Child sexual abuse and stress reactivity in women with premenstrual dysphoric disorder

Seksualinė prievarta vaikystėje ir reagavimas į stresą moterims, sergančioms premenstruaciniu disforiniu sutrikimu

Robertas BUNEVIČIUS[1], Susan S. GIRDLER[2]

[1]Institute of Psychophysiology and Rehabilitation, Kaunas University of Medicine, Palanga, Lithuania

[2]Department of Psychiatry, University of North Carolina at Chapel Hill, USA

SUMMARY

The aim of this report is a detailed review of three published studies on sensitivity of stress system in women with established diagnoses of premenstrual dysphoric disorder (PMDD) in association with histories of sexual and physical abuse as well as with treatment with clonidine. It was reported that:

1. Histories of sexual and physical abuse are associated with persistent alterations in stress-responsive systems in women, even in the absence of current psychiatric illness or medication use. PMDD women may be more vulnerable to the effects of abuse experiences on α-adrenergic receptor function as only PMDD women with abuse exhibited greater vascular tone and blood pressure levels relative to non-abused PMDD women.
2. Clonidine challenge probe indicate that the autonomic nervous system differences in abused PMDD women may be mediated, at least in part, by alterations in presynaptic α2-adreno receptor function. The use of a long lasting challenge with clonidine may be an useful tool for assessing sensitivity of central presynaptic α2-adreno receptor, when appropriate variables are measured.
3. There were found no evidence for the clinical efficacy of clonidine to treat premenstrual symptoms in a general group of women with PMDD. Moreover, the unfavorable profile of side effects seen with clonidine diminishes its usefulness in the treatment of PMDD.

Key words: Premenstrual dysphoric disorder, norepinephrine, alpha adreno receptor, clonidine, Trier social stress test.

SANTRAUKA

Šio straipsnio tikslas – detaliai apžvelgti tris straipsnius apimančius moterų sergančių premenstruaciniu disforiniu sutrikimu (PMDS) ir patyrusių seksualinę ar fizinę prievartą vaikystėje streso sistemos jautrumą, bei įvertinti taikytą gydymą klonidinu.

1. Seksualinės ir fizinės prievartos anamnezė yra susijusi su streso sistemos sutrikimais nepriklausomai nuo psichiatrinio sutrikimo buvimo ar gydymo. Moterys sergančios PMDS gali jautriau (per α-adrenerginius receptorius) reaguoti į patirą prievartą, nes prievartą patyrusių PMDS moterių, lyginant su prievartą nepatyrusioms PMDS moterimis, yra didesnis kraujagyslių tonas ir kraujo spaudimas.
2. Gydymas klonidinu parodė kad prievartą patyrusių PMDS moterų autonominės nervų sistemos funkcija lyginant su prievartos nepatyrusių yra, bent iš dalies, medijuojama presinaptinės α2-adreno receptorių funkcijos. Ilgalaikis klonidino mėginys gali būti naudingu instrumentu vertinant presinaptinių α2-adreno receptorių aktyvumą.
3. Klonidinas nebuvo efektyvus gydant premenstruacinius simptomus moterims sergančioms PMDS. Dar daugiau, nepalankus nepageidaujamo poveikio spektras mažina klonidino taikymo galimybes sergančioms PMDS moterims.

Raktžodžiai: Premenstruacinis disforinis sutrikimas, norepinefrinas, alfa adreno receptoriai, klonidinas, Triero socialinio streso testas.

INTRODUCTION

Population-based surveys in developed countries such as US have indicated that 13–27% of women were sexually abused as children. When adult sexual abuse and other forms of physical abuse are included, more than one third of women from the general population have had these experiences. The public health significance of abuse in women is underscored by the well-established links between histories of abuse and psychiatric as well as medical. Abuse rates for women in Lithuania are not established. However, having in mind high levels of aggressiveness of population in Lithuania, evident by very high suicide and homicide prevalence, it may be expected that proportion of sexual and physical abuse against women should be high in this country.

It is established that persistent alterations in neurobiological systems known to be stress responsive may contribute to the development of psychiatric illness in women with histories of physical and sexual abuse. The stress response system that has been most studied to date in relation to traumatic or abuse histories in humans is the hypothalamic-pituitary-adrenal (HPA) axis. Post-traumatic patients demonstrate mixed finding for lower cortisol concentrations or blunted cortisol reactivity to challenge. Fewer studies have examined noradrenergic function related to trauma or abuse suggesting increased noradrenergic (NE) activity in adults with prior traumatic stress [1]. The important interactive effects of depressive disorder and histories of abuse on HPA axis function have been reported. On the other hand strong evidence exist suggesting that histories of abuse have persistent effects on HPA axis function in women in the absence of current depression.

Premenstrual dysphoric disorder (PMDD) is estimated to afflict 5 to 8% of women in their reproductive years. Dysfunction in a variety of neurotransmitters has been implicated in PMDD,

Address for correspondence: Robertas Bunevičius, Vydūno al., 4, 00135 Palanga, Lithuania; e-mail: rob@ktl.mii.lt

including norepinephrine. Evidence suggests that women with severe premenstrual syndrome (PMS) and/or PMDD exhibit dysregulation in centrally-mediated adrenergic activity, adrenergic receptor (AR) functioning, and increased serum NE concentration at rest and during mental stress.

In prior research on sexual abuse and autonomic function in non-PMDD women, it has been difficult to assess the independent role of abuse history on neuroendocrine functioning, since many of the abused women had co-morbid post-traumatic stress disorder (PTSD). PMDD women with no current PTSD or other psychopathology, and who were not using medication, a history of abuse is associated with altered sympathetic function as reflected in resting NE levels and heart rate, AR responsivity to isoproterenol challenge, and NE reactivity to mental stress. Another strategy for investigating alterations in sympathetic function is to employ an adrenergic agent as a challenge test. Clonidine, a selective partial α2-AR agonist, has multiple effects on noradrenergic function. The rapid action of clonidine is mediated by stimulation of postsynaptic α2-AR and has been used as a challenge test in psychiatry as a means of measuring sensitivity of α2-AR in the brain, evident by increased growth hormone release from pituitary after clonidine. In contrast to a rapid action, longer-term effects of clonidine are mediated by stimulation of presynaptic α2-AR, where stimulation mediates biofeedback inhibition of noradrenergic activity. Such an inhibition in central sympathetic outflow is observed after oral administration of clonidine and is responsible for its cardiovascular action and behavioral effects [2].

Consistent with the evidence for heightened adrenergic function in PMDD, pharmacological agents whose mechanism of action involves augmenting NE activity have not proven effective for the treatment of PMDD. In contrast, medications blocking sympathetic activity have proven effective for premenstrual symptoms. Both the selective β1-AR blocker atenolol and the non-selective β-AR blocker propranolol were demonstrated to be effective in the treatment of PMS. Another pharmacological strategy to suppress noradrenergic activity is to stimulate α2-AR by clonidine suppressing NE output.

The aim of this report is a detailed review of published studies on sensitivity of stress system in women with established diagnoses of PMDD in association with histories of sexual and physical abuse as well as with treatment with clonidine.

METHODS

This is a review of three studies performed at the Department of Psychiatry of the University of North Carolina at Chapel Hill on impact of child physical and sexual abuse on biological profiles in women with PMDD in realtion to challenge with clonidine.

SUBJECTS

Twenty-five women prospectively diagnosed with PMDD and 42 non-PMDD controls were included to the study. All subjects were in good health, and none were taking any prescription medication, including oral contraceptives or psychotropic agents. Fourteen women agreed to participate in a subsequent clonidine intervention study. The protocol was approved by the University of North Carolina at Chapel Hill Committee on Protection of the Rights of Human Subjects.

PROCEDURES

Assessment of PMDD

The prospective record of the impact and severity of menstrual symptoms (PRISM) calendarwas used to classify PMDD women. In addition to symptom severity ratings, the PRISM calendar also incorporates measures of life-style impact, life events and the use of medications. Calendars were completed daily for 2 to 3 menstrual cycles.

Psychiatric histories

Structured clinical interviews (SCID) based on DSM-III-R criteria for Axis I disorders were conducted. All diagnoses were based upon a consensus diagnostic session with a psychiatrist. For past major depressive disorder (MDD), 7 months in full remission was required before testing. For other Axis I disorders, 3 years in full remission was required.

Sexual abuse histories

Subjects were asked about sexual abuse histories using a modified version of a validated interview (Leserman et al., 1997).

The version employed in the current study was modified by reducing the total number of questions, by excluding 'attempted' sexual abuse incidents, and by clarifying the definition of child sexual abuse (up to age 12). To meet criteria for sexual abuse incidents as an adult, there had to be clear threat of harm or force (pressure for sexual activity was not sufficient). To meet criteria as a child, the threat of force did not have to be as clearly established if it was implied by the age differential between perpetrator and victim. Sexual abuse was defined as any of two types of sexual experiences: those involving forced sexual touching (including oral sex and vaginal penetration with objects), and those involving intercourse.

Trier Social Stress Test (TSST)

Modified version of the TSST was used. The TSST is a stress test that reliably induces large and consistent HPA and cardiovascular responses. The TSST involves four components:

1. Pretask instructions: During pretask instructions, subjects were introduced to the "selection committee" who would later listen to their job talk. Subjects were also given the instructions for the mental arithmetic task. The duration of the instruction period averaged 5 min.

2. Speech preparation period: During this period, subjects were left alone for 5 min to prepare their talk.

3. Job speech: Immediately following the preparation period, the selection committee returned to the testing room and asked the subject to deliver his or her talk describing to the committee why he or she would be the perfect applicant for the position. If the subject finished before 5 min, the committee responded in a standardized way with prepared questions to ensure that the subject spoke for the entire period. Talks were tape recorded. Cardiovascular measures were taken at Minutes 1, 3, and 5 and averaged. Blood was sampled for plasma NE at the end of Minute 2.

4. Paced Auditory Serial Addition Test (PASAT): The PASAT involves the tape-recorded presentation of numbers from 1 to 9 and lasted 8.5 min. Subjects added each number presented on the tape to the immediately preceding number and stated the answer aloud. There were four series of

numbers, with progressively shorter interdigital intervals. The experimenter remained in the room to monitor performance. Cardiovascular measures were taken once each of the four series and averaged. Blood was sampled for plasma NE at the end of minute 2.

Stress recovery

Subjects rested quietly alone for 10 min. Blood was sampled at the end of this recovery period to capture the delayed plasma cortisol response to the TSST.

β-Adrenergic receptor responsivity testing

Mental stress testing was followed by a 20 min recovery period, during which the subject rested quietly in the supine position. Blood pressure was measured continuously using the Finapres (Ohmeda, Madison, WI) non-invasive blood pressure monitor. The standardized isoproterenol sensitivity test was used to evaluate β1-AR responsiveness in terms of the chronotrophic dose of isoproterenol required to increase HR by 25 beats/min (CD25). Progressively increasing bolus doses of isoproterenol (0.125, 0.25, 0.5, 1.0, 2.0, and 4.0 mg) were injected until an increase in HR of at least 25 beats/min was observed. HR responses following each dose were computed as the shortest of three successive ECG R-R intervals following drug injection, compared to the shortest three R-R intervals at rest (preinjection). The linear regression model of log dose/ HR response for each subject was used to determine CD25 exactly by interpolation. The CD25 measure provides an index of cardiac β1-AR responsiveness. A vascular β2-AR responsiveness index was also derived by determining the vasodilatory dose of isoproterenol required to decrease TPR by 40% (VD40), using log dose/TPR response interpolation. Both the CD25 and VD40 indicesare inversely related to receptor responsiveness.

Physiological recording procedures

During laboratory testing, blood pressures (BP) were recorded non-invasively using the auscultatory technique. A semi-automated blood pressure monitor was used to operate the blood pressure cuff, with cuff pressure and Korotkoff sounds (K-sounds) recorded in analogue form and displayed on a computer screen. Systolic blood pressure (SBP) corresponded to the onset of K-sounds and diastolic blood pressure (DBP) corresponded to the disappearance of K-sounds. Manual stethoscopic readings were taken initially using a sphygmomanometer in order to insure correct placement of the microphone. Impedance cardiography was used to permit non-invasive monitoring of cardiac performance. A custom-designed impedance cardiograph (HIC-100, Bioimpedance Technology Inc., Model 100, Chapel Hill, NC, USA) was used in conjunction with a tetrapolar band electrode configuration to record impedance dZ/dt and Z0 signals. Impedance and electrocardiogram signals were processed on-line by specialized computer software (BIT, Chapel Hill, NC) with subsequent manual editing to improve accuracy. For each minute of interest, a 30 s continuous sample of waveforms (obtained concurrently with BP) was processed to generate an ensemble-averaged cardiac cycle, from which stroke volume (SV) was determined by means of the equation and heart rate (HR) was determined by the mean interbeat interval. Cardiac output (CO) and total peripheral resistance (TPR) for these same minutes were then calculated using standard formula.

Laboratory testing procedures

Each subject was tested twice, once during her early follicular phase (days 2–6) and once 8–12 days after home urine testing revealed the luteinizing hormone surge. All cycles were later confirmed to be ovulatory using serum progesterone. Cycle phase at first testing was counterbalanced within groups. Before testing, subjects were instructed to refrain from all over-the-counter medications for 24 hr, caffeine for 8 hr, and nicotine for 1 hr. All laboratory test sessions began between 0730 and 0900.

During pretreatment luteal phase testing and during luteal phase testing following 2 months of clonidine versus placebo treatment, subjects were exposed to the following, identical testing procedures. Immediately upon arriving at the laboratory, subjects were instrumented for cardiovascular monitoring. Next, an intravenous (IV) line was established in an arm vein and once in place, a curtain was drawn that prevented the subject from viewing the IV. A minimum of 15 min elapsed between establishing the IV and beginning stress testing.

Clonidine intervention

A randomized, placebo-controlled, double-blind, cross-over design was used to determine treatment and the autonomic effects of oral clonidine. Thus, each woman was treated for 2 months with oral clonidine (0.3 mg/day, divided as 0.1 mg/capsule) and for 2 months with a masked, oral placebo, counterbalancing order of clonidine versus placebo. In order to increase tolerance to the sedative effects associated with clonidine, dose was titrated according to the following schedule: week 1=0.1 mg/day; week 2=0.1 mg, b.i.d.; and week 3=0.1 mg in the morning and 0.2 mg in the evening. In order to minimize placebo effects, the antihistamine loratadine (Claritin1) was chosen as an active placebo and administered according to the same schedule as clonidine (total dose=10 mg/day divided, into 3.33 mg/capsules). Loratadine is a second generation antihistamine, distinct from the first generation antihistamines as it does not readily penetrate the blood brain barrier and is free of effects on the central nervous system and does not affect cardiovascular measures. Thus, while loratadine should exert no central or cardiovascular effects in the present study, the use of an active placebo was intended to instill an expectation on the part of the participants that they were taking an active drug, thereby minimizing differences in expectations between the treatment and placebo conditions.

No PMDD subject dropped out during the clonidine intervention phase, though one subject who was assigned to receive placebo first dropped out during the second week on placebo. Another subject was lost to follow-up prior to initiating any treatment regimen. Thus, the 12 PMDD women who completed all aspects of the protocol in full compliance comprise this report.

Hormone and neuroendocrine assays

Plasma levels of NE were determined using the high performance liquid chromatography (HPLC) technique. The lower limit of quantification with this system is 25 pg/ml, and the intra-and inter-day coefficients of variation are less than 10%. Serum levels of progesterone were determined using RIA kits from ICN Pharmaceuticals, Inc. The specificity of the antiserum for progesterone is very high, showing only 0.01–2.5%

crossreactivity with other steroid compounds. Progesterone levels <3 ng/ml in the luteal phase of the cycle were considered reflective of an anovulatory cycle. Based on this criterion, all women included in this report exhibited ovulatory cycles during pretreatment, clonidine and placebo sessions.

DATA ANALYSIS

First analytical approach involved comparing abused and non-abused PMDD women for pretreatment differences in resting and, where relevant, stress-induced measures. Thus, the two groups were compared for differences that existed during the luteal phase test session that preceded randomization to treatment. These luteal phase levels constituted the pretreatment comparison data for examining treatment-related effects (see below). For the cardiovascular measures taken at rest and during mental stressors, data were analyzed using a 2 (Group) x 3 (Condition: Rest, Speech, Math) repeated measures analysis of variance (ANOVA), with condition as the repeated factor. For measures of b-adrenoceptor responsivity (CD25 and VD40 values), pretreatment comparisons were made using a one factor (Group) ANOVA.

In order to examine drug effects, for each dependent measure a delta score was created separately for clonidine and placebo conditions (treatment level – pretreatment level) such that negative values represented a decrease in the measure with drug while a positive value represented an increase. For the cardiovascular measures, data were then analyzed using a 2 (Group) x 2 (Drug: clonidine or placebo) x 3 (Condition) repeated measures ANOVA with Drug and Condition as the repeated factor. Where significant interactions emerged, subsequent simple effects analyses were conducted in order to determine the source of the effect. Paired comparisons t-tests were also employed to examine whether clonidine-associated changes in adrenergic measures were significantly different from zero.

RESULTS

A greater proportion of PMDD women relative to non-PMDD women had histories of both physical abuse (44% vs. 21%, p=0.05), and sexual abuse (40% vs. 14%, p=0.08).

PMDD women with abuse histories had greater body mass index than did non-abused PMDD women.

As expected, all women with histories of abuse (n=24) were more likely to meet criteria for histories of depression than were non-abused women (71% vs. 37%, p<0.01). However, the abused PMDD and abused non-PMDD groups did not differ in the proportion with prior depression (67% and 75%, respectively), nor did the non-abused groups (46% and 33%). In the PMDD sample only, 33% of the PMDD women with abuse histories also had histories of posttraumatic stress disorder (PTSD) compared with 0% of the non-abused PMDD women, (p<0.05), whereas abuse was not associated with different rates of prior PTSD in non-PMDD women.

Effects of Abuse Histories

All women with histories of abuse, regardless of PMDD diagnosis or menstrual cycle phase, exhibited significantly lower plasma NE concentrations at rest and during mental stressors relative to non-abused women, main effect of abuse (p<0.05). All women with histories of abuse also had significantly greater HR levels at rest and during stressors in both cycle phases, main effect of abuse (p<0.05). Subsequent simple effects analyses conducted separately in the two cycle phases revealed that only in the follicular phase did abused women tend to have lower plasma cortisol at rest and poststress relative to non-abused women (p<0.10).

Only for the PMDD women was prior abuse associated with elevated VRI measures at rest and during stress in both cycle phases(p=0.05). Similarly, for blood pressure only for PMDD women was prior abuse associated with significantly elevated SBP (p<0.05) and DBP.

There were no group or abuse-related effects for stroke volume index or CI. With the exception of cortisol, for each dependent measure significant main effects of condition were obtained (p<*0*.05), reflecting the significant change from baseline to stressors. Failure to observe a significant condition effect for cortisol (i.e., stress effect) was likely due to the fact that we tested all subjects in the morning, when diurnal effects on cortisol are greatest.

As expected, all PMDD women, regardless of abuse history, had greater symptom severity ratings, especially in the luteal phase (p<0.0001). An overall effect of abuse was also obtained, reflecting the generally greater symptom levels in abused versus non-abused women, (p<0.05), which was explored by examination of all least-squares means comparisons. These comparisons indicated that in the follicular phase, PMDD women with abuse had greater symptom severity for anger, irritability, depression, and headache than did non-abused PMDD women (all p<0.05), whereas abused, non-PMDD women had greater depression and fatigue ratings than did non-abused, non-PMDD women (p<0.05). In the luteal phase, the only significant effects to emerge regarding abuse histories were for the non-PMDD women, as abused, non-PMDD women had greater irritability (p<0.05) than did non-abused, non-PMDD women.

Effects of clonidine

As anticipated, for all PMDD women, clonidine significantly reduced circulating plasma NE concentrations relative to placebo (p=0.01), and significantly reduced both resting and stress HR, SBP and DBP, when compared with placebo (p<0.05). The effects of clonidine on β-AR function also was significantly different from placebo effects, clonidine increased both β1- and β2-AR responsivity as reflected in the greater decreases in CD25 and VD40 values relative to placebo (p<0.05). There were no significant effects of clonidine on CO or TPR.

A significant Drug x Abuse interaction was also obtained (p<0.05). Subsequent simple effects analyses conducted separately in the two groups indicated that, relative to placebo levels, clonidine lowered HR to a greater extent in the sexually abused PMDD women (p<0.01) than in the non-abused PMDD women (p<0.05), resulting in a significant group difference in the effects of clonidine on HR during the speech stressor (p<0.01).

The ability of the stressors to differentiate sexually abused from non-abused PMDD women was also evident for SBP as reflected in a significant Condition x Abuse interaction (p<0.05). Simple effects analyses conducted separately for each condition revealed that speech stress differentiated sexually abused PMDD women from non-abused PMDD women (p=0.05), during clonidine treatment (p<0.05). A similar tendency was seen for math stress. These effects are supported

by the results of the paired comparisons t-tests showing that only for the sexually abused women were the reductions in SBP significant from zero ($p<0.05$). Clonidine-associated reductions in DBP during speech stress were significant only in the sexually abused women ($p<0.05$), but significant in both groups during math stress ($p<0.05$).

In contrast to greater effects of clonidine in sexually abused women for measures of BP and HR, there was a tendency for the non-abused PMDD women to exhibit greater reductions in plasma NE with clonidine than the abused group ($p<0.10$), as supported by paired comparisons t-tests indicating that only in the non-abused group was the reduction in NE seen with clonidine significant from zero ($p<0.05$). Consistent with their greater clonidine-induced reductions in NE, only for non-abused PMDD women was the decrease in CD25 (i.e., increase in β1-AR responsivity) and VD40 (i.e., increase in β2-AR responsivity) statistically significant ($p<0.05$) after clonidine treatment, contributing to a significant group difference in VD40 ($p<0.05$) after clonidine.

Analyses of variance indicated that while clonidine and placebo had no effect on the depression or anxiety scales, there were treatment effects seen for some PMDD symptoms such as depression ($p<0.04$), irritability ($p<0.008$), lack of control ($p<0.03$), breast tenderness ($p<0.03$), headache ($p<0.03$) and concentration of NE ($p<0.04$). Post hoc analyses revealed that, when compared with pretreatment levels, placebo significantly affected five of the seven PMDD symptoms, improving symptoms of depression, lack of control, breast tenderness and headache; but unexpectedly, increasing symptoms of irritability. Clonidine affected only two symptoms, improving lack of control and worsening irritability, in comparison with pretreatment levels.

As expected, the effect of treatment on NE concentration was significant ($p<0.04$). In contrast to the clinical data, post hoc analyses revealed that relative to pretreatment levels, the decrease in concentration of NE was significant only after clonidine treatment ($p<0.05$) but not after placebo treatment. Thus, at the end of the treatment period plasma NE concentration was significantly lower in the clonidine compared with placebo condition ($p<0.05$).

DISCUSSION

The results of these studies add to a divergent yet growing body of knowledge indicating that early life exposure to abuse leads to persistent and long-term dysregulation in stress-responsive systems. Moreover, these studies are among the first to demonstrate persistent cardiovascular and neuroendocrine dysregulation in women with histories of abuse who are not currently suffering from psychiatric illness or using psychotropic medications. These studies are also among the first to examine noradrenergic mechanisms (without and with clonidine challenge) in adult survivors of abuse. It was found that irrespective of PMDD diagnosis or menstrual cycle phase, women with histories of abuse had lower circulating plasma NE concentrations at rest and during stress.

It should be noted that these findings of reduced plasma NE coupled with greater HR at rest and during stressors in abused women may at first seem paradoxical, as catecholamines, including NE, act to stimulate HR increases via stimulation of β-adrenergic receptors. However, this finding is, in fact, consistent both with pharmacological theory and with the findings from our earlier study showing lower circulating plasma NE coupled with increased β-adrenergic receptor responsivity in PMDD women with histories of abuse (Girdler et al., 2003). Increased β-AR responsivity would be consistent with pharmacological up-regulation of the receptors in response to diminished agonist (i.e., diminished NE) and would mediate, at least in part, the increased HRs that we documented in all abused women in the present study. This hypothesis is speculative, however, as no assessment of β-AR responsivity was made in these studies.

Although only a trend, our finding of lower cortisol in abused women, at least in the follicular phase, is consistent with many studies on HPA axis function in abused women, reporting lower cortisol concentrations or blunted response. However, our results suggest that the hypocortisolemia noted in so many studies of traumatized individuals may represent a persistent effect of the exposure to traumatic stress and is not necessarily a result of current comorbid clinical depression or PTSD or the use of psychotropic medications. These findings, taken together, are in keeping with the emerging evidence that chronic or severe stress exposure can result in persistent alterations in neurobiological systems that are stress responsive and that this can be manifest in hyporesponsiveness of the system to subsequent stressors.

It has been suggested, that a genetic vulnerability coupled with early stress in a critical and plastic period of development, may result in persistent alterations in neurobiological systems that are known to be stress responsive, resulting in dysregulation in stress responsiveness to even mild stressors in adulthood and forming the basis for the development of mood disorders. Despite the fact, that none of the women in the present study met diagnostic criteria for a current mood disorder, our finding expose, that all women with histories of abuse, who displayed persistent dysregulation in measures reflecting both the HPA axis as well as the sympathetic nervous system, had more severe daily emotional and physical symptom ratings than did non-abused women suggests a persistence of mood disturbance associated with abuse history even in the absence of meeting current clinical criteria. It is interesting to note, however, that greater symptom levels in abused versus non-abused PMDD women were evident only in their follicular phase. Although the reason for this remains unknown, we hypothesize that the magnitude of symptom severity evident in the luteal phase for all PMDD women, a defining feature of their disorder, may override the more subtle influence of abuse histories on symptom severity [1].

Clonidine treatment

We found that PMDD women with prior sexual abuse responded differently to a long acting challenge with clonidine than PMDD with no history of sexual abuse. Women with prior sexual abuse showed greater reductions in BP and HR with clonidine than non-abused women, even when controlling for pretreatment differences in BP, and this effect was especially robust during mental stressors as compared with baseline rest. While one explanation for the greater BP and HR reductions with clonidine in the sexually abused group relates to their higher pretreatment levels and thus, may reflect a regression to the mean with repeat testing, the strict counterbalancing

of order of clonidine versus placebo, combined with the statistical control for pretreatment values argues against this interpretation in favor of one involving sympathetic nervous system mechanisms associated with a history of sexual abuse.

In contrast, in PMDD women with no prior history of sexual abuse, clonidine reduced plasma NE concentrations and increased β-AR responsivity to a greater extent than in PMDD women with prior sexual abuse. The effects of clonidine on β-AR responsivity in non-abused PMDD women are likely secondary to their greater reductions in plasma NE concentrations, an interpretation consistent with pharmacological theory, since diminished levels of agonist would be expected to up-regulate receptors. While at first, it may seem paradoxical that the reductions in circulating NE were greater in the non-abused PMDD women, one possibility is that the greater reduction in NE with clonidine in the non-abused group reflects the law of initial value, since they had nonsignificantly higher pretreatment NE concentrations.

Another plausible explanation for the lower pretreatment NE concentrations coupled with the diminished reduction in NE with clonidine seen in the sexually abused PMDD group is consistent with Selye's model of the general adaptation syndrome. There is now considerable evidence that dysregulation of the stress systems, resulting from exposure to chronic or severe stressors, may be expressed either as hyperfunction or as hypofunction in neurohormonal systems. Hypo-function in neuroendocrine systems might result from chronic hyperstimulation of the stress axes that eventually leads to a down-regulation in the system.

Thus, lesser decreases in NE concentration in response to a long-term clonidine challenge, as we observed in sexually abused PMDD women, may indicate hyposensitivity of presynaptic α2-AR in this subgroup of PMDD patients in the same way that short-term clonidine challenge tests indicate hyposensitivity of postsynaptic α2-ARs in other psychiatric populations. While speculative, this could account for the differentially greater effects of clonidine on BP and HR in sexually abused PMDD women, contrasted with the greater effects of clonidine on plasma NE in non-abused PMDD women.

Owing to the small sample size, especially the small cell sizes generated as a function of sexual abuse, the present results should be considered preliminary and interpreted accordingly. Another limitation of the present study is the lack of a non-PMDD comparison sample, the inclusion of which would have allowed for interpretations regarding whether PMDD women are more vulnerable to abuse-associated adrenergic dysregulation, or whether all sexually abused women would have responded differently to clonidine than non-abused women. Despite these limitations, the study has several notable strengths that should also be underscored. First, we used very strict diagnostic criteria to confirm PMDD, we employed validated structured interview to confirm abuse histories, and we examined the effects of clonidine using a double-blind, randomized, placebo-controlled design. Second, we excluded women with current psychiatric disorders, somatic disorders or who were receiving any pharmacological treatment, thereby addressing confounds that exist in the vast majority of prior studies of abuse and autonomic function [2].

The results of our study have not confirmed positive effects of clonidine on premenstrual symptoms in women with PMDD. In contrast to the only other placebo controlled trial of clonidine to treat premenstrual symptoms (Giannini et al., 1988), this study did not demonstrate that clonidine was superior to placebo in treating patients with PMDD.

While it is possible that reduced statistical power due to a small sample size may have affected the likelihood of detecting beneficial effects of clonidine, the direction of the differences towards reduced premenstrual symptoms when patients were receiving placebo renders this possibility unlikely. Though the reduction in premenstrual symptoms with placebo is no greater than would be anticipated as part of the 'placebo' effect, when contrasted with the negative side effects of clonidine, a greater benefit/risk ratio is seen for placebo.

The fact that no clinical benefit of clonidine was found but a significant decrease in plasma NE concentrations with clonidine, not seen with placebo, confirms that the women were compliant with the treatment regimen, but it also suggests that alterations in NE concentration may not play a primary role in the pathophysiology or manifestation of clinical symptoms of PMDD. Clonidine, a centrally acting α2-AR agonist, stimulates α2-ARs that are autoreceptors on noradrenergic nerve terminals, and decreases NE output but has no clinical benefit on PMDD symptoms. On the other hand, stimulation of central noradrenergic output has no significant clinical effect in PMDD either. This is supported by pharmacological studies that demonstrate an ineffectiveness of noradrenergic antidepressants in the treatment [3].

CONCLUSIONS

1. Histories of sexual and physical abuse are associated with persistent alterations in stress-responsive systems in women, even in the absence of current psychiatric illness or medication use. Our results also suggest, however, that PMDD women may be more vulnerable to the effects of abuse experiences on α-adrenergic receptor function as only PMDD women with abuse exhibited greater vascular tone and blood pressure levels relative to non-abused PMDD women.

2. The results of the clonidine challenge probe indicate that the autonomic nervous system differences in abused PMDD women may be mediated, at least in part, by alterations in presynaptic α2-AR function. The use of a long lasting challenge with clonidine may be an useful tool for assessing sensitivity of central presynaptic α2-AR, when appropriate variables are measured.

3. There were found no evidence for the clinical efficacy of clonidine to treat premenstrual symptoms in a general group of women with PMDD. Moreover, the unfavorable profile of side effects seen with clonidine diminishes its usefulness in the treatment of PMDD.

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