

CLINICAL REVIEW

Sleep EEG, depression and gender

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KEYWORDS

sleep EEG, depression, gender, sex differences, sleep regulation

Summary Despite clear evidence of an intimate connection between sleep, major depressive disorders (MDD) and gender, few studies have explored gender differences in either sleep or in wakefulness in patients as a means of better understanding the psychogenic components of MDD. Indeed, few sleep studies focus on characterising gender differences in any population. This paper will present a review of the literature on gender differences in sleep and depression. The theoretical and clinical implications of the findings will also be discussed. The premise of the present review is that there is an inherent increased vulnerability to depression in women that arises out of basic gender differences in brain organisation and state regulation, particularly in response to a “biological challenge” during sleep. It is argued that the inherent properties of organisation and regulation of sleep EEG in healthy men and women, elicited under challenge conditions, show gender-specific vulnerability to organisational abnormalities that model homeostatic abnormalities in depressed men and women and contribute to the genesis of depression. © 2001 Harcourt Publishers Ltd

EPIDEMIOLOGY OF DEPRESSION AND GENDER DIFFERENCES

Diagnosis of major depressive disorder (MDD) in research studies is usually based on a structured clinical interview for depression (SCID). DSM-IV criteria require a minimum symptom duration of 2 weeks with no manic or hypomanic episodes for a diagnosis of single or recurrent MDD. Note, however, that the average is about three episodes of MDD throughout an individual's lifetime and thus MDD is largely a recurrent illness. Approximately 10–15% of the population undergoes an episode of

depression each year and the average age of onset is mid to late 20's. Women are at twice the lifetime risk for the development of MDD compared to men [1]. This increased risk begins at puberty and continues until menopause. Prior to puberty and after menopause, males and females are at equivalent risk for MDD, implicating gonadal hormone regulation in the etiology of the illness.

Until recently, it was believed that the incidence of increased depression in women was an artifact response bias. In fact, numerous careful studies conducted over the past decade clearly indicate a true increased risk for depression in women [1]. Interestingly, however, there are few data to indicate that the clinical course of illness differs substantially between men and women. Average age of onset, symptom severity, clinical response to antidepressant therapies, time to respond and risk of relapse and recurrence do not appear to differ between men and women [1], although other studies have demonstrated differential response rates

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by gender [2]. In addition, there is some evidence to suggest that the specific symptoms of the illness and at what point in the episode medical intervention is sought does seem to differ by gender [3, 4]. Further, the biological and psychosocial factors that increase risk for MDD may also show gender differences [5]. Women with depression are more likely to present with “atypical” symptoms including weight gain, rejection sensitivity, irritability and hypersomnia [2]. They are more likely to seek treatment earlier in the episode and more likely to focus on the interpersonal cost/difficulties associated with their illness [3, 4]. Men, on the other hand, may focus more on job-related or goal-directed behavioral difficulties, and may not be as aware of the onset of episode until it is severe [4].

Notably, there are also a number of recent studies that show significant gender differences in the pharmacokinetics and pharmacodynamics of antidepressant medications. Moreover, men and women show different sensitivities to the side-effects of antidepressants (and other) medications. This issue is particularly important with newer antidepressants that have selective affinity toward one neurotransmitter system (e.g. serotonin), and provides evidence that physiological response to medications may differ by gender [6].

Collectively, these findings have been taken as evidence that the pathophysiology of depression differs for men and women. Some of the strongest evidence for this position comes from sleep EEG data [7]. Additional support for this view has been demonstrated in neuroendocrine and neurotransmitter response to pharmacological challenge [8] in the effects of selective serotonin reuptake inhibitors on both self-rated sleep measures and on sleep EEG [9].

SLEEP AND DEPRESSION

Sleep disturbances are key features of depressive symptomatology, with subjective sleep complaints in more than 80% of patients [10]. Persistent sleep disturbance increases the risk of relapse and recurrence of depressive episodes and the risk for suicide [11, 12]. In addition, insomnia of at least 2 weeks duration increases the lifetime risk of developing depression [12]. Moreover, significantly more prescription for adjunctive hypnotic or anxiolytic medications are written for depressed patients treated with antidepressants that further exacerbate

or do not improve sleep disturbances [9]. Laboratory-based studies of sleep electrophysiology (EEG) have demonstrated sleep abnormalities in patients during an episode of depression and in clinical remission [10, 13, 14]. For ease of reviewing this literature, several key terms are described below.

NOMENCLATURE

Since the nomenclature in describing sleep physiology differs across studies, several key terms are defined here for ease of readership. Sleep macroarchitecture refers to the measure derived from visual stage-scoring of sleep EEG including sleep latency, rapid eye movement (REM) latency, total sleep time, and the minutes and percentages of stages 1–4 of non-rapid eye movement (NREM) sleep, REM and awake [15]. Sleep microarchitecture denotes the parameters derived from all-night, computerised, quantitative EEG analyses in beta, sigma, alpha, theta and delta EEG bands [16]. In sleep research, the most common quantitative EEG analyses are: period amplitude analysis (PAA), a time-domain strategy used to describe wave incidence and amplitude and power spectral analysis (PSA), a frequency domain technique used to describe power (area under the curve). There is substantial overlap between the two techniques, particularly in describing slow-frequency delta and theta activity [7]. There are several excellent sources for detailed descriptions of quantitative EEG procedures [cf 7, 16–19]. Slow-wave sleep refers to stages 3 and 4 of NREM sleep and specifically requires the presence of very high amplitude delta waves ($>75 \mu\text{V}$) for more than 20% of each 30 s epoch for stage 3 and more than 50% of the epoch to define stage 4 sleep, according to standard criteria [15]. Slow-wave activity (SWA) refers to delta, amplitude and power in NREM sleep and requires neither a minimum amplitude nor a percentage of the epoch criterion.

SLEEP MACROARCHITECTURE

Numerous overviews of normal sleep macroarchitecture have been published in the last 30 years [21]. In healthy adults, sleep onset occurs 10–15 min after lights out, followed shortly thereafter by the progression of deeper stages 2, 3 and 4 of NREM sleep. The first REM period terminates the first

slow-wave sleep (stages 3 and 4) episode and occurs about 90 min after sleep onset. The first REM period is short in duration (1–5 min) but lengthens progressively across successive REM periods. Non-REM and REM sleep alternate throughout the night at about an 80–125 min period length. However, slow-wave sleep is concentrated in the beginning of the night and is not present in abundance in the latter half except in younger adolescents and children. Short duration intermittent awakenings do occur in both healthy children and adults, but generally only 2–5% of total sleep time.

There is an extensive literature on sleep macroarchitecture in MDD, with over 1300 published reports dating back to mid 1970s, and including several seminal review articles [7, 10, 22, 23]. The “classic” sleep profile of a symptomatic but unmedicated adult with MDD is a prolonged sleep latency (sleep onset insomnia), bouts of intermittent wakefulness, increased light, non-restorative stage I sleep, decreased slow-wave sleep, a shortened latency to the first REM period accompanied by increased phasic activity and an elevation in eye movement density. As a general rule, the majority of studies on macroarchitecture have reported abnormalities in the timing and/or distribution of sleep stages as primary characteristics of those with MDD.

Theory regarding the specific source of the sleep disturbance has focused either on REM or NREM control mechanisms. With regard to REM-based theory, disinhibition or increased sensitivity of cholinergic neurotransmission has been offered as the explanation for the early onset of REM sleep [24] or the increased phasic activity reported in those with MDD [10, 23]. Others have suggested that an impairment in homeostatic control of NREM sleep, and specifically SWA, underlies sleep abnormalities in MDD [25]. This latter suggestion is based on the two-process model of sleep regulation [26] where the amount of SWA at night is determined by the amount of prior wakefulness, the level of sleep propensity during the day and depth of sleep at night (process S). Process S accumulates during waking hours as sleep propensity rises and dissipates over the night as SWA declines. The second process (process C) reflects the circadian control of sleep propensity that is highest at 03:00–05:00 when it is very difficult to overcome the need to sleep and is lowest at 16:00, where sleep propensity is minimal. Process C is presumed to reflect internal clock control of circadian rhythms,

the threshold for maintaining wakefulness and REM sleep control, and is unaffected by the amount of prior wakefulness. It is assumed that in a healthy brain, the propensity for REM sleep increases as SWA dissipates, thus explaining the short duration first REM period when SWA pressure is high, and the proportionate increase in REM as SWA dissipates across the night [26]. Thus, the time course of SWA approximates process S, not the total amount of SWA. There are numerous reports on the distribution of SWA in healthy adults using period analysis [27–29] and power spectral analysis [30–34]. Almost all studies indicate a substantial exponential or linear decrease in SWA over successive NREM periods as predicted by the process S model. Borbély and Wirz-Justice [25] have further suggested that reduced slow-wave sleep in MDD results from an impairment in homeostatic, process S. They postulated that SWA pressure and accumulation was reduced in MDD permitting both the early onset of REM with a prolonged duration and an abnormal dissipation of SWA across the night.

More recent sleep studies have been less successful in demonstrating significant differences between patients and controls. A meta-analysis of published work by Benca *et al.* [35], for example, has indicated that no single sleep macroarchitectural variable reliably differentiates MDD patients from controls or from other psychiatric groups. Moreover, some studies have shown that only 40–60% of patients with MDD show substantial sleep disturbance in the laboratory. On the other hand, the Pittsburgh group has begun to focus on clusters or profiles of sleep measures as more accurate descriptors of sleep disturbance in MDD than any one single variable [14]. Studies that have utilised quantitative sleep EEG techniques have sufficiently provided a more sensitive discrimination between patients and controls.

SLEEP MICROARCHITECTURE

Much of the early work on sleep microarchitecture, dating back to the late 1960s, focused on describing the EEG frequency structure of REM and NREM sleep stages [18, 36, 37]. Initially, it was suggested that REM sleep was primarily associated with activation of the right hemisphere whereas NREM sleep involved more left hemisphere activation. Follow-up studies could not replicate these initial findings [38] and, conversely, indicated that REM sleep

was associated with minimal asymmetry in either beta, theta or delta incidence or amplitude compared to NREM. Asymmetries in these EEG bands were larger in slow-wave sleep than in either stage 2 or REM, but were still only on the order of a 10% difference between the hemispheres. In addition, it was the absolute difference between the hemispheres that covaried with sleep stage, not greater right or left hemisphere activation. Rather, the alternation of REM and NREM sleep seemed to be characterised by alterations from hemispheric balance to asymmetry in healthy individuals [38].

By contrast, patients with MDD appear to show greater asymmetry in both REM and NREM stages compared with healthy adults and both more alpha and more beta activity overall [39, 40]. The elevation in fast-frequency activity appears more dramatic in women with MDD than in men [7, 41]. It is not just the overall amounts of fast-frequency activity or hemispheric asymmetries that identify greatest abnormality in women with MDD, but the organisation and temporal coherence of 90-min rhythms in sleep EEG frequencies are also more severely impaired in women than in men with MDD.

TEMPORAL COHERENCE

Temporal coherence has been used as a measure of the degree of synchronisation between EEG frequencies of the same periodicity. In the case of sleep, the focus has been on 90-min ultradian rhythms between the two hemispheres (inter-hemispheric coherence) or between frequency bands within a hemisphere (intra-hemispheric coherence). Several studies have shown significantly lower inter and intra-hemispheric coherence in patients with MDD, primarily in women [7, 42]. What is more, significantly more women than men with MDD show low coherence, indicating that it is more than just an average or group characteristic. Approximately 80% of women with MDD and 35% of men with MDD show low coherence compared to healthy controls. Further, low coherence may persist into clinical remission [42].

We have argued that low temporal coherence results from an erratic or inconsistent phase relationship between sleep EEG frequency bands and between the two hemispheres, i.e. the loss of predictive regularity. This represents a more dynamic or chaotic organisation of sleep EEG rhythms, further

evidence of dysregulation and organisational instability that is most dramatic in women with MDD [7]. Recent work indicates that adolescent girls with MDD also have significantly lower temporal coherence than boys, although both groups were lower than healthy adolescents [43]. Note that adolescence is also the time period during which the increased risk and prevalence of depression in females becomes evident. It is not clear whether it is the onset of first menses, and hence changes in gonadal hormone regulation, which contributes further to decreased coherence and risk for MDD in girls or whether psychosocial factors play a more important role.

Interpreted in this context, sleep micro-architecture is more clearly disturbed in depressed women than men and thus more likely contributes to the genesis of depression and the increased risk in females. However, not all microarchitectural abnormalities are most dramatic in women. What appears to be consistent across all sleep measures is that gender differences are more dramatic in patients than they are in healthy controls.

SLOW-WAVE ACTIVITY

Considerable data are also available for evaluating SWA during sleep in patients with MDD. Using power spectral analysis (PSA), based on the fast-Fourier transform, Borbély *et al.* [40] demonstrated lower SWA in nine adult unipolar, unmedicated, depressed patients compared to age and gender-matched healthy normal controls. This initial finding was confirmed in a group of younger patients with MDD (20–30 years old), compared with age-matched controls [44]. Slow-wave activity did not, however, differentiate older patients (>50 years) from gender-matched controls in the same age range [45], and may not be a characteristic of bipolar patients [46].

Kupfer *et al.* have also utilised delta wave-count statistics, based on period amplitude analysis (PAA) to quantify the incidence of SWA in NREM sleep. In several studies, they have reported lower delta wave counts in patients with MDD compared with controls, and these differences were largely restricted to the first NREM period of the night [47]. In fact, Kupfer's group has suggested that delta wave counts in patients with MDD are higher in the second NREM period than in the first, taken as evidence of process S impairment. They have also

suggested that this delta ratio is related to the clinical course of illness [47]. A more recent study has been unable to replicate either lower delta wave counts or a consistent elevation in delta in the second NREM period in patients with MDD [7]. However, the delta wave counts from the Kupfer *et al.* studies and from Armitage *et al.* both emphasised high-amplitude SWA ($>75 \mu\text{V}$) and are unlikely to accurately describe changes in amplitude-independent SWA across NREM periods. The Armitage *et al.* study did indicate that the distribution of SWA across successive NREM periods was abnormal in those with MDD, consistent with the process S deficiency hypothesis. Nevertheless, the differences in SWA between patients and controls have not been as large as the model would predict. The failure to assess gender differences may very well contribute to the discrepant findings among some of these studies [7].

SLOW-WAVE ACTIVITY AND GENDER

With specific regard to gender differences in healthy individuals, Dijk *et al.* [34] reported higher SWA power in women than in men under 30 years of age, persisting throughout all NREM sleep periods. The percentage of slow-wave sleep did not differentiate between the groups, attesting to the enhanced sensitivity of SWA in detecting gender differences. However, there was no evidence that decline in SWA was slower in women and thus the gender difference in global EEG power did not appear to relate to process S *per se*. The authors concluded that anatomical factors such as skull thickness and head size, known to influence the detection of electrical potentials, accounted for the gender difference rather than homeostatic or sleep regulatory differences between healthy men and women. As discussed below, the skull thickness hypothesis is not viable in those with MDD.

Another study confirmed higher SWA in healthy women than in men under 30, but not when analyses were restricted to stages 3 and 4 sleep alone. Although the authors suggested that the gender differences in healthy young adults were relatively subtle in those under 30 [7], confirmatory evidence of this suggestion has been provided recently, indicating that healthy women do show significantly more SWA than men, but only after 30 years of age [48].

In a large-scale study of 302 MDD men and women, Reynolds *et al.* [49] demonstrated significant gender main effects for slow-wave sleep and delta wave counts across the whole night and particularly in the first NREM sleep period. Men with MDD had less slow-wave sleep and lower delta counts than women with MDD. Moreover, a NREM period by gender interaction was found, suggesting that the temporal distribution of delta wave counts differed for men and women with MDD. Gender differences in both slow-wave sleep and delta wave counts $>75 \mu\text{V}$ were also evident in younger patients (20–29 years old) with MDD and diminished with increasing age, though not monotonically. Reynolds *et al.* concluded that age effects were stronger than gender differences and there was little evidence of a differential maturational time course in men and women with MDD. Published reports from our own group are not consistent with the interpretation by Reynolds *et al.* The discrepancy, however, can be easily reconciled. First, in the Reynolds *et al.* study, delta wave counts were lower in both younger and older MDD men than in women. Thus, women with MDD retained more delta even later in life. This is evidence that the maturational time course differs in our view and that gender differences in the pathophysiology of depression may persist throughout adulthood.

Several of the recent studies in our laboratory have focused on gender differences in SWA regulation in patients and controls. The initial study of 22 patients and 23 controls revealed significant group by gender interactions on the amplitude and power of SWA across successive NREM periods, and SWA time course [50]. Men with MDD had a significantly slower rate of decay with lower predicted SWA power and amplitude parameters from exponential regression analysis, compared with all other groups. Women with MDD, healthy men and healthy women did not differ from each other. Most importantly, a comparison study with schizophrenic men indicate that abnormalities in the time course of SWA were specific to MDD. Although some men with schizophrenia showed lower SWA amplitude than healthy men, they did not differ on the accumulation or dissipation of SWA over NREM sleep time. The men with MDD, on the other hand, differed significantly ($P < 0.05$) from both healthy and schizophrenic men.

That baseline SWA was more likely to be abnormal in men with MDD was replicated in a follow-up study of 131 subjects, 20–40 years of age [41].

Analysis of SWA across successive NREM periods produced a significant group by gender interaction, although this effect was largely restricted to the first NREM period. Again, SWA in the men with MDD was significantly lower compared with all other groups, with no significant differences among normal control (NC) men and women and women with MDD. Approximately 70% of men with MDD fell below mean SWA in the control group. By contrast, only 20% of women with MDD fell below the mean SWA for healthy women. Exponential regression analyses confirmed that the time course of SWA was abnormal in men with MDD, whereas no differences were found among NC men and women, and women with MDD. Men with MDD showed both lower predicted SWA with a slower accumulation and dissipation across the night. Regression parameter estimates in men with MDD were outside the 95% confidence intervals of all other groups ($P < 0.05$), whereas normal control men and women and MDD women did not differ from each other. It is difficult to reconcile these findings with the suggestion that gender differences are due to factors such as skull thickness since both disease and gender-dependent components were identified. If gender differences were due simply to divergent electrical conductivity, then no interaction with group should be evident. Further, both the time course and amplitude differentiated men with MDD from all other groups. Such findings make a stronger case for sleep regulatory processes that are influenced by both disease and gender. The definitive test of the SWA regulation hypothesis would require directly manipulating prior wakefulness and homeostatic regulation of SWA. Although numerous sleep deprivation studies have been conducted in patients with MDD, to our knowledge none have evaluated group by sex interactions in SWA [51].

Our own group has conducted two related studies, although they are on a much smaller scale and best viewed as preliminary. Nevertheless, they provide additional support for disease and gender-dependent influences on sleep regulation. The first evaluated SWA response to 40 h of total sleep deprivation in 15 healthy young men and women. Although SWA was enhanced in both groups, the effects were stronger in women ($P < 0.02$). What is more, both the amplitude and time course may show a proportionately larger response to sleep deprivation in women [52].

The second study examined the effect of increasing prior wakefulness by 2 h in nine patients with MDD and eight healthy controls. As expected, a group by gender interaction was obtained ($P < 0.0004$) with the greatest SWA enhancement in MDD women and the smallest effect in MDD men. As seen in baseline SWA, the gender differences within the MDD group were more than twice as large as those obtained in healthy controls [53].

INTERPRETATION AND THEORETICAL IMPLICATIONS

This body of work clearly indicates that the sleep microarchitectural abnormalities associated with MDD differ for men and women. Women with MDD are more likely to show low coherence and ultradian rhythm dysregulation whereas dampened SWA regulation is more prevalent in men. As such, these data provide very strong support for a gender-dependent pathophysiology of MDD. Although women are clearly at greater risk for MDD, both men and women are vulnerable to the disease. How the sleep and biological abnormalities contribute to the genesis of MDD may also be gender specific. The strength of this position is further enhanced by evidence of gender differences in brain organisation and function regardless of disease. Indeed there is a strong theoretical and empirical foundation for sexual dimorphism in humans and animals. Brain morphology, distributions of neurotransmitter receptors, cerebral evoked potentials, glucose metabolism in brain, overall metabolic rates and asymmetries during task performance all show strong gender differences [54–56]. Sex steroids which regulate the synthesis and activity of neurotransmitters, receptors, enzymes and hypothalamic pituitary adrenal (HPA) axis (all of which impact sleep EEG organisation and regulation) show sexual dimorphism across species [7, 8, 57].

As mentioned previously, gender differences in sleep EEG in healthy individuals are relatively subtle under baseline conditions [7]. They are more evident under conditions that probe or challenge brain organisation. Sleep deprivation, stress or pharmacological challenge all appear to elicit larger gender effects that are evident at baseline. Rubin *et al.* have also shown a greater neuroendocrine response to cholinergic challenge in women than in men [58, 59]. In fact, Rhodes and Rubin [60] suggest that males are anatomically or morphologically distinct

from females (i.e. cell density and size) whereas females are functionally distinct. Numerous studies, including our own work, support greater response to challenge in women than in men [5, 8, 38, 52]. These findings may reflect greater adaptive response or functional plasticity in women, that manifests as more dynamic organisation of sleep micro-architecture [7, 42].

Moreover, it is our view that there are gender-specific vulnerabilities to organisational abnormalities that emerge under extreme challenge conditions in healthy individuals which provide insight into understanding gender differences in those with MDD. Challenging a more dynamic or adaptive regulatory system to maximum capacity would be likely to produce hyper-responsivity and perpetual reorganisation. On the other hand, a more static, less responsive system may very well move toward inertia and hyporesponsivity. We suggest that the former describes women with MDD and the latter men with MDD.

What evidence is there that women with MDD are more responsive to challenge or show more dynamic organisation of sleep EEG? Neuroendocrine challenge studies indicate a larger response in women with MDD than in healthy men and women or MDD men [59]. Women with MDD show more fast frequency (beta and alpha) EEG activity during baseline sleep [7, 40] but do not show less SWA [41]. Although increased beta activity during sleep has often been interpreted as "hyperarousal" [39], it may be best viewed as evidence of more dynamic brain organisation since it is not accompanied by lower SWA. As argued earlier, more dynamic brain organisation would be expected to decrease co-ordination of EEG rhythms and produce lower temporal coherence, a finding that is more prevalent in women than men with MDD [42]. Moreover, our preliminary data suggest that women with MDD show a larger SWA response to sleep delay than all other groups, including healthy women. Taken together, these findings strongly suggest that women with MDD show an exaggerated response to challenge, as evidenced by enhanced SWA response, and more dynamic organisation of sleep EEG, reflected in lower coherence, even in the absence of a challenge. Men with MDD, on the other hand, show less SWA at baseline, a very small response to sleep delay and extended wakefulness, and are only half as likely to show low coherence. Nevertheless, both men and women with MDD show evidence of SWA

regulatory abnormalities but it is hyper-responsivity in women and hyporesponsivity in men. The neuroendocrine data from Rubin *et al.* fall directly in line with this interpretation [58–60]. Moreover, a very recent special issue of *Biological Psychiatry*, 2000; 48(8) focuses on the contribution of neural plasticity to MDD. Post mortem studies have shown a high incidence of neuronal loss and damage in depression. Importantly, most post mortem tissue was collected from men who had depression. Conceivably, neuronal loss could contribute to reduced delta activity and the SWA abnormalities reported in men with MDD. If this speculation is correct, women with MDD should show greater neuronal plasticity and cell survival. However, this remains to be demonstrated.

Our theoretical position accounts for gender differences in the pathophysiology and perhaps the psychology of depression [61], but does not *prima facie* explain the increased prevalence of depression among women. Part of the explanation for increased risk for depression in women may lie in the time course of increased prevalence – during the reproductive years, from puberty to menopause. Circulating gonadal hormones, most notably estrogens, may further escalate the propensity to homeostatic hyper-responsivity and dysregulation in women. Estrogen has been shown to increase neuronal firing rates, i.e. induce greater responsivity, and there are also other conditions under which hormonal variation induces mood dysregulation and altered regulatory response: premenstrual dysphoria; postpartum depression; and perhaps the peri-menopausal period [62]. The timing of increased risk for depression among women does suggest that gonadal hormone regulation may elevate the propensity for dysregulation, but is unlikely to be a sufficient condition to induce it in and of itself. With regard to men, it is also possible that testosterone acts as an active homeostatic stabiliser, and increases the propensity toward hyporesponsivity.

This highly speculative view requires substantial confirmation and is a major focus of our ongoing work. Nevertheless, it is included in this paper to illustrate how studying gender differences in healthy individuals can be of value in understanding MDD and many other illnesses, particularly those with differential risk or prevalence.

As pointed out by Frank and Young [63], the gender differences in biology and physiology undoubtedly interact with psychosocial factors and stressors that collectively elevate the risk for depression in women. The failure to include both

genders and to evaluate gender effects statistically will ultimately limit our ability to understand sleep regulation, brain organisation and depression, and are likely to be of clinical consequence.

CLINICAL IMPLICATIONS

The data reviewed here do have clinical implications and raise a number of important clinical questions. For example, do these findings indicate that depression is a different disease in men and women? Certainly, the evidence is fairly convincing that at least the neurobiological correlates differ by gender. There is also growing support that the specific symptom improvement and side-effect profiles of some antidepressant medications differ in men and women with MDD [2, 64]. Should patient management strategies be tailored by gender? It is possible that due to increased responsivity, women with MDD may benefit more from behavioral management of sleep disturbances, particularly when used as an adjunct to pharmacotherapy. In a similar vein, the "cost" of prescribing antidepressants that reduce SWA and are alerting to sleep may be higher among women. If future research addresses these important clinical questions, taking gender into consideration in managing depression may very well become standard practice [9].

Practice Points

Gender differences in depressed patients are evident in:

1. Lifetime risk and prevalence.
2. Pharmacokinetics and pharmacodynamics.
3. Neurotransmitter and neurosteroid regulation.
4. Sleep EEG.
5. May also be evident in some clinical measures such as symptom profiles and risk factors.

Research Agenda

In the future we need to:

1. Quantify sex differences in basic, human and clinical work.
2. Understand the biological and psychological correlates of depression.
3. Determine the treatment relevance of gender differences in pathophysiology.

ACKNOWLEDGEMENTS

We are grateful to our collaborators: Graham Emshie, M.D., Mark Fulton, M.D., A. John Rush, M.D., and Madhukar Trivedi, M.D. for their tremendous contribution to our research and to the technical team of the Sleep Study Unit (Darwynn D. Cole, B.A., supervisor).

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