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LEADING ARTICLE

New Pharmacological Approaches to the Management of Premenstrual Dysphoric Disorder

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Abstract

Premenstrual symptoms are experienced by many female individuals during their fertile age. Premenstrual dysphoric disorder (PMDD), a sex-specific mood disorder, affects about 5% of female individuals during the luteal phase of the menstrual cycle. Treatment with selective serotonin reuptake inhibitors represents a valid solution to manage PMDD for many, but not all, patients. Owing to maladaptive neural reactivity to gonadal hormone fluctuations, that is, the putative mechanism postulated to underlie PMDD, drugs suppressing or stabilizing such variations have been tested. Recently, a clinically significant reduction in the severity of the mental symptoms of PMDD was observed upon treatment with a selective progesterone receptor modulator (SPRM), as demonstrated when comparing ulipristal acetate with placebo in a randomised controlled trial. Stable and low progesterone levels, with maintained low-medium oestradiol levels, define the endocrine profile of this treatment. Importantly, the efficacy of SPRM treatment was accompanied by negligible side effects. These promising results represent a headway to understanding the mechanisms behind PMDD symptomatology and opening up new solutions in the management of PMDD. They also call for studies on the long-term efficacy, safety, and viability of SPRMs in female individuals during their fertile age to further support the development of targeted management of female's mental ill-health in relation to the menstrual cycle. The present overview thus seeks to inform about current and new pharmacological approaches to the management of premenstrual dysphoric disorder.

Key Points

Premenstrual dysphoric disorder (PMDD) is triggered by gonadal hormone fluctuations.

Treatment with selective serotonin reuptake inhibitors represent a valid solution to managing PMDD.

Selective progesterone receptor modulator is a potential new treatment for PMDD.

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1 Female Mental Health

At the intersection between the endocrine and nervous systems, the ovarian hormones oestradiol and progesterone extend their influence beyond the hypothalamic–pituitary–gonadal axis to gene expression, neurotransmission, neurogenesis, and neuroprotection across the entire brain [1]. Indeed, these ovarian hormones easily pass through the blood–brain barrier and their nuclear and membrane receptors are widespread in brain areas of relevance to emotion and cognition [2], as also illustrated by neuroimaging findings in female individuals [3]. Taking account of this functional crosstalk, and the additional in loco production of neuroactive progesterone metabolites, also called neurosteroids (e.g. allopregnanolone) [4], the brain of a woman is exposed, during each menstrual cycle, to fluctuations of these hormones throughout her entire reproductive period [5].

Female individuals per se display greater susceptibility to develop mood disorders in comparison with male individuals, especially after the onset of puberty and at stages of life associated with changes in the hormonal milieu [6]. Along with the major hormonal transition periods (i.e. puberty

and menopause), pregnancy and postpartum, the hormonal changes occurring throughout the menstrual cycle have also been associated with manifestation of mood symptoms. The menstrual cycle consists of two phases: the follicular (or proliferative) phase, characterised by folliculogenesis, and in the absence of pregnancy, the luteal (or secretory) phase, during which the corpus luteum is formed and degenerated. At the beginning of the follicular phase, both oestradiol and progesterone are at their nadir levels; then, oestradiol levels increase to reach a pre-ovulatory peak 1–2 days ahead of ovulation. Following ovulation, the oestradiol levels decrease and, during the early luteal phase, increase again, together with the progesterone levels. The peak of both hormones is in the mid-luteal phase, after which both oestradiol and progesterone levels drop until reaching the lowest levels in the late luteal phase [7]. The neuroactive metabolite of progesterone, allopregnanolone, tightly follows the levels of circulating progesterone across the menstrual cycle with an offset of 1–3 days [4, 8].

The luteal phase has been associated with a spectrum of mood disturbances, spanning from premenstrual discomfort to severe clinical symptoms [9] that may include suicidal thoughts or behavior [10, 11]. Even though mild premenstrual somatic, mood and behavioral distress is commonly experienced by many female individuals of reproductive age [9, 12–15], a minority of them experiences affective symptoms of a higher intensity that severely impairs daily functioning, thus meeting the diagnostic criteria of premenstrual dysphoric disorder (PMDD) [16, 17]. The prevalence rate of PMDD (around 5%) seems similar between countries and steady over time [15, 18]. Notably, the prevalence of subthreshold PMDD cases is many times higher, making PMDD the tip of the iceberg [15, 18, 19]. Despite PMDD bringing about a burden of disease comparable to the one of major depression [18, 20], the neurobiology underlying PMDD and its treatment remains largely understudied [21, 22].

2 PMDD Symptomatology and Diagnosis

PMDD is a mood disorder, included in the DSM-5 [16, 17], and recently also in the WHO international classification of disease (ICD-11 GA34.41). The diagnostic criteria for PMDD, indicated in the DSM-5, include 11 symptoms, 4 of which are core affective symptoms (i.e. depressed mood, anxiety irritability, affect lability) and the remaining 7 relate to the cognitive–behavioral and somatic domains (i.e. difficulty concentrating, feeling overwhelmed, decreased interest in usual activities, lack of energy, change in appetite, hypersomnia or insomnia, physical symptoms) [16, 17]. The PMDD diagnosis is made if at least one affective core symptom and a total of five symptoms are present during the luteal phase and the woman is nearly asymptomatic during the follicular phase. Symptom occurrence needs to display cyclicity (i.e. with the onset occurring during the luteal phase, and offset after onset of menstrual bleeding) and chronicity over time (i.e. being present in the majority of menstrual cycles). Regarding clinical significance, the severity of the symptoms must be associated with clinically significant distress, or markedly interfere with the educational or occupational activities and the social life of the female individuals experiencing them. Moreover, the disturbance should not be merely an exacerbation of the symptoms of other psychiatric disorders, and not attributable to the physiological effects elicited by drugs or medications or other medical conditions [16, 17].

The diagnosis must be prospectively confirmed through daily charting of the symptoms for at least two consecutive symptomatic menstrual cycles [16, 17]. Amongst the scales that have been validated for PMDD diagnosis, the Daily Record of Severity of Problems (DRSP) [23] contains 21 items that describe the 11 PMDD symptoms defined by the DSM-5, and can be combined with the Carolina Premenstrual Assessment Scoring System (C-PASS) [24]. Undesirably, misdiagnosis and underdiagnosis are common, leaving people with PMDD untreated for long periods of time [25].

3 Proposed Neurobiology of the Disorder

The aetiology of PMDD is likely multifactorial, involving constitutive and environmental factors [21]. The specific timing underlying PMDD symptoms supports the relevance of luteal phase hormonal fluctuations for the occurrence of symptoms. Yet circulating levels of ovarian hormones in people with PMDD have been found to fall in the standard range [26], thus suggesting that this disorder is not linked to a hormone imbalance, but rather to a heightened sensitivity of the brain to the otherwise physiological endocrine variations [21, 22].

The underpinnings of this pathological susceptibility remain to be identified and are expected to be linked to a multifactorial aetiology, including genetic and environmental influences [27–30]. A plausible neurobiological factor is the modulation that ovarian hormones exert on synaptic transmission [2]. The reduction of PMDD symptoms following serotonergic antidepressant administration further supports this hypothesis and will be presented in the following section. This is corroborated by a positron emission tomography study, albeit very small, that found that the serotonin 1A receptor (5-HT_{1A}) availability in the dorsal raphe nuclei increases from the follicular to the late luteal phase in healthy controls, but not in individuals with PMDD, thus suggesting a dysregulation in their serotonergic system [31].

Moreover, other neurochemical systems have been suggested to be altered in PMDD. The predominant inhibitory

system in the brain, gamma-aminobutyric acid (GABA), as well as its receptor A, have been hypothesised to play a role in PMDD as target of the neurosteroid allopregnanolone, a metabolite of progesterone [32, 33]. Acute administration of allopregnanolone exerts anxiolytic and anaesthetic effects and causes sedation [4, 34]. Heightened sensitivity to allopregnanolone is illustrated by the altered pharmacodynamic response to allopregnanolone shown by individuals with PMDD across the menstrual cycle, in comparison with controls [4, 35, 36]. A proton magnetic resonance spectroscopy (^{1}H-MRS) study found that, contrary to healthy controls ($n = 14$), individuals with PMDD ($n = 9$) experience an increase in cortical GABA levels from the follicular to the mid-late luteal phase [37], supporting the hypothesis of an altered responsiveness to circulating neuroactive steroids, in particular allopregnanolone that acts as a modulator of the $GABA_A$ receptor [4, 8].

On the contrary, the ovarian steroid oestrogen has been sparsely linked to PMDD, despite its modulatory role on multiple neurotransmitter systems that regulate mood and cognition [2, 38, 39], thus of relevance to the domains characterising the complex constellation of PMDD symptoms. Individuals with PMDD are as sensitive to oestradiol add-back as to progesterone add-back upon suppression of gonadal hormonal fluctuations [40], though other studies highlight the relevance of the combined exposure to oestradiol and progesterone is causing symptom reinstatement [41, 42]. Moreover, symptom surfacing seems dependent on the dose of estradiol [42]. Meanwhile, sparse and equivocal evidence has been shown so far on the beneficial effect of treatment of premenstrual symptoms with non-contraceptive oestrogen-based preparations [43].

4 Treatment of PMDD

Owing to the variety and variability of symptoms underlying PMDD and the lack of knowledge about the neurobiological underpinnings of PMDD, a variety of treatments has been tested. Selective serotonin reuptake inhibitors (SSRIs), which block the reuptake of serotonin in the presynaptic space, are the first-line therapy in the treatment of PMDD (systematically reviewed by [44, 45]). Treatment doses correspond to the starting dose for treatment of depression, and augmentation is rarely needed. An aspect that distinguishes PMDD from other conditions for which SSRIs represent the first-line treatment is the fact that clinical efficacy is achieved within a few days from the start of treatment, while for depression and anxiety disorders it takes up to several weeks to obtain tangible improvements [45, 46]. This extraordinarily rapid efficacy enables SSRI administration not only in a continuous regimen, but also intermittently during the luteal phase only [47, 48], hence improving compliance levels. The rapid action of SSRIs in individuals with PMDD is hypothesised to be due to the simultaneous targeting of 5-HT receptors and interaction with allopregnanolone levels in the brain, thus indirectly modulating the function of $GABA_A$ receptors [21, 49]. Indeed, allopregnanolone levels in the cerebral spinal fluid increase upon treatment with SSRI and related to symptom improvement with patients with depression [50], while decreasing in the blood of women with premenstrual syndrome [51]. Adding to this, PMDD has been associated with peripheral luteal-phase heightened levels of this neurosteroid compared with healthy female individuals but lower levels in the most versus the least severe cases [52], which may be explained by the stabilising effect of SSRI treatment on allopregnanolone in individuals with PMDD depending on their baseline serum levels [53]. The role of each intertwined factor contributing to this rather complex phenomenon is yet to be fully unravelled. Findings on rodents provide mechanistic evidence on the link between SSRIs and increased allopregnanolone in the brain as being mediated by alterations in the synthesis or metabolic pathway of this neurosteroid [54–56], as well as the relevance of this interaction to oestrus cycle phase-specific, anxiety-like behaviour [57]. SSRIs are albeit reported to induce some adverse side effects, such as gastrointestinal complaints, sexual dysfunction, insomnia, and other effects on the central nervous system. Moreover, not all individuals with PMDD respond to SSRIs treatment [45, 58], and almost half of individuals with PMDD stop taking SSRIs within the first 6 months [59].

In support of allopregnanolone's role in the mechanisms behind PMDD, individuals with PMDD who received 5α-reductase as treatment to block the synthesis of allopregnanolone reported significantly reduced mood symptoms [60] (a randomised, double-blind, placebo-controlled, cross-over trial including 16 patients and 16 controls). Complementary to this, inhibition of allopregnanolone by isoallopregnanolone reduces PMDD symptoms [61, 62] (a randomised, double-blind, placebo-controlled study including 26 controls and 126 patients, and a randomised, parallel double-blind study including 206 patients, respectively). Though less studied, isoallopregnanolone, which is also metabolised from progesterone, antagonises allopregnanolone's effect on the $GABA_A$ receptor [33, 63–67].

Suppression of ovulation, thus eliminating the hormonal fluctuations triggering PMDD symptoms, has been tested as treatment as well [21]. Upon administration of gonadotropin-releasing hormone (GnRH) agonists, PMDD symptoms usually, but not necessarily, are either relieved or disappear (systematically reviewed by [68, 69]). However, GnRH agonist treatment leads to complete suppression of not only progesterone, but also oestradiol, the latter leading to vasomotor symptoms. Thus, add-back treatment with oestradiol and progestogen is needed, which makes this treatment effective

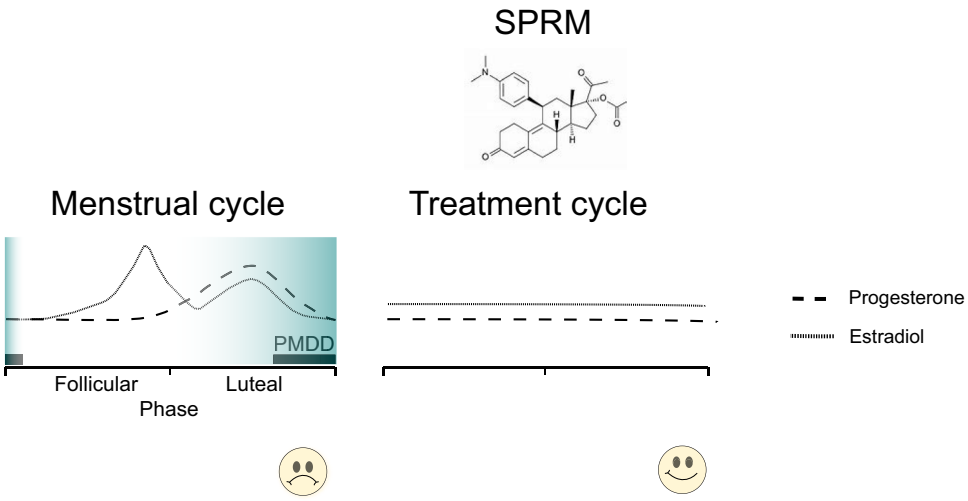

Fig. 1 New promising pharmacological treatment for premenstrual dysphoric disorder (PMDD). Continuous, low-dose treatment with ulipristal acetate (Selective Progesterone Receptor Modulator, SPRM) for 3 months shows beneficial effects on mental symptoms of PMDD [79]. *PMDD* premenstrual dysphoric disorder, *SPRM* selective progesterone receptor modulator

[41] but invasive. Further, when individuals with PMDD, who benefitted from GnRH agonist treatment, are given hormone add-back, some degree of symptom recurrence is expected [41, 69, 70]. GnRH antagonists combined with low dose oestradiol and progestogens, developed for treatment of gynaecological disorders, may prove a viable oral alternative [71], but have not yet been tested in individuals with PMDD. Combined hormonal contraceptives (COC) also suppress ovulation and maintain the endogenous levels of oestradiol and progesterone stable and low; thus, they have been proposed as treatment for PMDD [72]. However, COCs provide high levels of ethinyl oestradiol and progestogens (i.e. synthetic versions of the endogenous hormones). For this reason, it is not surprising that a recent meta-analysis found no significant improvement in terms of depressive symptoms upon treatment with COCs [73], while COCs with antiandrogen activity have shown mixed effects on premenstrual symptomatology [73] (as for example [74–76]).

Finally, surgical management through oophorectomy and/or hysterectomy has also been investigated. Nevertheless, due to its invasive and irreversible nature, this approach should be considered as a last-resort treatment option [20].

Yet another way of reducing progesterone levels is to use progesterone receptor antagonists. The major advantage in comparison with the GnRH agonists is that treatment leads to supressed ovulation, while maintaining sufficient oestradiol levels. In the 1990s, two small trials tested a progesterone receptor antagonist for PMDD, but the drug was either given too late in the luteal phase to be effective or the power was limited [77, 78]. Interestingly, recent findings point to a more ecological and non-invasive pharmacological treatment based on progesterone antagonism, specifically a selective progesterone receptor modulator (SPRM) (i.e. ulipristal acetate, UPA) [79]. A multi-centre, double-blind, placebo-controlled trial researching its potential as a treatment option for PMDD, including 95 female individuals, showed that when individuals with PMDD received UPA over a 3-month period their mood symptoms were significantly reduced [79]. Some 85% of subjects taking the medicine experienced either complete or partial remission of symptoms [79]. Half of the treated individuals experienced a complete recovery, while 21% of the individuals, receiving placebo felt the same improvement. The drug especially helped with mental symptoms such as anger, irritability, and depression (Fig. 1). The somatic symptoms were, however, not affected [79]. The treatment resulted in anovulation in most participants, evidenced by low progesterone levels. The oestradiol levels, on the other hand, were maintained at mid-follicular phase levels [79]. In this study, side effects experienced by the subjects were rare and generally mild, primarily headache, nausea and fatigue [79]. Conceptualized as a proof of concept, this is the first study testing such medication for PMDD; thus, independent replication using larger populations is needed before treatment can be recommended. Nowadays, SPRMs are used acutely and in higher doses as an emergency contraceptive as well as in low dosage and for prolonged time for the treatment of uterine fibroids [80, 81]. Concerns and caution with this new treatment regard its sustainability in terms of liver function as highlighted by adverse reactions in older females with uterine fibroids [82]. Newer and well-tolerated SPRMs could potentially offer a welcome option in the future for individuals struggling with PMDD. Notably, the findings on SPRM as potential new treatment for PMDD holds the potential to be informative to the broader field of affective disorders by providing insights on the therapeutical potential of hormonal treatments [83]. New efficacious treatment alternatives will furthermore be relevant to those female individuals experiencing worsening of psychiatric symptoms of another mental condition during the premenstrual phase [84].

Non-pharmacological treatment options are also mentioned in the literature, ranging from natural remedies to

psychotherapy [85]. Nutritional agents target putative vitamin and mineral deficiencies, or lifestyle, while relaxation techniques aim to empower the patients in the management of their distress. Finally, amongst the herbal supplements that have been considered as treatment strategies, chasteberry (Vitex Agnus Castus) shows promising beneficial effects [86–88]. However, the efficacy and neurobiological mechanisms of actions of these therapeutical alternatives remain to be ascertained.

5 Future research

Neuroimaging is the candidate tool of choice to assess the brain in vivo to explore the hormone-related changes and neural markers of PMDD and to investigate structural, neurochemical and functional effects associated with symptoms relief upon treatment. Accumulative evidence from human and animal studies indicates that brain structure and function undergo variations because of menstrual cycle hormone fluctuations [3]. Despite the paucity of studies on PMDD, their methodological flaws, and the inconsistencies among their results, the neurobiological features of PMDD are increasingly being defined (for a review, see Dubol et al. [89]), thus facilitating the process of identifying relevant targets and the development of adequate treatment strategies.

The most robust brain signature underlying PMDD symptoms points to altered corticolimbic connectivity during processing of emotional stimuli [89]; specifically, the brain functional reactivity is lower in the anterior cingulate cortex (ACC) of individuals with PMDD [90], and higher in regions anatomically and functionally connected to the ACC, namely the amygdala, insula, and dorsolateral prefrontal cortex (dlPFC). Moreover, the reactivity of ventromedial prefrontal cortex was also found to be altered in the brains of individuals with PMDD, but the direction of this effect is unclear [89]. Along the same lines, multiscale and multimodal magnetic resonance imaging analyses point to morphological differences between female individuals with PMDD and healthy controls, particularly to structural alterations in grey matter volume and surface metrics [91] as well as white matter microstructure [92] in regions or tracts involved in corticolimbic networks. Moreover, neuroanatomical differences in such areas correlate with the severity of PMDD symptoms [92, 93]. Of interest to emotion processing is the amygdala, which expresses receptors for oestrogen and progesterone. Progesterone administration, resulting in luteal-phase range serum concentrations, increases amygdala reactivity in healthy female individuals (van Wingen et al., 2008). Moreover, the grey matter volume of the amygdala was smaller in individuals with PMDD and negatively correlated with PMDD symptoms [93]. These corticolimbic alterations can provide an explanation of the core symptoms of PMDD: as a matter of fact, the impaired top-down inhibitory processes (represented by altered reactivity of regulatory areas such as dlPFC and ACC) during the late luteal phase would be associated to diminished emotional control and increased negative mood symptoms [89]. On the contrary, exaggerated amygdalar and insular responses by bottom-up processes have been found to correlate with ratings of two core symptoms of PMDD, namely anxiety and depression [89]. While the smaller volume of the amygdala [91] and its inverted relationship with symptoms severity [93] could be seen either as a compensatory mechanism or a risk predisposition, both lead to heightened activation upon stimulation. These regions could represent the target of future psychological and/or pharmacological treatments.

The mechanism through which progesterone fluctuations during the luteal phase trigger PMDD is not known. Progesterone easily passes through the blood–brain barrier [94]. Receptors for this hormone exist throughout the brain [95, 96], including the amygdala, prefrontal cortex, hippocampus, and other brain areas of relevance to affective and cognitive function [4]. SPRM that binds to and inhibits progesterone receptors [97], thus preventing the hormone from triggering a maladaptive reactivity of the brain, can provide insights to progesterone's role in the pathophysiology of the psychological symptoms of PMDD [79]. On this note, the neural correlates of SPMR treatment have been started to be delineated. By neuroimaging the brains of these patients before and during treatment, magnetic resonance imaging has been used to profile the structural and functional brain signatures that can explain the relief of PMDD symptoms. Thus far, studies have indicated that SPRM treatment is associated with enhanced reactivity in the dorsal anterior cingulate cortex and dorsomedial prefrontal cortex during aggressive response [98]. Corroborating this, higher aggressive responses were associated with lower reactivity in fronto-cingulate regions only in the placebo and not the SPRM-treated group [98]. Aggressiveness is a potential outcome of the core PMDD symptoms of irritability and anger. These results suggest a beneficial effect of progesterone receptor antagonism on top-down emotion regulation in PMDD. Furthermore, the absence in the short term of SPRM treatment effects on grey matter structure [99] could be seen as reassuring for individuals who need SPRM treatment but are concerned about the invasiveness of such treatment.

Overall, the effect of ovarian hormones on the brain are complex and yet to be clarified. They seem to be dependent on duration and combination of hormone exposition. These hormones participate in neurotransmission modulation [2]. Sex steroids affect several neuronal networks in the female brain and are hypothesised to contribute to neuroplasticity changes. They have been shown to interact with glutamatergic, GABAergic, dopaminergic and serotonergic networks and activate multiple intracellular pathways [2].

Many brain regions involved in emotion and cognition have a high expression of progesterone and oestrogen receptors. Such areas are, for example, the amygdala, the hypothalamus, and the hippocampus which also play an import role in the plasticity of the adult brain and are likely oversensitive in individuals with PMDD. For instance, on the cellular level, in female rodents, ovarian hormones are for instance involved in rapid fluctuations across the oestrous cycle, of dendritic density in the hippocampus and amygdala, key regions in the emotional circuitry and rich in hormone receptors [100–103]. The in loco production of neurosteroids adds on to the complexity of neuroendocrine interactions. Of relevance, serum allopregnanolone levels have been negatively associated with serotonin transporter binding in the prefrontal cortex of healthy female individuals during the follicular phase [104]; the common psychological wellbeing experienced in this phase when allopregnanolone levels are low in relation to serotonergic neurotransmission and the importance of the prefrontal cortex for higher cognitive functions and top-down regulation of emotions is likely to be relevant to PMDD. SSRIs in low doses have been suggested as steroidogenic stabilisers; for instance, a pilot study on individuals with PMDD treated with an SSRI, though not including a placebo group, points in this direction [53] and thus calls for multidimensional approaches to PMDD.

6 Conclusions

In PMDD, profound mood lability, depression, anxiety, and irritability are severe enough to negatively impact daily life activities. PMDD is often neglected by healthcare professionals, while current PMDD treatments are not sufficient. The first-line pharmacological treatment, SSRIs, is not suitable for all female individuals. Given the limited options for treatment as of now, progesterone receptor modulators represent a promising effective and well-tolerated alternative. In addition, this treatment more specifically addresses the mechanism(s) underlying PMDD. To advance knowledge on the neural basis of PMDD and its treatment, our pharmaco-neuroimaging findings point to the involvement of the fronto-cingulate cortex in symptoms relief. Future studies are needed to define the neural correlates of switches between mental health and ill health states of PMDD and its treatment, thus promoting the development of targeted treatments.

Declarations

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Conflict of interest ISP has served occasionally on advisory boards or acted as invited speaker at scientific meetings for Asarina Pharma, Bayer Health Care, Gedeon Richter, Peptonics, Shire/Takeda, Sandoz, and Lundbeck A/S. EC has no conflict of interest to declare.

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Author Contributions ISP and EC contributed equally. All authors have read and approve the final version of the manuscript, and agree to be accountable for the work.

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Consent to participate Not applicable.

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