

# Comorbid Premenstrual Dysphoric Disorder in Women with Bipolar Disorder: Management Challenges

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**Abstract:** Bipolar disorder (BD) and premenstrual dysphoric disorder (PMDD) are two cyclic mood illnesses, sometimes presenting together. Their comorbidity appears to be linked to common biological mechanisms and usually results in more severity of mood symptoms and a poorer long-term outcome. Nevertheless, the management of comorbid PMDD/BD has been scarcely studied. Therefore, the aim of the present paper was to review the published literature on the treatment of comorbid PMDD/BD and to provide point-by-point hypotheses to address these complex clinical cases. We searched PubMed to identify the studies focused on the treatment and management of comorbid PMDD/BD using the following search words, alone and in combination: premenstrual dysphoric disorder, bipolar disorder, comorbid, treatment, management, pharmacotherapy, psychotherapy. The search was conducted on the 1st of June 2019 and yielded 55 records. Four papers met our inclusion/exclusion criteria and were therefore included in our qualitative synthesis. Integrating the few data pertaining to the treatment of comorbid PMDD/BD with the large amount of published data on the two conditions separately, we can suggest that the management of comorbid PMDD/BD needs as a first step to stabilize the bipolar symptoms by means of optimal dosages of mood stabilizers. Then, in euthymic BD patients, the PMDD symptoms could be treated with estrogen-progestins (first-line treatment). On the contrary, during acute phases of BD, antidepressants (for major depressive episodes) and atypical antipsychotics/hormonal modulators (for manic episodes) could be considered as promising add-on treatments to mood stabilizers. In case of resistant PMDD/BD symptoms, combined strategies should be taken into account, as well as alternative treatments, such as lifestyle changes. In conclusion, RCTs on comorbid PMDD/BD are still lacking. The management of this complex condition is therefore challenging and it requires a tailored treatment.

**Keywords:** womens' health, comorbid mood disorders, combined intervention, treatment challenges

## Introduction

Premenstrual dysphoric disorder (PMDD), recently included in the DSM-5 Mood Disorder Section, is characterized by psychological (and sometimes physical) symptoms, such as mood swings, depression, irritability, dysphoria, that begin during the luteal phase and recede after the menses.<sup>1</sup> PMDD has an estimated prevalence of 2–7% in women during their reproductive age.<sup>2–4</sup> In a recent study on a Brazilian community sample, the prevalence of PMDD is over 15% in young adult women, probably due to cultural differences and a wider age span.<sup>5</sup> PMDD is

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often diagnosed many years after its first onset, thus resulting in a long period of untreated symptoms,<sup>6</sup> with a huge impact on functioning and quality of life.<sup>7,8</sup> Although PMDD can be observed in women without other psychiatric disorders,<sup>9</sup> comorbid conditions are reported in up to 70% of cases, especially anxiety disorder, post-traumatic stress disorder, major depression and bipolar disorder (BD).<sup>10,11</sup>

BD is a serious psychiatric illness, defined by recurrent depressive, manic and mixed episodes, separated by periods of clinical remission, with an estimated lifetime prevalence of 3–7%.<sup>12,13</sup> In a large community sample, the prevalence of BD in women with PMDD was about 10%, seven-times higher than what observed in those without PMDD.<sup>14</sup> A systematic review conducted in 2014 reported that 15–27% of women with BD met an adjunctive diagnosis of PMDD, supporting the hypothesis that a subgroup of BD may have a hormonal sensitivity.<sup>15</sup> On the other hand, retrospective ratings of PMDD are often inaccurate, with a high percentage of false-positive reports.<sup>16,17</sup> Moreover, beliefs about premenstrual syndrome were found to strongly influence the diagnosis,<sup>18–20</sup> thus suggesting the use of prospective ratings to correctly assess the prevalence of PMDD in women with and without comorbid conditions.<sup>21</sup>

BD and PMDD are two cyclic mood illnesses and their comorbidity appears to be linked to common biological mechanisms, such as polygenic risk factors. In particular, the Brain-derived neurotrophic factor (BDNF) and catechol-O-methyltransferase (COMT) polymorphisms, have been found in both conditions.<sup>22,23</sup>

However, other studies have failed to demonstrate similar pathophysiologic pathways of cyclical symptom change in PMDD and premenstrual exacerbation of chronic mood disorders. For example, PMDD-specific treatments, such as drospirenone-containing combined oral contraceptives, GnRH analogues and isallogestrol, were not effective for patients with premenstrual exacerbation of depression.<sup>24–26</sup>

Recent evidence suggests a crucial role of estradiol and progesterone in neuroregulation and the cyclic changes of their levels may significantly affect mood and behavior in susceptible women. In particular, reproductive steroids regulate the synthesis of important neurotransmitters such as dopamine, serotonin, noradrenaline, GABA and glutamate,<sup>27</sup> thus resulting in significant changes in the activation of limbic and prefrontal brain regions involved in attention,<sup>28</sup> reward<sup>29</sup> and emotional processing.<sup>30</sup> The

rapid changes of progesterone levels during the different phases of the menstrual cycle and the estrogen influence on serotonin may result in premenstrual symptoms even in case of normal ovarian function.<sup>31–33</sup>

Hormonal fluctuations during the menstrual cycle may influence the clinical course of BD: women with BD and premenstrual exacerbation of mood symptoms have a poorer outcome and shorter time to relapse.<sup>34</sup> In patients affected by BD, low levels of estrogen were found during episodes of post-partum psychosis.<sup>35</sup>

Patients with comorbid BD and PMDD showed an earlier age of BD onset, more frequent acute mood episodes and a higher rate of rapid cycling.<sup>36</sup> Two different comorbidity studies pointed out that PMDD seems to be more frequent in BD type II (BD-II), with respect to BD type I (BD-I) patients.<sup>37,38</sup> On the other hand, the possible confounding effect of a higher medication load, which might reduce the comorbidity rate suppressing the PMDD symptoms in BD-I, should be taken into account.<sup>39</sup> A recent paper by Ogasawara et al<sup>40</sup> criticizes the APA decision attributing PMDD to depressive disorders, suggesting instead to consider it an illness with several bipolar features, such as mood lability, agitation and dysphoria.

In those subjects affected by PMDD without psychiatric comorbid condition, selective serotonin reuptake inhibitor antidepressants and low doses of combined contraceptives (oral estroprogestins) are considered first-line pharmacological treatments.<sup>9,41,42</sup> On the other hand, the presence of a comorbid BD brings out an important safety consideration regarding the use of SSRI and the consequence risk of mood switches.<sup>43,44</sup>

Aim of the present study was therefore to provide a review of the relevant literature on comorbid BD-PMDD and a set of hypotheses to test going forward in RCT studies, in order to manage these complex cases in the most complete and personalized manner.

## Methods

We searched PubMed to identify the studies pertaining to the treatment and management of comorbid PMDD and BD. The following search words were used, alone and in combination: premenstrual dysphoric disorder, bipolar disorder, comorbid, treatment, management, pharmacotherapy, psychotherapy.

The search was conducted on the 1st of June 2019 and yielded 55 records. Inclusion criteria were the following: original articles, written in English, including women affected by comorbid BD and PMDD. Animal studies,

in vitro experiments, reviews and commentaries were excluded.

By reading title and abstract, we excluded 14 records. By reading the full texts of the 41 remaining articles, we found four papers which met our inclusion/exclusion criteria and were therefore included in the qualitative synthesis (Figure 1).

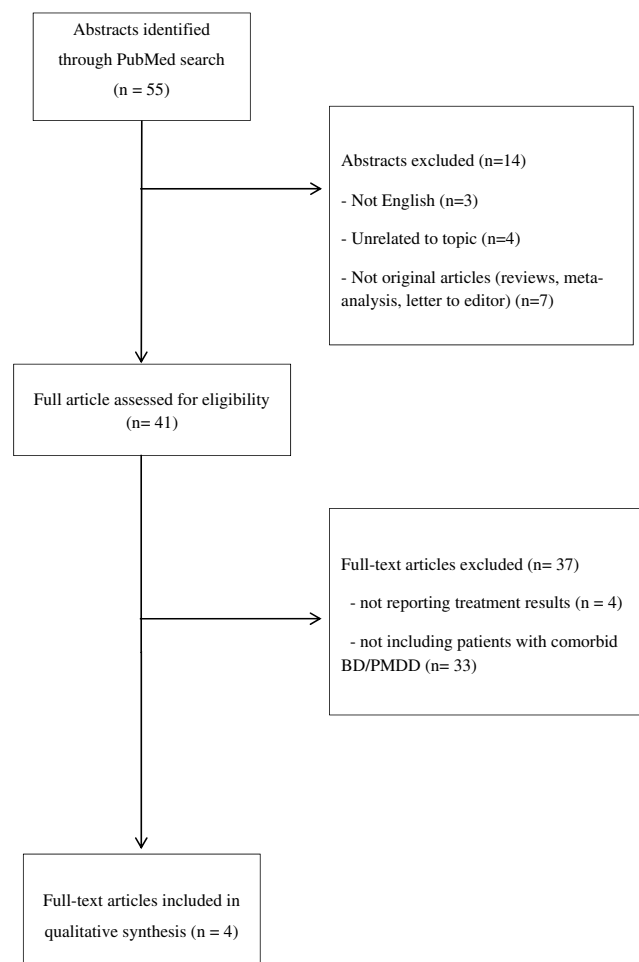
## Results

We included in our qualitative synthesis a total number of four papers pertaining to the treatment of comorbid PMDD in women affected by BD. All the included articles were case report/case series. A total of six patients were included.

The treatments suggested were the following:

### 1. Psychopharmacological treatments:

Mood stabilizers: a single case report, finding a significant efficacy of lamotrigine in reducing the follicular phase



**Figure 1** Flow chart of the systematic review.

depressive and luteal phase mood elevation symptoms in a woman affected by a treatment-resistant rapid cycling BD-II was published.<sup>45</sup>

We cannot find any published studies reporting the treatment of comorbid PMDD/BD with antidepressant or atypical antipsychotics.

### 2. Hormonal therapies: we found two papers, for a total of four patients with comorbid BD/PMDD, treated with estroprogestins.

In their study, Frey and Minuzzi<sup>46</sup> reported three cases of women affected by comorbid BD/PMDD that, after stabilizing the BD symptoms with a combination of mood stabilizers, antipsychotics and antidepressants (lamotrigine + aripiprazole + bupropion, lithium + quetiapine and fluoxetine + olanzapine, respectively) showed a good response after adding oral (drospirenone/ethinylestradiol) or transdermal (norelgestromin/ethinylestradiol) estroprogestins. In two cases, estroprogestins were well tolerated, whereas in the third one they had to be discontinued due to weight gain and headaches. A young woman affected by BD-I and a comorbid diagnosis of PMDD, after achieving euthymia by means of aripiprazole, also reported a reduction of PMDD symptoms adding an oral contraceptive (estradiol plus levonorgestrel).<sup>47</sup>

### 3. Psychotherapeutic interventions and alternative treatments.

We could not find any paper using psychotherapies to treat comorbid BD/PMDD. For what regard alternative treatments (wake therapy, lifestyle modification, supplements, herbal medicine, light therapy), we found two case reports.<sup>47,48</sup>

In the above mentioned case of BD-I with comorbid PMDD,<sup>47</sup> over hormonal and pharmacological therapy, psychoeducation and lifestyle changes are recommended by the authors, together with vitamin supplementation with 600 mg of elemental calcium twice daily and 100 mg/d of vitamin B6 in order to alleviate premenstrual symptoms. Also, based on PMDD treatments literature, the authors recommended cognitive behavioral therapies (CBT) to reduce affective PMDD symptoms.

A recent case report provides encouraging results obtained with nonpharmacological approach with a 45-year-old woman female with a history of diagnosed BD with psychotic features, PMDD, panic disorder, and repeated suicide attempts.<sup>48</sup> She reported scarce results

through conventional (ie, pharmacological) treatment. Alternative treatment was based on lifestyle interventions (11 mins of daily practice of a meditation called Kirtan Kriya), daily dry-skin brushing to stimulate lymph drainage and coffee enemas to support liver function, together with dietary changes (inclusion of organic/pastured meat, wild fish, pastured eggs, organic vegetables, fruit, nuts, and seeds). Outcomes indicate significant clinical remission after cessation of medication treatment and engagement of alternative, mind-body techniques.

## Discussion

### Therapeutic Options for Comorbid BD/PMDD

#### Pharmacologic Interventions

##### Antidepressants (ADs)

We could not find any published data focused on the treatment of comorbid BD/PMDD with ADs and it's almost surprising, due to the large use of this class of drugs in the treatment of both psychiatric conditions.

Several studies reported a gender difference in treatment response to antidepressants in mood disorders.<sup>49</sup> In particular, there is some evidence that women respond better to SSRI with respect to men<sup>50,51</sup> (probably due to the interactions between estrogen and serotonin in the brain).<sup>52</sup> When considering PMDD, The Korean Medication Algorithm project for Depressive Disorder, second revision, reported AD monotherapy as the treatment of choice.<sup>53</sup> A recent review reported that the efficacy of SSRI was equivalent for continuous versus intermittent (only during the luteal phase) dosing.<sup>54</sup>

On the other hand, ADs should be used with caution in subjects affected by BD, for the possible occurrence of a manic switch.<sup>43</sup> A treatment-emergent mania (TEM) was found in 35–50% of BD patients during AD monotherapy,<sup>55,56</sup> especially during the first month of treatment.<sup>57</sup> A recent meta-analysis assessing the efficacy and safety of long-term antidepressant treatment for bipolar disorders reported a good efficacy of ADs in reducing depressive symptoms and a low risk of TEM when ADs were administered in combination with mood stabilizers (MSs).<sup>58</sup> The risk profiles for the development of an AD-related TEM in BD differ significantly according to gender, with higher risk in females with a family history of BD-I and comorbid thyroid disorders, and in males with a history of suicide attempts and alcohol abuse.<sup>59</sup>

So, even with the lack of published data, we can speculate that ADs should be used in comorbid BD/PMDD only during the acute depressive episodes of BD, in addition to MS. Their use should be avoided during the manic states of BD and limited to refractory cases of PMDD during euthymic states.

##### Mood Stabilizers (MSs)

MSs are a key treatment in BD. Lithium is an old drug with high efficacy in manic and depressive episodes and in reducing relapses in euthymic bipolar patients.<sup>60</sup> In case of manic or mixed episode, lithium is often administered in combination with other MSs, such as valproate and carbamazepine,<sup>61,62</sup> whereas in the depressive phase of the illness, lamotrigine is usually preferred.

MSs have been rarely used in women affected by PMDD. An old study conducted in 1993 reported a good efficacy of low doses valproate in only 38% of subjects with premenstrual mood changes.<sup>63</sup>

In a small pilot study including seven patients with PMDD, a promising effect of levetiracetam in reducing the symptoms was observed in 85% of the cases, without severe side effects.<sup>64</sup> In a woman affected by a severe form of PMDD, partially responding to SSRI and with a contraindication for the use of estrogen-progestins, adding lamotrigine resulted in a significant improvement in premenstrual symptoms.<sup>65</sup> In an observational study by Karadag and colleagues,<sup>66</sup> 34 euthymic women with treatment-responsive BD on mood-stabilizers (lithium and/or valproate) for at least 6 months and 35 normal comparisons with regular menstrual cycles were prospectively followed up for at least two consecutive menstrual cycles using the Daily Record of Severity of Problems-Short Form (DRSP).<sup>67</sup> Seven BD women (20.8%) and 31 controls (88.6%) reported 30% or more increase in symptom severity during the premenstrual phase when compared with the postmenstrual phase within a cycle for 2 consecutive months. To explain the significant lower rate of premenstrual mood changes in the group of BD, when compared to normal women, the authors suggested a prophylactic effect of lithium and valproate against premenstrual symptom changes.

The only published study focused on comorbid BD/PMDD was a case report: in a woman affected by a treatment-resistant rapid cycling BD-II with follicular phase depressive and luteal phase mood elevation symptoms, lamotrigine significantly reduced the severity and frequency of menstrual-related mood changes.<sup>45</sup>

Even though the published data involving patients with comorbid BD/PMDD are very few, the large amount of data supporting the efficacy of MS in both acute (manic/depressive episodes) and euthymic states of BD suggest to use them as first-line maintenance treatment in comorbid BD/PMDD, in order to stabilize the BD and then focus in ameliorating the PMDD symptoms.

### Atypical Antipsychotics (AAPs)

AAPs, alone or in combination with mood stabilizers, are considered first-line treatments during acute manic episodes and maintenance in BD-I.<sup>43,68</sup> Conversely, there is only a double-blind, placebo-controlled study reporting a good efficacy of quetiapine as an add-on therapy in women affected by SSRI-resistant PMDD.<sup>69</sup>

No studies were found pertaining to the treatment of comorbid BD-PMDD with AAPs, even though few cases of premenstrual manic symptoms successfully treated with sulpiride (continuously or only during the premenstrual period) were published.<sup>70</sup> In the rare occurrence of premenstrual psychosis, olanzapine was found to reduce the symptomatology in a young woman,<sup>71</sup> whereas none of the administered AAPs (oral or injectable aripiprazole and risperidone) were efficacious in reducing the auditory hallucination and persecutory delusion in another case of cyclic psychosis.<sup>72</sup> In a case of BD-I with severe premenstrual mood instability, confusion, and psychosis, high doses of lithium and lurasidone were required to achieve remission.<sup>73</sup>

We can therefore suggest the use of AAPs to treat PMDD in women with BD-I and a story of premenstrual exacerbation of mood instability and psychosis.

### Hormonal Therapies

#### Estroprogestins

To date, oral contraceptives with shortened to no hormone-free interval are considered one of the most efficacious therapeutic options for PMDD without psychiatric comorbidities,<sup>1,9,47</sup> especially the combination ethinyl estradiol/drospirenone (DROS/EE).<sup>74</sup> On the contrary, the evidence supporting the effectiveness of non-contraceptive estrogen-containing preparations was lower.<sup>75</sup>

We found only anecdotal reports on the use of hormonal agents in the treatment of comorbid BD/PMDD.

A total of four patients with comorbid BD/PMDD responded well to oral or transdermal contraceptives as an add-on therapy to mood stabilizers and antipsychotics.<sup>46,47</sup>

### Hormonal Modulators

The selective estrogen receptor modulator tamoxifen was found to have promising anti-manic effects in women with BD.<sup>54</sup> Tamoxifen has different mechanisms of action, such as anti-estrogenic properties and luteotropic effect, increasing progesterone levels during the luteal phase in normal women,<sup>76</sup> but to date, it has not yet used in patients with comorbid BD/PMDD.

GABAergic neuroactive steroids have significant mood-stabilizing effects and are today considered a new frontier in the treatment of BD, especially for those patients showing menstrual exacerbation of mood symptoms.<sup>77</sup> Pregnenolone, a precursor of allopregnanolone and progesterone, reduced the clinical symptoms in acutely depressed BD patients.<sup>78</sup> Another endogenous steroid, allopregnanolone (a metabolite from progesterone), may induce depressive symptoms in sensitive women during the luteal phase, via its effects on GABAA system.<sup>79</sup> In a recent randomized, double-blind, placebo-controlled multicentre study, Sepranolone (UC1010), a GABAA modulating allopregnanolone antagonist, was found to significantly reduce negative mood and improve quality of life in women affected by PMDD.<sup>80</sup> However, studies pertaining to the treatment of comorbid BD/PMDD with GABAergic steroid modulators are still lacking.

In summary, we can consider oral estroprogestins as the treatment of choice, in addition to MSs, in euthymic BD women with comorbid PMDD. Other hormonal treatments, such as estrogen receptor modulators and GABAA modulating steroids, seem to be promising strategies in manic and depressive states, respectively.

### Psychotherapy and Alternative Treatments

Several researches have investigated the effectiveness of psychotherapy in women with PMDD. The efficacy of cognitive therapy may be due to the modification of negative thoughts and increasing coping strategies.<sup>81</sup> The effect of Cognitive behavior therapy (CBT) alone and combined with pharmacological treatment has been tested in a Randomized Controlled Trials (RCT) on one hundred and eight women with PMDD.<sup>82</sup> After 6 months of treatment, a more rapid improvement in association with Fluoxetine was observed. Furthermore, follow-up 1-year post-treatment revealed a better maintenance of treatment effect with CBT than with Fluoxetine. No additional benefit of combining the two treatments resulted. Actually, as



analyzed in a systematic review published in 2009 on empirical studies that investigated the use of CBT for PMDD, the research by Hunter and colleagues was the only RCT study carried out up to 2009 with proper intent-to-treat Repeated Measures ANOVA assessment of CBT effectiveness, which was non-significant.<sup>83</sup> Based on the collected data, the authors concluded that more than psychotherapies based on thought and behavior modification, other kind of treatment may be considered for women with PMS/PMDD. Specifically, Acceptance and Commitment Therapy (ACT), a treatment focused on thoughts acceptance and techniques to allow patients to recognize and live according to their values or personal commitments.<sup>84</sup> Subsequent meta-analysis and reviews considering both pharmacological and CBT efficacy in PMDD treatment do not find convincing effectiveness proof deriving from CBT empirical studies, mainly due to the small sample sizes, variable methodologies and results.<sup>81,85</sup> Kleinstaubner and colleagues indicate an individually tailored approach to face the PMDD broad spectrum of symptoms. In line with this suggestion, a case report on the treatment course of a fourteen-year-old young woman diagnosed with PMDD provides encouraging evidences of combined approach.<sup>86</sup> The authors have chosen to combine Fluoxetine and CBT taking into account patient and family preference, and the need to conservatively use medications with young patients. Furthermore, the effectiveness of CBT as nonpharmacological treatment for PMDD patients has been considered in two recent reviews that included a large sample of studies.<sup>9,87</sup>

Interestingly, a recent randomized clinical trial evaluated the effect of Internet-based CBT (iCBT) to reduce the burden of PMDD.<sup>88</sup> ICBT is a cognitive behavioral therapy provided through a computer or a mobile device. A total of 174 PMDD patients, randomized to treatment group or waitlist control group participated. Treatment group received an 8-week therapist-guided iCBT. Statistical analysis indicated interaction effects on functional impairment and psychological impairment, impact on everyday life, symptom intensity, and symptom disability in favor of the group under treatment. These data suggested a good efficacy of iCBT treatment for PMDD symptoms reduction, and the importance to address coping styles and stress management in the treatment.

CBT has been also proposed as an efficacious add-on therapy in patients affected by BD. Specifically, CBT improved quality of life and compliance, also reducing the frequency and duration of acute mood episodes.<sup>89</sup> A recent

review explores Internet-based cognitive behavioral therapy (ICBT) cost-effectiveness and its impact in rural areas.<sup>90</sup> The authors investigation reveals that ICBT is used to manage various psychiatric disorders as, among others, bipolar disorder. Its employ seems to be encouraged in order to avoid some disadvantages of traditional therapies, including cost inefficiency and a lack of follow-up.

In the same field, a systematic review evaluated the efficacy of adjunctive psychological interventions for BD in middle-income countries, starting from evidences that combining psychological and pharmacological approaches has better efficacy in preventing or delaying relapse and improving outcomes compared with pharmacotherapy alone.<sup>91</sup> A total of 18 adjunctive studies were included, with following treatments: psychoeducation, family intervention, group cognitive-behavioural therapy (CBT) and group mindfulness-based cognitive therapy (MBCT). Results suggested that psychoeducation and family psychoeducation improved treatment adherence, knowledge of and attitudes towards BD and quality of life, together with reduction of relapse rates and hospital admissions. CBT and MBCT reduced depressive-manic and emotional dysregulation, respectively. In general, psychological treatments alone are not validated to treat BD, but they are currently administered in combination with pharmacological treatments.

Another recent review provides further evidences on the efficacy of psychological treatments. Specifically, Interpersonal and social rhythm therapy (IPSRT – a modified version of interpersonal therapy based on the hypothesis that disturbance of social rhythms associated with life events causes relapse) was shown to increase the time until a new episode in BD. Furthermore, CBT with sessions of 90 min or more was demonstrated to decrease relapse rate, severity of depression and mania, and to improve psychosocial function, with more enhanced efficacy for BD I than BD II.<sup>92</sup> The authors also strongly suggest combined CBT with neurofeedback treatments. In the same field, a recent systematic review and meta-analysis aiming to address the efficacy of CBT as an adjuvant to pharmacotherapy in BD patients included 19 RCTs, for a total number of 1384 patients with BD-I and BD-II. Results indicate that CBT could lower the relapse rate and improve manic and depressive symptoms, and psychosocial functioning, with a mild-to-moderate effect size.<sup>93</sup>

Even though we could not find any paper focused on the treatment of comorbid PMDD/BD by means of psychotherapies, we can hypothesize their effectiveness as

adjunctive treatments, based on their good proven efficacy on BD and PMDD separately, in accordance with Smith and Frey's recommendations.<sup>47</sup>

Several research papers explored the effect of other treatments (ie, neither pharmacological nor psychotherapeutic approaches) on PMDD. Among these approaches, we found wake therapy, lifestyle modification, supplements, herbal medicine, light therapy.

Specifically, a research tested the hypothesis that wake therapy exerts antidepressant effects in PMDD women by altering the relationship between the circadian rhythms of sleep and melatonin secretion. Based on this hypothesis, sleep has been experimentally shifted with respect to melatonin in 19 women with PMDD compared with 18 controls.<sup>94</sup> Results suggested that decreasing morning melatonin secretion is not necessary for the therapeutic effects of wake therapy in PMDD. Light therapy and acupuncture have also been described as alternative treatments, but in studies with several methodological issues (see Pearlstein 2012 for a review).<sup>81</sup> In this field, a recent study has investigated the pattern of use of Light Therapy by office-based physicians, in order to understand if this treatment was considered appropriate for different disorders. They obtained 13.5% of affirmative answers for PMDD.<sup>95</sup>

A research study also tested the efficacy of massage therapy in 24 women randomly assigned to a massage group or relaxation control group. The authors observed in massage group women a reduction in affective PMDD symptoms immediately after the first and the last massage sessions, thus suggesting that massage treatment could be considered as an adjunct therapy for treating severe premenstrual symptoms.<sup>96</sup>

Lifestyle modifications (ie, regular aerobic exercise, avoiding stressful events, etc.) are considered as generally correct for health but their efficacy alone was not experimentally demonstrated (see Kelderhouse & Taylor 2013 for a review).<sup>97</sup> Dietary modification as reducing the consumption of sugar and eating small, frequent meals, as well as increasing daily intake of complex carbohydrates has been considered to alleviate mild symptoms.<sup>98</sup> Elsewhere, cessation of smoking, limited alcohol, and regular sleep, as well as stress management, anger management, self-help support groups, and light therapy are considered beneficial.<sup>99</sup>

Among supplements, vitamins B6 and E, calcium carbonate, magnesium, and tryptophan have demonstrated short-term benefits,<sup>87,99,100</sup> together with increased daily

vitamin D intake.<sup>101</sup> These data were confirmed by a recent review, but the systematic evaluation of their efficacy is still absent.<sup>102</sup>

Chasteberry (*Vitex agnus castus* – VAC) has been reported to be efficacious for decreasing premenstrual emotional and physical symptoms compared with placebo, with an effectiveness equivalent to fluoxetine and vitamin B6.<sup>101,103</sup> Other described herbal remedies are *Hypericum perforatum*, *Ginkgo biloba* and *Crocus sativus/saffron* (see Pearlstein 2012; Sepede et al 2016 and Appleton 2018 for a review).<sup>9,81,102</sup> Interestingly, an interdisciplinary expert meeting of general gynecologists, gynecological endocrinologists, psychiatrists and psychologists from Switzerland was held in 2016 to provide an algorithm on PMDD management. Among different nonpharmacologic treatments, only chasteberry is approved for PMDD treatment in Switzerland.<sup>104</sup> Nevertheless, in a simultaneous review and meta-analysis considering PMDD treatment studies with *Vitex agnus castus* preparation, the authors conclude that there is no convincing and conclusive evidence that VAC effectively reduces symptoms of PMDD.<sup>105</sup> Their results on 17 randomized controlled trials indicated that VAC extracts are not superior in efficacy compared to SSRIs or oral contraceptives, but are potentially effective compared to placebo, dietary supplements and other herbal preparations.

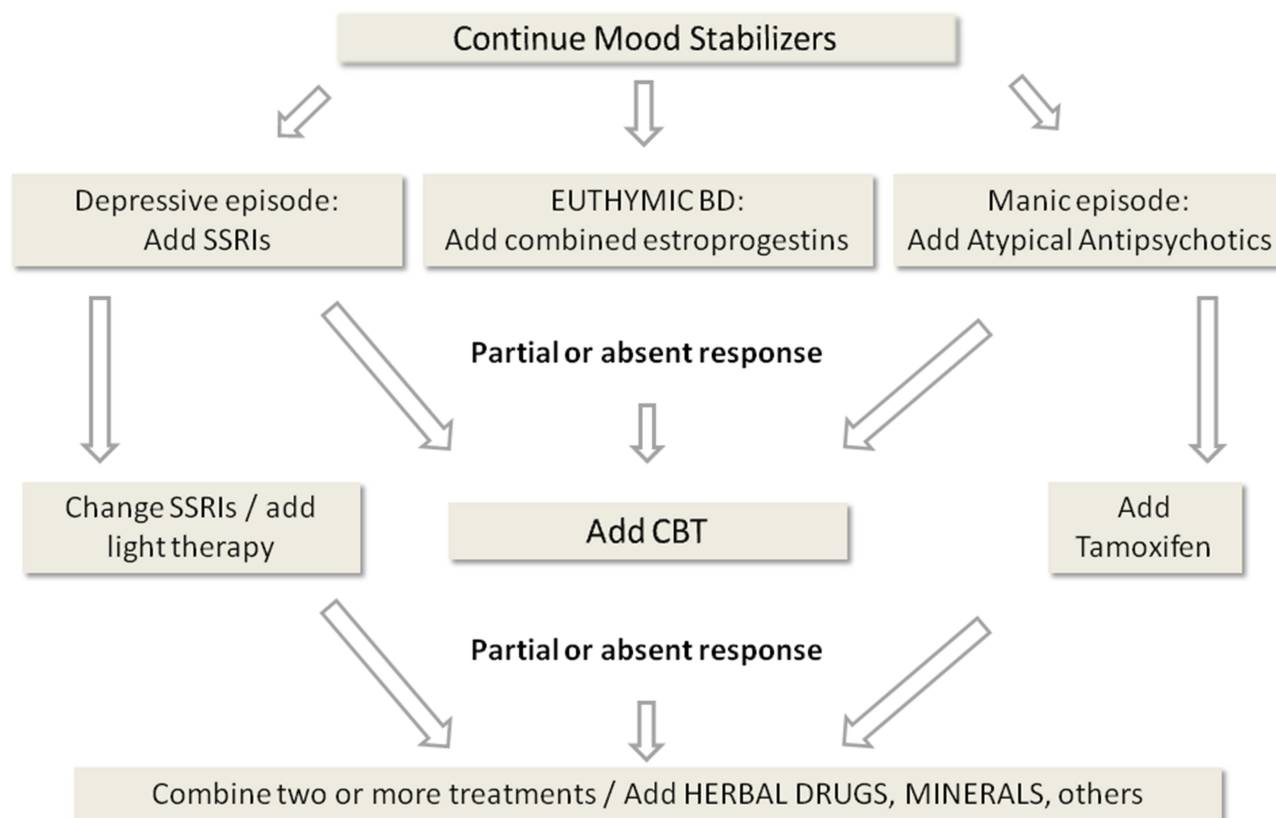
For what regards alternative treatments for BD, a systematic review verified the efficacy and tolerability on of different treatments for mood disorders which act on the biological clock (affective chronotherapeutics) – bright light therapy (LT), dark therapy (DT), treatments utilizing sleep deprivation (SD), melatonergic agonists (MA), interpersonal social rhythm therapy (IPSRT) and cognitive behavioral therapy adapted for BD (CBTI-BP). Results indicate that chronotherapies were generally safe and well-tolerated.<sup>106</sup> Finally, given the paucity of literature on comorbidity of Bipolar Disorder and Premenstrual Dysphoric Disorder, exhaustive nonpharmacological treatments indications on this issue are missing, and other studies are required to better address the use of those therapeutic options.

## Conclusion

### How to Manage Women Affected by Comorbid PMDD/BD (Figure 2)?

Even though BD and PMDD could present together, with a significant impact on the course of both mood conditions, only anecdotal data have been published regarding

## BD WITH COMORBID PMDD



**Figure 2** Management of comorbid PMDD/BD cases.

**Abbreviations:** BD, Bipolar Disorder; PMDD, Premenstrual dysphoric disorder; SSRI, selective serotonin reuptake inhibitor; CBT, Cognitive-Behavioral Therapy.

the treatment of women affected by comorbid BD/PMDD. RCTs of various treatments in this specific comorbid population should be conducted soon.

However, based on the large amount of data pertaining to BD and PMDD separately, we can hypothesize that the management of comorbid PMDD/BD needs as a first step to stabilize the bipolar symptoms by means of optimal dosages of mood stabilizers. Then, in euthymic BD patients, the PMDD symptoms could be treated with estroprogestins (first-line treatment). The ADs should be used with caution due to the risk of inducing mood switches and preferably reserved the treatment of acutely depressed patients. In case of partial or absent response, changing ADs or adding light therapy should be considered. Instead, when facing manic episodes of BD, a good strategy seems to be adding anti-psychotic agents and hormonal modulators, in order to reduce both manic and premenstrual dysphoric symptoms.

For what regard psychotherapeutic approaches, CBT seems to be a good second-line treatment in addition to

the above mentioned pharmacological treatments in both euthymic and acute states of BD.

In case of resistant PMDD symptoms in women affected by BD, combined strategies should be taken into account, as well as alternative treatments, such as lifestyle changes, herbal drugs and supplements.

Due to the broad spectrum of symptoms experienced by women with comorbid PMDD/BD, tailoring the therapy to the individual needs of the patients should be a mandatory point, in order to significantly improve their symptoms and their quality of life.

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