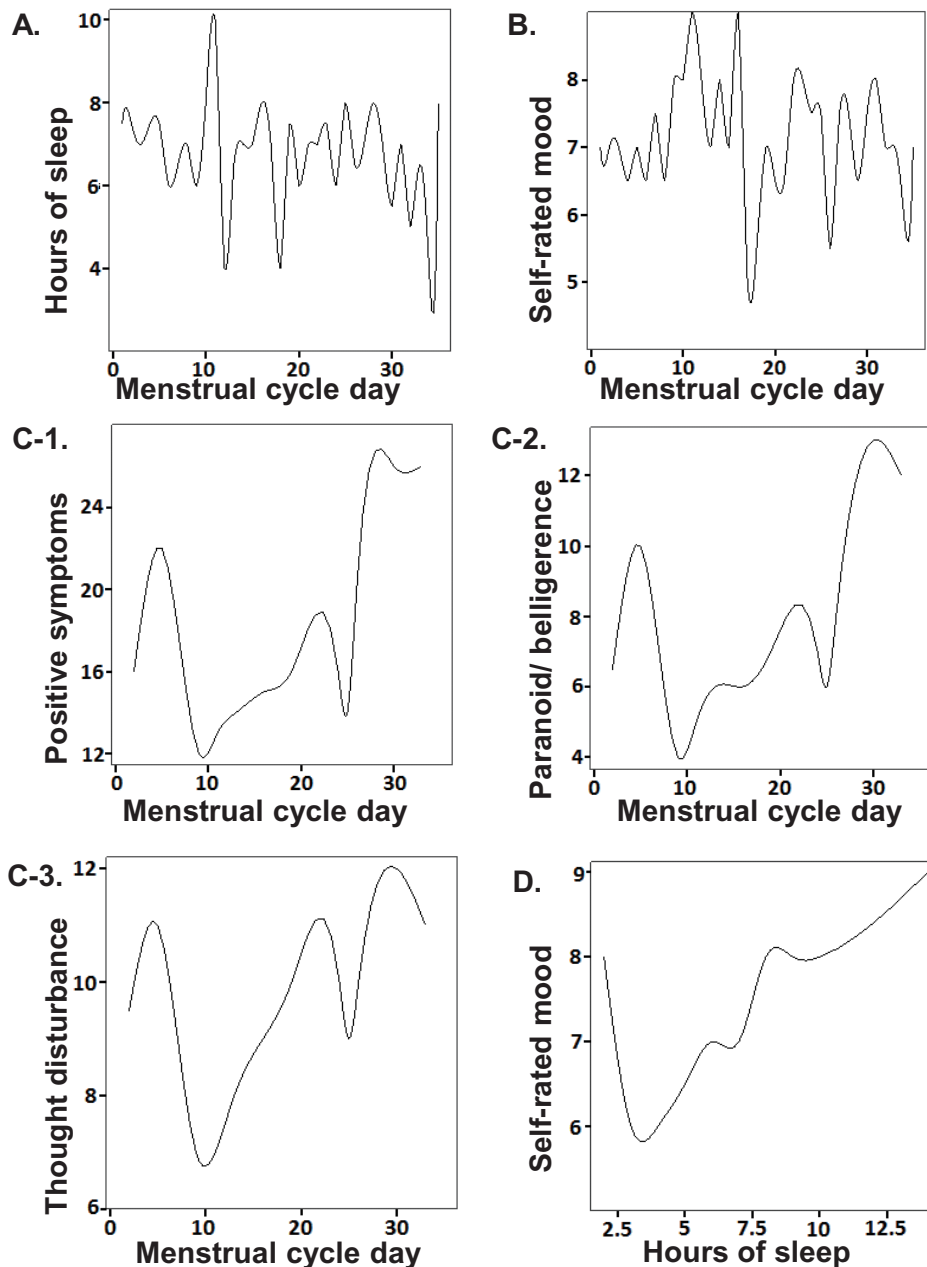

Figure 1. Patient's records of sleep and subjective moods, and clinician-observed of psychopathology in an ovulatory cycle. Cycle day 1 = first day of the period. The median values for each cycle day over 9 cycles (254 days) prior to sustained clinical stability are represented, including the period of clinician-only ratings prior to beginning the patient's 123 days of self-monitoring. (A) hours of sleep, (B) patient-rated moods (1-10: 1 = lowest ever, 10 = highest ever, 5 = usual in the past year), (C) PANSS factor scores: (C-1) positive psychotic symptoms, (C-2) paranoid/ belligerence, (C-3) thought disturbance, (D) relationship between hours of sleep and self-rated mood.

lar phases. With self-titration and monitoring, the patient was able to develop a system to prevent decompensation by early detection of subtle changes in sleep, irritability, and anxiety. Subjective mood rating alone was not an effective self-monitoring tool, as psychotic decompensations were often preceded by insomnia with expansive moods (Fig. 1D). She settled at olanzapine in ODT 5–15 mg/day, with higher doses used perimenstrually. The patient found the ODT formulation to be easier to self-titrate than the tablets due to what she described as faster and more reliable time to effect. She had residual symptoms at these doses, but learned to cognitively compensate for them, and is able to ignore voices and functionally resist disabling compulsions and paranoid thoughts. Her other medication was unchanged, maintained on extended-release venlafaxine 150 mg/day.

With a flexible antipsychotic treatment regimen, the patient maintained clinical stability for a year with a stable job and relationship for the first time in her life.

Case discussions

Comorbid PMDD and PCOS

It is difficult to discern which symptoms change as a result of changes in ovarian steroids. It is also difficult to decide whether patients have menstrual worsening of existing psychotic disorder or psychotic disorder comorbid with a menstrual disorder. In this patient, excessive somnolence during the follicular phase is likely to have been an adverse medication reaction. An alternative explanation is a compensation for premenstrual sleep deprivation. Patient's insomnia prior to menses and notable changes in appetite, sweet cravings, along with anger, affective lability, and other psychiatric and physical symptom worsening also suggest the possibility of schizophrenia with comorbid premenstrual dysphoric disorder (PMDD). It is also possible that premenstrual changes in the hormonal milieu and consequent sleep deprivation led to the worsening of psychiatric symptoms. Although the patient does not meet strict criteria, many reproductive endocrinologists may consider treating this patient clinically as having polycystic ovarian syndrome (PCOS). PCOS may be as common as metabolic syndrome in patients with schizophrenia, with a potential relationship to antipsychotic use.[7]

It is unknown what proportion of women with schizophrenia have cyclical changes in psychiatric symptoms or what proportion of ovulatory cycles are symptomatic. Only a subgroup of patients with schizophrenia exhibit cyclical psychoses in clinical practice. In these patients, not all cycles have prominent fluctuations in psychiatric symptoms. This may be because not all menstrual bleeds were preceded by ovulation (e.g. due to PCOS). Also in PMS or PMDD, not all cycles are symptomatic.

Estrogen and sensory gating

In the clinical example, the patient's experience of "increas-ingly loud environments" progressing to auditory hallucinations preceding her menses may be associated with changes in sensorimotor gating. Gating deficit is thought to be a main endophenotype of schizophrenia and appears to be attenuated by estrogen. Animal models show that estrogen withdrawal resulted in reduced sensorimotor gating associated with altered forebrain dopamine systems.[8,9] In healthy women, estrogen administration prevented prepulse inhibition deficits induced by serotonin 1A receptor activation.[10]

Dopamine-Estrogen interactions

Dopamine levels in the prefrontal cortex seem to depend on the phase of the estrous cycle and may account for the changes in drug sensitivity throughout the cycle.[11] Estradiol has been shown to downregulate dopamine transmission.[12] Downregulation of dopamine transmission by estradiol is thought to mimic or augment antidopaminergic action of antipsychotic medications. In clinical patients with schizophrenia, adjunctive estradiol with antipsychotic treatment led to more rapid improvement in psychotic symptoms.[13] Efforts to prevent menstrual psychosis with contraceptives have included monophasic oral[2,13] and transdermal contraceptives.[14] However, the long-term efficacy and risks of estrogen augmentation are unknown, especially additive risks of thromboembolism from contraceptive and antipsychotic combination.

Drug adverse reactions also seem to be affected by the menstrual cycle. Stiffness and tremors, in this case, were interpreted to be extrapyramidal symptoms (EPS). EPS are reportedly more frequently in women, which may be attributed to additive effects of estrogens and antipsychotics in dopaminergic receptor blockade.[15] Although literature search did not find associations between EPS and menstrual cycle, it is biologically plausible that with the same dose of antipsychotic medication, the emergence of EPS is more likely during periods of high estrogen availability in the brain.

Olanzapine pharmacology in women

In a study of olanzapine plasma concentrations by sex, women had higher concentrations of olanzapine.[16] Olanzapine is mainly metabolized through CYP1A2, which is suggested to be less active in women,[17] likely explaining the low dose of antipsychotic needed for symptom control. It is also speculated that steroid hormones have an effect on CYP1A2 expression,[18] suggesting the possibility of menstrual cycle-related changes in the pharmacokinetics of olanzapine. Glucuronidation is also a major mode of metabolism for olanzapine. Olanzapine efficacy is affected by Pgp and COMT polymorphisms. These are discussed further in the clinical pharmacology section that follows.

Brain biology continues to change throughout the menstrual cycle

There is sexual dimorphism in brain development, organization, and degeneration. The female brain develops differently

and ages differently. Moreover, the neurobiology of the female brain changes throughout the menstrual cycle. Through modulation of gene transcription, ovarian steroid hormones play important roles in all stages of neural development, including neurogenesis, synaptogenesis, neural migration, growth, differentiation, survival, and death. The ovarian steroid hormones modulate the synthesis of metabolic enzymes and receptor proteins for many neurotransmitters and neuropeptides. In addition to nuclear events, rapid effects are observed from events at the cell surface through ion channels and second-messenger systems. Effects of sex steroids occur in complex interactions with the environment, including expression and activation of co-regulators and tissue-specificity.[20]

Sex steroids affect clinical pharmacology

In the systemic circulation, various factors may lead to sex differences in pharmacokinetics.[21] In a subgroup of women with bipolar disorders, phasic differences in lithium levels were observed.[22] Lower gastric acid secretion in reproductive-age women and prolonged gastrointestinal transit time during the luteal phase may result in sex-related or menstrual cycle variations in drug absorption. The volume of distribution may have sex-differences owing to differences in adiposity as well as menstrual cycle variations associated with changes in fluid retention and transcapillary fluid dynamics. Changes in hepatic microsomal oxidase systems may occur due to changes in levels of sex hormones, and interindividual genetic variations, such as polymorphisms in CYPs, will influence hormone metabolism.

In addition to phase I metabolism, it is also important to think about phase II metabolism in women as steroids undergo glucuronidation. UGTs are found in all sites where membranes/barriers are important, including the brain. Also, COMT is sexually dimorphic.

In contrast to the drug-metabolizing enzyme data, relatively little information is available concerning the transporters that govern the disposition of estradiol and its metabolites. With relevance to the brain, estradiol is a substrate of ABCB1, also known as P-glycoprotein (P-gp), while testosterone, progesterone are inhibitors of ABCB1. Sex hormones also seem to affect the brain permeability of various substances, including nutrients via alterations of paracellular[23] and transcellular[24] transport across the blood-brain barrier. Psychotropic medications that are substrates or inhibitors of these transporters need additional attention.

Menstrual-cycle dependent medication dosing may be better calculated by clinical response time than the drug's pharmacokinetic properties. This is because sex steroids act through both genomic and nongenomic mechanisms with different latency of effects. Perhaps individual variability in gene expression (e.g., due to epigenetic factors) could lead to different symptomatic periods, e.g., for some women immediately premenstrual, for some, at the initiation of menses, for some a week before menses, etc. Adding to the complexity is that apparently paradoxical responses may be observed because a metabolite may have opposite effects on the parent hormone.

Proposal for future research

The concept of adjusting medication dosages with the ovulatory cycle in reproductive women warrants further studies in schizophrenia, as well as, in other medical illnesses in which ovarian hormones may affect the symptom manifestations and drug treatment responses.

We propose a potential clinical study design for studying sex-specific medication dosing (a schematic representation in Figure 2). The study will mainly comprise of two phases: (1) lead in observational phase followed by (2) randomized
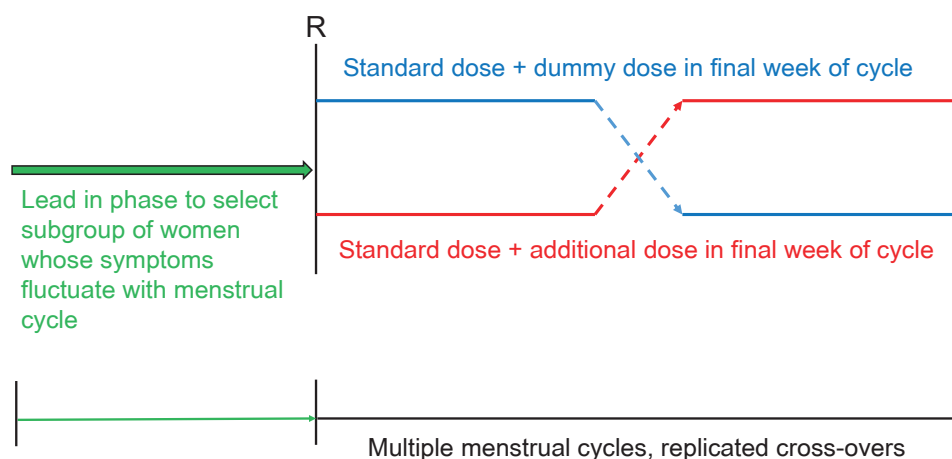

Figure 2. The first phase of the study will prospectively assess symptom changes throughout the menstrual cycles on continuous fixed-dose treatment. For patients who have less than 2 of 3 symptomatic cycles, the trial ends after the lead-in phase. Those with at least 2 of 3 symptomatic cycles will progress to the second phase of the trial. All patients will continue to receive the standard fixed-dose. Patients are randomized to receive an additional dose premenstrually of either medication or dummy. The patients are crossed-over to the other group multiple times.

replicated cross-overs, and an optional observational extension phase.

The first phase of the study will prospectively assess symptom changes throughout the menstrual cycles on continuous fixed-dose treatment, with a rescue treatment option. The lead-in phase will require multiple cycles to see the individual ratio of symptomatic and asymptomatic cycles. Patients who have at least two out of three cycles during which symptoms exhibit menstrual changes will proceed to the second phase of the study. For patients with fewer symptomatic cycles, the trial stops after the initial observational phase. Observation over increasing number of cycles will allow better examination of the proportion of cycles involved as well as the extent of symptom changes. Limiting the observational phase to three cycles would yield a more practical trial than a more extended first phase. The National Institute of Mental Health (NIMH) diagnosis of premenstrual syndrome (PMS) proposed two out of three cycles of increased sadness or anxiety/irritability.[25] ICHD-II requires that headaches meeting migraine criteria occur in two of three menstrual cycles during a five-day window extending from two days before to three days after menses.[26] Although prospective assessment of cycle-related changes is recommended to minimize recall bias, for patient groups that are able to give a more reliable history, the lead-in phase could potentially be replaced with a historical assessment of menstrual-related symptom changes.

The threshold for categorically defining symptomatic vs. asymptomatic cycles is not established. For PMS, NIMH proposed at least a 30-percent change in symptoms between the pre-and post-menstrual weeks of their monthly cycles.[25] Smith and colleagues[27] studied variable premenstrual and post-menstrual thresholds for refining the accuracy of capturing symptomatic cycles in PMS.

We think the definition of symptomatic and asymptomatic cycles will have to be defined individually for each medical condition. For example, the threshold for change may differ for positive psychotic symptoms, affective symptoms, pain, blood sugar, blood pressure, etc. However, each threshold should take into consideration the impact on clinical outcomes, such as patient distress or physician observed clinical decline.

In the second phase of the trial, all patients will continue to receive a standard fixed-dose from the lead-in phase. Patients are randomized to receive an additional dose premenstrually of either medication or dummy. The patients are crossed-over to the other group multiple times. Replicated crossovers will allow estimation of intra-subject variability and separation of the effects of sequence and carry-over. We propose that the second phase be four to six menstrual cycles. The amount and timing of the additional dose should reflect the extent of symptom changes and the medication's time to clinical onset. Alternatively, the second phase may allow additional self-dosing as needed with a predefined maximum dose.

Lastly, following interim analysis of the second phase of the trial, those patients who benefited from additional premenstrual dosing can enter an optional open-label observational extension phase. This phase will allow medication dosage fine-tuning.

Despite the perceived difficulties, collective efforts are needed to adequately serve a significant portion of the patient population—women.[28]

Conclusion

For reproductive women, clinical care needs to consider hormonal and clinical changes with the menstrual cycle.

Further research is needed to understand the disease phenomena better and find optimal treatment strategies in women whose clinical manifestations change with cyclical changes in ovarian hormones. However, the results of such randomized clinical trials should never negate the variable symptom manifestations and treatment responses in individual clinical patients. Multidisciplinary collaborations are needed for sex-specific medicine.

Acknowledgments

Conflict of interest

- Authors: Nothing to declare
- Reviewers: Nothing to declare
- Editors: Nothing to declare

References

1. Lingjaerde P, Bredland R. Hyperestrogenic cyclic psychosis. Acta Psychiatr Neurol Scand 1954;29:355-364.

2. Felthous AR, Robinson DB, Conroy RW. Prevention of recurrent menstrual psychosis by an oral contraceptive. Am J Psychiatry 1980;137:245-246.

3. Endo M, Daiguji M, Asano Y, Yamashita I, Takahashi S. Periodic psychosis recurring in association with menstrual cycle. J Clin Psychiatry 1978;39:456-466.

4. Berlin FS, Bergey GK, Money J. Periodic psychosis of puberty: a case report. Am J Psychiatry 1982;139:119-120.

5. Dalton K. Menstruation and acute psychiatric illnesses. Br Med J 1959;1:148-149.

6. Riecher-Rössler A, Häfner H, Dütsch-Strobel A, Oster M, Stumbaum M, van Gülick-Bailer M, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry 1994;36:492-494.

7. Yum SK, Kim T, Hwang MY. Polycystic ovaries is a disproportionate signal in pharmacovigilance data mining of second generation antipsychotics. Schizophr Res 2014;158:275-276. doi: 10.1016/j.schres.2014.06.003.

8. Byrnes EM, Bridges RS, Scanlan VF, Babb JA, Byrnes JJ.. Sensorimotor gating and dopamine function in postpartum rats. Neuropsychopharmacology 2007;2:1021-1031.

9. Dazzi L, Seu E, Cherchi G, Barbieri PP, Matzeu A, Biggio G.. Estrous cycle-dependent changes in basal and ethanol-induced activity of cortical dopaminergic neurons in the rat. Neuropsychopharmacology 2007;32:892-901.

10. Gogos A, Nathan PJ, Guille V, Croft RJ, van den Buuse M.. Estrogen prevents 5-HT1A receptor-induced disruptions of prepulse inhibition in healthy women. Neuropsychopharmacology 2006;31:885-889.

11. Riecher-Rössler A. Oestrogen effects in schizophrenia and their potential therapeutic implications--review. Arch Womens Ment Health 2002;:111-118.

12. Behrens S, Hafner H, DeVry J, Gattaz WF. Estradiol attenuates dopamine-mediated behaviour in rats: implications for sex differences in schizophrenia. Pharmacopsychiatry 1992;25:96.

13. Kulkarni J, de Castella A, Smith D, Taffe J, Keks N, Copolov D.. A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr Res 1996;20:247-252.

14. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, et al. A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. Arch Womens Ment Health 2002;5:99-104.

15. Seeman MV, Lang M. The role oestrogens in schizophrenia gender differences. Schizophr Bullettin 1990;16:185-194.

16. Kelly DL, Conley RR, Tamminga CA. Differential olanzapine plasma concentrations by sex in a fixed-dose study. Schizophr Res 1999;40:101-104.

17. Usall J, Barcelo M, Marquez M. Women and schizophrenia: sex-based pharmacotherapy. Current Psychiatry Reviews 2006;2:95-101.

18. Miners JO, McKinnon RA. CYP1A. In: Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds) Metabolic Drug Interactions. PA, Lippincott Williams & Wilkins; 2000:66.

19. Riecher-Rossler A, Hofner H, Stumbaum M, Maurer K, Schmidt R.. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull 1994;20:203-214.

20. Rubinow DR, Schmidt PJ, Meltzer-Brody S, Harsh V. The neurobiology of menstrual-cycle related mood disorders. In: Charney DS and Nestler EJ (eds) Neurobiology of Mental Illness, 3rd edn. New York, NY, Oxford University Press; 2009:544-555.

21. Yonkers KA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. Am J Psychiatry 1992;149:587-595.

22. Chamberlain S, Hahn PM, Casson P, Reid RL. Effect of menstrual cycle phase and oral contraceptive use on serum lithium levels after a loading dose of lithium in normal women. Am J Psychiatry 1990;147:907-909.

23. Cho MM, Ziats NP, Pal D, Utian WH, Gorodeski GI.. Estrogen modulates paracellular permeability of human endothelial cells by eNOS- and iNOS-related mechanisms. Am J Physiol 1999;276:C337-C349. doi: 10.1152/ajpcell.1999.276.2.C337.

24. Shi J, Simpkins JW. 17 beta-Estradiol modulation of glucose transporter 1 expression in blood-brain barrier. Am J Physiol 1997;272:E1016-E1022.

25. Rubinow DR, Roy-Byrne P. Premenstrual syndromes: overview from a methodologic perspective. Am J Psychiatry 1984 Feb;141:163-172.

26. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004:24 Suppl 1:9-160

27. Smith MJ, Schmidt PJ, Rubinow DR. Operationalizing DSM-IV criteria for PMDD: selecting symptomatic and asymptomatic cycles for research. J Psychiatr Res 2003;37:75-83.

28. Bolea-Alamanac B, Biley SJ, Lovick TA, Scheele D, Valentino R. Female psychopharmacology matters! Towards a sex-specific pharmacology. J Psychopharmacol 2018;32:125-133. doi: 10.1177/0269881117747578.