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Current Practical Progress and Dilemmas in the Study of Premenstrual Dysphoric Disorder

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Abstract: Premenstrual dysphoric disorder (PPD) refers to a range of symptoms which are related to the menstrual cycle, which is not only accompanied by severe physical symptoms, but often by severe emotional symptoms as well. This can have a serious impact not only on the patient's daily life, but also on the social costs. To date, however, the etiology of this disorder is not well understood and there are not very accurate, objective diagnostic methods or universally applicable special treatment options. This article aims to summaries some of the research literature relating to the etiology, diagnosis and treatment of PPD, over the last approximately 15 years, with a view to providing some insight into future research on PDD. The etiology of PDD may be related to 5-HT, GABAergic dysregulation and abnormal response of GABAA receptors to allopregnanolone. PDD's diagnosis relies primarily on a number of scale assessments and information from medical history and physical examination. Common first and second line treatment options are antidepressants and oral contraceptives (OCs) respectively. Symptoms of PDD can also be reduced with some psychosocial treatment.

Keywords: premenstrual dysphoric disorder (PDD), menstruation, dysphoria, women's health

1. Introduction

Premenstrual symptoms are symptoms affecting emotional and physical health that occur during the luteal phase of menstruation. It usually disappears shortly following the beginning of menstruation. Common symptoms include physical and emotional discomfort. Premenstrual syndrome（PMS）can be diagnosed as moderate to severe when these symptoms persist for two menstrual cycles [1]. Further, premenstrual dysphoric disorder (PDD) is generally considered as most severe form of PMS, a disorder featured primarily by emotional discomfort. Another necessary diagnostic criterion for PDD is that the individual exhibits clinical difficulty in learning, working, or socializing and that the condition is not triggered by another chronic illness or mental illness [2].

Moreover, PDD is classified in DSM-5 as a diagnostic category of depression [3]. Symptoms must appear within the first week before the menstrual period begins and worsen a few days after the menstrual period begins, then decrease rapidly until the symptoms disappear completely. Moreover, these symptoms should have been experienced for most of the previous year's menstrual

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cycle. What is more, there must be at least five symptoms including a 'core' symptom and other underlying symptoms Premenstrual symptoms should relate to severe distress or dysfunction, and should not simply be a worsening of symptoms of another mental illness, nor be attributed to the effects of medications, substances or medical conditions [2]. What is more, a ‘core’ symptom and other four underlying symptoms need to be observed. The 'core' symptoms of PDD are emotional instability such as irritability, anxiety or depression. Underlying symptoms can also manifest in a variety of ways, such as physical discomfort, difficulty sleeping, difficulty eating, concentration, reduced interest, loss of control and overwhelm.

A range of behavioral and psychological factors may affect individuals' PDD levels. In a study of risk factors for PMS, smoking has been found to related with an elevated risk of premenstrual disease, including PDD [4]. In addition, it is now established that traumatic events are risk factors for PDD and that they can significantly increase the probability of developing PDD at follow-up. At the same time, a history of anxiety disorder and elevated daily conflict scores predicted PDD [4].

On average, PDD last for six days, and the strongest symptoms occur between two days and the day before the onset of menstrual blood flow. There are usually emotional symptoms such as anxiety, anger and depression, which may cause serious damage to interpersonal relationships. What is more, PDD not only significantly reduces the quality of life of individual women, but also increases the social costs related to reduced productivity, truancy and absence from work and more utilization of health care services. These undoubtedly suggest that research into PDD is imperative and important. This article hopes to summaries the etiology, diagnosis and treatment of PPD through a review of previous literature, with a view to providing some insight into future research on PDD.

2. Methodology

This study was conducted mainly through a literature review. The reference documents of this article are from CNKI and Pubmed, which are almost the documents of the past 15 years, mainly including the epidemiological survey results, etiology, prevalence, comorbidity, impact on individuals and society, diagnostic tools and treatment methods of PDD.

3. Results and Discussion

The results and discussion in this article focus on some of the etiology, diagnosis and treatment options for PDD.

3.1. Etiology

Some of the current studies mainly suggest that the onset of PDD symptoms may be related to the abnormal response of allopregnanolone to GABAA receptors in PDD-susceptible women. Previous studies have found that women without fluctuating gonadal steroids do not develop PMS/PDD, nor when gonadal steroid levels are high but fairly stable (e. g. high progesterone status during pregnancy) [5]. However, some women's PMS is not related to their fluctuating progesterone. As can be seen, the symptoms of PDD are not directly explained by fluctuations in progesterone in the female body at different times. Some researchers then went further and introduced allopregnanolone and the GABAergic System into the etiological studies of PDD. The metabolite of progesterone, allopregnanolone, allows it to play a very important role in the central nervous system. Progesterone forms isoprogesterone from the joint effects of 5α-reductase and 3α-hydroxysteroid dehydrogenase. It binds to variable sites on the gamma-aminobutyric acid (GABA) reactor and serves as a strong positive regulator of the GABAA reactor, achieving increased synaptic and extrasynaptic cortical inhibition by increasing the sensitivity of the GABAA receptor to GABA which is an inhibitory

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neurotransmitter that reduces symptoms of stress, anxiety, alertness and other symptoms [6]. From the above studies, it can be inferred that PDD symptoms may arise from an abnormal response of allopregnanolone to GABAA receptors in women.

Other studies indicated that PDD symptoms is also related to a dysregulation of 5-hydroxytryptamine (5-HT) in susceptible women, and that the parts of the brain that process emotions such as anxiety are deeply affected in these patients. Previous studies have also suggested that women with PDD may exhibit 5-hydroxytryptamine(5-HT) dysregulation, as they may show reduced plasma 5-HT levels during the luteal phase and higher non-luteal 5-HT responsiveness [7]. Based on the pathological mechanism of PDD, prior study provides further discussion on the potential most effective treatment for PDD from a physiological perspective. However, this study concluded that further research on the safety of agonists is necessary. In particular, the differences in dosing for women of different age groups may be an issue worthy to be explored in depth. Moreover, side effects of the medication and the risk of abuse need to be confirmed before it is officially put into use.

3.2. Diagnostic Tools

At present, the main diagnostic tools for PDD are a number of symptom assessment scales and a past medical history, after excluding other causes (e. g. medication and other somatic diseases). Scales to assess symptoms of PDD include visual analogue scales (VAS) and Likert scales, which would focus on rating the severity of the patient's symptoms and functional items on a daily basis [8]. The prognostic scores can be used to determine the time of symptomatic onset and to preclude underlying disorders that worsen before menstruation. The prospective score can be used to determine the timing of symptom onset and to rule out potential psychiatric disorders that worsen before menstruation. In addition, clinicians can use the Premenstrual Symptom Screening Tool to assess symptoms or dysfunction during a previous period cycle in patients with PDD [9].

Currently, there are no objective criteria for the diagnosis of PDD, but current studies have explored some of the abnormalities (e. g. abnormalities in the 5-HT system) in patients with PDD by using imaging tests to detect information about functional activity and structural changes in the human brain, which may in future become an objective test to improve the accuracy and sensitivity of the diagnosis of PDD. For example, Positron Emission Computed Tomography (PET) combined with radioactive 5-HT ligand-receptor techniques have identified significant changes in 5-HT1A receptor binding in the dorsal suture nucleus from the follicular to the luteal phase relative to normal female brain, which are virtually absent in patients with PDD [10], suggesting that 5-HT system disorders may contribute to the development of PDD.

What is more, Magnetic Resonance Spectroscopy (MRS) may also provide a scientific basis for accurate diagnosis and individualised treatment of patients with PDD, as it is the only non-invasive way to detect metabolites in living tissues. One study using BOLD-fMRI found that in the late luteal phase the amygdala is more responsive to negative stimulation. In addition, the response of the amygdala to positive emotions is diminished [11]. In addition, Baller et al. demonstrated that PDD patients' activation in prefrontal areas from late luteal mindfulness to early follicular phase was positively correlated with disease duration and symptom severity, particularly in the dorsolateral prefrontal cortex, and suggested that dysfunction in the dorsolateral prefrontal cortex is a risk substrate for PDD [12]. Meanwhile, a study by the Wyatt's team found that the orbitofrontal cortex (OFC) may be an important substrate for emotional loss in PDD, as the OFC is less responsive to negative tasks and stimuli during negative moods in PDD patients [13]. In summary, PDD symptoms can be diagnosed from a variety of perspectives including questionnaire measures, biological indicator measures, and neuroscientific indicator measures. However, these diagnostic methods still need to be further popularized in practice. The monetary cost of diagnosis and the

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specialization of physicians' related competencies may be important factors that hinder the development of diagnosis regarding PDD. Therefore, it is necessary for physicians to develop a stage-specific diagnostic system for PDD. In this system, the patient's condition can be diagnosed quickly and at low time and cost. More precise biological or neurological diagnosis can be provided to the patient if needed. Current diagnostic tools for PDD tend to make retrospective diagnoses, which are somewhat unpredictable for the future development of the patient's disease. Many studies have emphasis the need for prospective diagnosis. In order to ensure the accuracy of prospective diagnosis, it is necessary to continue to study PDD in depth from psychological, physiological and neurological perspectives.

3.3. Treatments

Currently, the first and second line of treatment usually recommended for PDD are both pharmacological, namely antidepressants and OCs respectively. In addition, some psychological treatments (e. g. CBT) may also reduce the symptoms of PDD to some extent.

3.3.1. Antidepressant & Oral contraceptives (OCs)

The antidepressant SSRI is considered to be the first line of treatment for PDD. Prior study found that PDD symptoms were significantly reduced in patients with SSRIs compared to the control group [14]. Compared to placebo, SSRIs could lead to significant improvements in psychological and somatic symptoms as well as function. However, it may also cause some side effects, the most common of which are dose-related and include nausea, drowsiness, fatigue, and decreased libido. In addition, this meta-analysis study showed that the efficacy of SSRIs is somewhat short-term. In other words, SSRIs cannot be an effective treatment for patients with PDD over a longer period of time. Therefore, the research recommends combining psychotherapy with medication to maximize the treatment effect.

Second-line treatment for PDD is often considered OCs. Commonly used OCs in clinical practice include drospirenone ethinyl estradiol, levoprogesterone ethinyl estradiol, and mifepristone.

3.3.2. Other Ovulation-suppression Treatments

A study has shown that GnRH agonists improve premenstrual mood and somatic symptoms [13]. This may be because the GnRH receptors in the hypothalamus are downregulated by gonadotropin-releasing hormone (GnRH) agonists, resulting in suppression of ovulation, along with a decrease in luteinizing hormone in the pituitary gland, and ultimately progesterone as well. After relieving PDD symptoms with GnRH agonists, the medical consequences of a low estrogen state due to prolonged anovulation can often be addressed using a 'hormone supplementation' strategy. Although increased gonadal steroids due to a 'hormone supplementation' strategy may increase emotional symptoms in women, the use of the lowest possible dose of gonadal steroids may go some way to avoid reducing the efficacy of GnRH agonists in PDD [15].

3.3.3. Psychosocial Treatments

Bluth et al. conducted a mindfulness-based intervention in women with symptoms like PDD to validate the feasibility and tolerability of the treatment. The study complete before and after the mindfulness-based intervention to assess patient premenstrual symptom severity, catastrophizing, mood changes, rumination, and self-compassion, as well as pain sensitivity and cardiovascular response to mental stress. Eighty-eight percent of the participants completed all interventions and assessments in the study, and the results found that these women experienced a significant decrease

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in the severity of some premenstrual symptoms. They also had increased pain tolerance and decreased blood pressure responsiveness to stress [16].

A meta-analysis that included at least 20 relevant studies evaluated the efficacy of psychotherapy and antidepressant treatment on PDD. The study used a random-effects model as an index of effect size and ultimately obtained effect sizes for cognitive behavioral interventions (CBT) and 5-HT antidepressants. The results of this study suggest a slight advantage of CBT in reducing premenstrual symptoms, especially mood symptoms [17]. However, studies on psychotherapy for patients with PDD have not strictly controlled for additional variables, which may lead to inaccurate results. Relatively few studies have utilized structured clinical interviews to exclude possible confounding by co-morbidities. In addition, because some women do not have knowledge PDD, they often do not think that their discomfort is due to PDD. Therefore, some of the samples on the efficacy of psychotherapy for PMS may be small, and the conclusions based on this statistical analysis may not be reliable.

4. Suggestion

In summary, although changes in progesterone and its metabolites do not fully explain the pathogenesis of PDD. However, in future studies, it may be possible to investigate in more depth the abnormal biochemical responses between progesterone and its metabolites and the GABAA receptor and 5-HT in women with PDD and the links between each abnormal response. These may help to improve the clinical diagnosis and treatment options for PDD.

In addition, the diagnostic criteria currently used for PDD rely mainly on the assessment of relevant scales and the collection of information such as medical history, which are subjective and make the diagnosis of PDD cumbersome, while also increasing the likelihood of missed and/or misdiagnosis. Therefore, in the future, there is a need to further improve the objective diagnostic criteria, such as the inclusion of non-invasive imaging tests, to make the diagnosis of PDD more efficient and accurate. Due to the wide range of patients affected by PDD and the diversity of PDD symptoms, it is particularly important to develop an individualized treatment approach for patients. Current research on PDD has partially used randomized controlled trials, and future research could focus more on comparing differences between psychotherapies in the natural state.

Finally, there may also be a need to increase knowledge about PDD among women in the future community health care, so that potential PDD patients are motivated to seek treatment and help to reduce the negative impact of the disease on them and society. It is necessary for the public to realize that the physical and psychological discomfort women experience around the time of their periods is a sign of illness, not a way of faking it to gain sympathy.

5. Conclusion

PDD can have a serious impact not only on an individual's work and quality of life, but also on society. Its etiology of PDD may be related to 5-HT, GABAergic dysregulation and abnormal response of GABAA receptors to allopregnanolone. Although the diagnosis of PDD currently relies on a number of scale assessments as well as information from medical history and physical examination. However, in the future, some imaging methods may also become its objective diagnostic criteria. Both their first- and second-line treatment regimens are primarily administered through oral medications, separately antidepressants (such as SSRIs) and oral contraceptives. Some other treatments may also be effective for PDD, such as Psychosocial Treatments. However, in order to improve treatment efficiency and prognosis, future studies will need to investigate the effectiveness of single treatments and combinations of different treatments using different pathways.

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