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Depressed suicidal adolescent males have an altered cortisol response to a pharmacological challenge

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Abstract

Dysregulation of the HPA axis and the dysfunction of the central serotonin (5HT) system are the most replicated biomarkers of depression and suicidal ideation and behavior. However, few studies have examined the two systems simultaneously. In this study, cortisol response was measured in depressed adolescents, following the administration of a central serotonin receptor agonist, meta-chlorophenylpiperazine (mCPP). Adolescents with major depression (MDD; $n = 44$; males = 15, females = 29; mean age $\pm$ SD = 15.5 ± 1.5) were divided into two groups: non-suicidal or those who reported passive suicidal ideation ($n = 21$), and those who had either threatened suicide or engaged in suicidal acts ($n = 23$). Sequential infusions of normal saline and mCPP were administered, and serial blood samples were collected for cortisol response. A differential time by group pattern of cortisol response following mCPP was found in the entire group ($F_{6,242} = 2.6$, $p = 0.018$). However, this was mostly attributed to males ($F_{6,73} = 2.3$, $p = 0.043$) who had threatened or engaged in suicidal acts and displayed a higher cortisol response at 10 and 25 min after the infusion of mCPP, which was not affected by the severity of depression. This differential pattern of cortisol secretion in response to a serotonergic agonist may be a biomarker for more severe forms of suicidal ideation and behavior in adolescent males.

Keywords

Adolescent-MDD; Serotonin; Cortisol

1. Introduction

Suicidal ideation and behavior are relatively common in adolescents in the general population and among those diagnosed with psychiatric conditions. In 2007, 14% of 9–12th graders in the USA reported suicidal ideation, while 6.9% had made a suicide attempt during the past year (Centers for Disease, 2007; Eaton et al., 2008). These behaviors are associated with significant morbidity and mortality and impose an enormous burden on health-care services. In addition, they have serious clinical implications. For instance, among patients seen in hospitals following self-harm, up to 5% die by suicide within 9 years (Skegg, 2005).

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Although there has been an extensive examination of psychiatric, social and demographic correlates of suicidal behavior in adolescents, relatively less is known about the biological markers of these behaviors. Suicidal ideation and behavior occurs across several psychiatric disorders, making it important to differentiate between symptom-specific (that is, related to suicidal ideation and behavior alone) and disorder-specific correlates.

Several neurobiological factors, irrespective of age, have an association with suicidal ideation and behavior. At a molecular level, serotonin (5HT) is believed to be a key neurotransmitter involved in these behaviors. Therefore, genes coding for proteins involved in serotonergic neurotransmission have been extensively studied (Souery et al., 2003). Other factors identified are the over-activation of the HPA axis (hypothalamic–pituitary–adrenal axis) summarized by Young and Coryell (2005); low cholesterol levels (Coryell and Schlessler, 2007); augmented cortisol response to 5-hydroxy-tryptophan in adults with either bipolar or unipolar affective disorder who had engaged in suicidal acts (Meltzer et al., 1984); and, disturbance of the central serotonin activity modulated by the HPA axis via serotonergic projections from the dorsal raphe (Lopez et al., 1997). These factors appear to act in combination, resulting in a final common pathway that may lead to suicidal acts and in some cases, suicide. Lopez et al. (1997) summarized the HPA-5HT interaction at the central nervous system level that suggests that elevated circulating cortisol reduces indices of serotonin turnover, which exert effect via 5HT_{1a} and 5HT_{1b} receptors in the hippocampus and 5HT_{2a} receptors in the cortex. (Lopez et al., 1997).

The overlap between the HPA and 5HT systems is further supported by Sher (2007a,b) who hypothesize that adolescents with a genetic vulnerability inherited by multiple interacting genetic loci of modest effect. These adolescents may be susceptible to both alcohol misuse and suicidal behavior through interaction between serotonergic and HPA axis via glucocorticoid and mineralocorticoid receptors located in the serotonergic projections from the dorsal raphe nucleus in the midbrain to the hippocampus (Sher, 2007a,b). Also, consistent with this theoretical framework, suppressed level of cortisol was found in response to infusion with a serotonin precursor, 5-hydroxy-tryptophan (L-5HTP), among children who were either currently depressed or at high risk for depression (Birmaher et al., 1997). Clearly, there is strong evidence for a dynamic interaction between the HPA axis and central serotonergic systems, offering potential for a better understanding of the biological basis of suicidal behavior.

Cortisol dysregulation has been extensively studied among adolescents who are depressed, suicidal or both. The heritability of cortisol secretion is supported by findings among children of alcoholics (Sher, 2007a,b) and offspring of parents with bipolar disorder (Ellenbogen et al., 2010). With regards to clinical relevance of cortisol secretion during depression, onset of depression during a 12-month period among a subgroup of high-risk adolescents was predicted by elevated cortisol at 8 a.m. or by elevated dehydroepiandrosterone (DHEA), an adrenal steroid, at 10 p.m., with an additive effect conferred by higher depressive symptoms and personal disappointments (Goodyer et al., 2000). Dahl et al. (1991), in one of the earliest studies of this phenomenon, found an association between suicidal ideation and behavior and cortisol hypersecretion during the peri-sleep onset period among adolescents who were depressed, suicidal and hospitalized

(Dahl et al., 1991). Goodyer et al. (1998) found that children and adolescents with a higher cortisol/DHEA ratio (at 8 pm and midnight) during a first depressive episode were more likely to experience a persistent illness course and stressful life events. They suggested that biological vulnerability (i.e., higher cortisol/DHEA) may confer additional risk of experiencing psycho-social stress and a higher likelihood of engaging in suicidal behaviors (Goodyer et al., 1998). Another study found that depressed adolescents with higher cortisol levels at 4, 6 and 12 h prior to sleep, and lower cortisol 2–4 h after sleep-onset, were more likely to attempt suicide 10 years after their initial diagnosis and cortisol measurement (Mathew et al., 2003), suggesting the clinical relevance of cortisol secretion as a biomarker for future suicidal ideation and behavior. Thus, there is compelling justification for measuring cortisol dysregulation in depressed, suicidal adolescents.

In an attempt to study the HPA axis and central serotonin system simultaneously, we employed m-chlorophenylpiperazine (mCPP), a directly acting central nervous system serotonin receptor agonist, which is known to increase the secretion of cortisol, prolactin, and ACTH. In comparison with other frequently employed methods used to investigate the HPA axis (baseline cortisol, CRH challenge, and dexamethasone suppression test) mCPP, which is a major metabolite of trazodone, has the advantage of being a potent post-synaptic agonist at the central 5HT₁ and 5HT₂ receptor level. (Hamik and Peroutka, 1989). Based on these actions, this probe has been used as a pharmacological tool to measure 5HT receptor function (Murphy and Mueller, 1986; van Praag et al., 1987). Secretion of cortisol in response to a mCPP challenge is believed to reflect direct central 5HT function, including 5HT receptor activity which is involved in suicidal behaviors (Souery et al., 2003).

The data for the present study were collected over a three-year period to identify hormone responses to mCPP among depressed adolescents and was a part of a study funded by the NARSAD Foundation and the NIH (M01-RR00042). The aim of the study was to identify cortisol response to mCPP and saline in a homogenous group of depressed adolescents. The study was approved by the IRB and written, informed consent of a parent and assent of the adolescent were obtained. We hypothesized that a differential cortisol response may be associated with the severity of suicidal behavior, in response to a physiological stress (saline infusion) and to the serotonin agonist, mCPP.

2. Procedures and methods

Inclusion criteria were: (1) primary diagnosis of MDD, (2) age 13–17 years, (3) absence of illicit drug or alcohol use during the past 4 weeks and absence of a life-time substance abuse/dependence diagnoses, and (4) not receiving a psychotropic medication for 2 weeks (3 weeks for fluoxetine) at the time of participation in the study (study design did not permit discontinuing psychotropic medications for the purpose of the study). Exclusion criteria were: (1) imminently suicidal (defined as immediate risk of inflicting self-harm), (2) presence of a psychotic disorder (schizophrenia, schizoaffective disorder or psychosis-not otherwise specified; psychotic depression was not an exclusion), (3) presence of a significant medical disorder determined by history-taking, physical examination or laboratory tests (EKG, CBC, liver and thyroid function tests, urine toxicology), (4) pregnancy (urine pregnancy test was completed for all female participants) or lactation.

Participants were adolescents diagnosed with MDD ($n = 44$; age range = 13–17; mean age in years = 15.5 ± 1.5 ; females = 29 [66%] Caucasians = 37 [84.1%]) admitted to a research unit of a University child psychiatry department. Other characteristics were: Tanner stage range = 3–5; menstrual phase of females: proliferative = 16, secretory = 8, no menarche = 1, missing or unknown menstrual phase = 4; age of first psychiatric contact = 11.1 ± 4.1 ; mean Children's Depression Rating Scale-R = 52.1 ± 15.8 ; comorbid anxiety disorders = 8 [18%] comorbid dysthymia = 9 [20.5%]). Each participant received a psychiatric evaluation, a structured diagnostic-Diagnostic Interview Schedule for Children (DISC; Costello et al., 1985; Fisher et al., 1993); a battery of standardized psychiatric rating scales; physical examination; laboratory tests (EKG, CBC with differential count, urine toxicology, thyroid and liver function tests and urine pregnancy test for females). None of the participants were diagnosed with a psychotic depression, possibly due to exclusion based on the presence of any psychotic disorder. Also absent was any significant medical disorder in this group.

The battery of psychometric instruments consisted of the following: (1) CDRS-R: Children Depression Rating Scale-Revised (Poznanski et al., 1984), is a semi-structured clinician-interview to identify the severity of depression. It covers 17 symptom areas and uses parent and adolescent reports. A score of 40 is generally indicative for clinical depression (Poznanski et al., 1984); (2) CBCL: The Child Behavior Checklist (Achenbach and Edelbrock, 1981) is a 118-item questionnaire completed by an adult who lives with and knows the child well. It is designed for 5th grade reading skills. It may be completed by an interviewer who writes down the answers of the parent/child care worker; (3) YSR: Youth Self Report (Achenbach and Ruffle, 2000), is a 119-item, self-rated questionnaire designed for 11–18 years old with mental age of at least 10 years and fifth grade reading skills. It provides a standardized summary of competencies and problems reported by a youth compared to those reported by other youths of the same sex; (4) GAF: Children's Global Assessment of Functioning, is a 100-point clinician rating scale that provides a global score based on a child's psychological, social and school functioning; (5) SSB: Spectrum of Suicidal Behaviors scale (SSB; Pfeffer, 1979), is a clinician-rated scale for measuring suicidal behavior for the past week, 6 months and lifetime, and was specifically designed to measure the severity of suicidal behavior. Ratings are 1 = non-suicidal, 2 = suicidal ideation, 3 = suicidal threat, 4 = mild attempt, 5 = serious attempt. A rating of 3 or above is generally considered indicative of serious suicidal intent or behavior. Using this scale, suicidal ideation and behavior experienced during the past six months was measured and two groups were defined: High SSB (HSSB; SSB score of 3 or greater, i.e., expressed a suicidal threat, history of a mild or a serious attempt) and Low SSB (LSSB; SSB score of less than 3, i.e., expressed either no suicidal ideation or passive suicidal thoughts).

Participants were hospitalized to a research unit one night prior to study procedures. They were allowed to drink only water after midnight; no food was permitted. Also, smoking and exercise were not allowed, although normal physical activity was permitted. Next morning, an IV cannula was placed in the antecubital fossa at 7 a.m. Each participant received a saline and mCPP infusion, using a fixed order (saline followed by mCPP 0.1 mg/kg) in a single blind manner (staff, but not the participants, were aware of the order of infusions). Serial blood samples were collected at 14 time points, 2 blood draws before (3 and 10 min “Time0” just prior to each infusion) and 5 during each (20, 35, 50, 95, 120 min post infusion)

saline and mCPP infusions. Blood samples were placed into vacutainer tubes containing ethylenediamine-tetra-acetic acid (EDTA). Tubes were placed on ice and centrifuged immediately after collection. Plasma was aliquotted and stored at -70°C until cortisol assay and levels were assessed.

3. Analyses and results

A series of Chi-square or t-tests were performed to compare baseline characteristics of the two groups (HSSB and LSSB; see Table 1) and to identify covariates that were used in further analyses. Total cortisol responses were examined using area under the curve (AUC) as described by Pruessner et al. (2003) and repeated measure analysis of variance (ANOVA) to identify the pattern of cortisol secretion over time. Significance set at $p = 0.05$.

Cortisol levels were compared between and within the HSSB and LSSB groups. The group differences, summarized in Table 1, were found to not differ significantly in terms of age, gender, age at first psychiatric contact, race, pubertal development, and CBCL externalizing scores. However, the HSSB group had significantly higher baseline CDRS-R scores ($p = 0.006$), lower GAF scores ($p = 0.009$), higher total problem CBCL scores ($p = 0.04$) and higher internalizing CBCL scores ($p = 0.05$). Gender differences included that a greater proportion of females in the HSSB group were in their secretory phase (defined as the 2-week time-period prior to anticipated onset of the next menstrual cycle), while a higher proportion in the LSSB group were in the proliferative phase (defined as time-period between the first day of previous menstruation until 2 weeks prior to the anticipated date of next menstruation; $p = 0.03$). The groups based on SSB scores were significantly correlated with CBCL total scores ($r = 0.38$, $p = 0.02$) and internalizing scores ($r = 0.31$, $p = 0.05$) but not with CBCL externalizing score ($r = 0.28$, $p = 0.07$). Therefore, CBCL scores were not included in the subsequent analyses due to its correlation with SSB-groups.

Cortisol secretion decreased significantly between baseline measurements (computed as the average of the first two recorded measurements at 7:50 and 7:57 a.m.) and 10:00 a.m. in both the LSSB and HSSB groups after saline infusion ($t = 4.2$, $df = 20$, $p < 0.001$ and $t = 6.0$, $df = 22$, $p < 0.001$, respectively). This was consistent with the expected physiological diurnal decline during that time. There was no significant difference between the LSSB and HSSB groups in baseline cortisol at 8:00 a.m. ($t = 0.76$, $df = 42$, $p = 0.452$) or cortisol at 10:00 a.m. ($t = 0.391$, $df = 42$, $p = 0.698$), and the change from 8:00 a.m. to 10:00 a.m. did not differ significantly between the two groups ($t = 0.971$, $df = 42$, $p = 0.337$). We next examined the cortisol-change score between the two baseline cortisol measurements, controlling for baseline depression severity (CDRS-R) and for gender. These results did not change appreciably when controlling for gender and CDRS-R score (Fig. 1).

Next, the total cortisol response, AUC, during the two infusions (saline and mCPP) was compared for all subjects. The entire group experienced a significant increase in their mean cortisol AUC response during mCPP infusion compared to saline infusion (Mean saline AUC = 81.9 ± 28.0 , Mean mCPP AUC = 92.8 ± 29.4 , $t = 2.47$, $df = 43$, $p = 0.02$). The cortisol AUC responses, following saline and mCPP infusions, were not significantly different within the LSSB group (Mean saline AUC = 81.8 ± 22.6 , Mean mCPP AUC = 92.4

± 38.4 , $t = 1.55$, $df = 20$, $p = 0.136$). However, the cortisol responses showed a trend toward significance within the HSSB group (Mean saline AUC = 81.9 ± 32.7 , Mean mCPP AUC = 93.1 ± 18.8 , $t = 1.91$, $df = 22$, $p = 0.07$). There was not a significant difference in the change score (AUCdiff calculated as = Mean AUC after mCPP infusion minus Mean AUC after saline infusion) between the two groups ($p = 0.953$). The change score between the two infusions was not significantly different for the two groups ($p = 0.857$), after controlling for depression severity scores (CDRS-R total) and gender (Fig. 2).

A repeated-measures ANOVA was used to separately compare the pattern of cortisol response among HSSB and LSSB adolescents, during saline and mCPP infusions. The model included the main effects of time (7 time points), SSB group, and their interaction. During the saline infusion, as expected, there was a significant time effect ($F_{6,241} = 16.6$, $p < 0.001$), but the effect of group was not significant ($p = 0.978$) and the interaction between time and group was also not significant ($p = 0.135$). During the mCPP infusion, there was a significant time effect ($F_{6,242} = 111.9$, $p < 0.001$), and again there was no significant main effect of group ($p = 0.970$), but there was a significant group by time interaction ($F_{6,242} = 2.6$, $p = 0.018$), indicating that the pattern of change over time for the two SSB groups was significantly different. Results did not change appreciably when the analysis was controlled for CDRS-R and gender; the interaction between SSB group and Time was still nonsignificant for the saline infusion ($F_{6,240} = 1.64$, $p = 0.136$); however, the interaction between SSB group and time was again significant for the mCPP infusion ($F_{6,241} = 2.6$, $p = 0.018$). A post hoc comparison of the mean cortisol levels for the two groups at each time of the mCPP infusion revealed no significant difference between the mean cortisol levels for the LSSB vs. HSSB groups at any time point.

The effect of menstrual phase was examined next by comparing cortisol response to saline and mCPP infusion among females who were in their proliferative phase of menstrual cycle ($n = 10$ LSSB, $n = 6$ HSSB), again controlling for CDRS-R. The analysis was restricted to this subgroup of girls in proliferative phase due to the small numbers in the secretory menstrual cycle phase (there was only one girl in the secretory phase in the LSSB group, and there were 7 girls in the secretory phase in the HSSB group). The significant interaction between time and SSB group that was seen in the analysis of mCPP infusion for all subjects was not seen for this subgroup of females ($F_{6,82} = 0.426$, $p = 0.859$), nor was there a significant difference in mean cortisol levels for the LSSB and HSSB groups for these females at any time point. Having examined cortisol responses among females separately, we also compared the effect of mCPP infusion over time for males ($n = 8$ LSSB, $n = 7$ HSSB). A significant interaction between group and time during mCPP infusion observed for all subjects was also present for this subgroup ($F_{6,73} = 2.3$, $p = 0.043$). In addition males among the HSSB group had a significantly higher mean cortisol level than the LSSB group at 10 min and 25 min after infusion ($p = 0.016$ and 0.013 , respectively) (Fig. 3).

Having found this difference in males, we re-examined the AUC between LSSB and HSSB for males and females separately. In this analysis there was still no significant difference between LSSB and HSSB groups among females or males ($p = 0.560$ and $p = 0.175$, respectively). In summary, the two SSB groups displayed a differential *pattern* of cortisol

response over time, even when controlling for depression severity; however, this difference in pattern was mainly attributed to males.

4. Discussion

The overall findings of the present study identify male gender as a significant factor in respect with cortisol secretion. A differential pattern of cortisol hypersecretion was found only in males who had reported higher suicidal ideation and behavior, as defined for the purpose of this study. Other noteworthy findings are: (1) there were no *baseline* cortisol differences related with the severity of suicidal ideation and behavior or gender; (2) the *total quantity* (AUC) of cortisol secreted during saline or mCPP did not differentiate between the two groups based on severity of suicidal ideation and behavior and gender; (3) the *differential pattern* of cortisol hypersecretion found during the mCPP infusion was evident only in males who had reported higher suicidal ideation and behavior. Females and males did not significantly differ by race, Tanner stage, hospitalization status, global functioning, depression-severity or comorbid disruptive behavior disorders.

Findings related to cortisol dysregulation among adolescents with depression with/without suicidal ideation or suicidal behaviors are complex and are influenced by several confounding variables. These may include the time of measurement, chronicity of illness, presence of co-morbid diagnoses, developmental stage of the adolescent, gender, psychosocial factors and possibly other, yet unknown, factors. Nevertheless, the existing literature suggests that subgroups of depressed adolescents experience either episodic or sustained cortisol hypersecretion, that subtle or qualitative findings in addition to quantitative findings should be examined, and that such findings are relevant for predicting long-term clinical outcome. This overall theoretical framework was supported by our findings, which suggest that, episodic cortisol hypersecretion may be a biomarker of more severe suicidal ideation or behaviors among males. The present study adds to the existing literature which supports the overlap between central serotonergic and HPA mechanisms in suicidal behavior and ideation in adolescents (Kruesi et al., 1992; Goodyer et al., 1996; Tyano et al., 2006). It is noteworthy that we had previously reported elevated cortisol in response in adolescent males, compared with females, with no interaction evident for the type of infusion (saline or mCPP) or with time (Ghaziuddin et al., 2003).

Few studies have examined the effect of gender on cortisol secretion. A Dutch population based study (TRAILS; Tracking Adolescent's Individual Lives Survey), examining the effect of social stress on gender, found that boys compared to girls had a lower cortisol response upon awakening but a stronger cortisol response to social stress (Bouma et al., 2009). The study, however, was limited by the absence of a depressed or a suicidal group. Studies which did include a depressed group, but did not find a gender-effect on cortisol secretion, include Forbes et al. (2004) and by Dorn et al. (1996). Lack of association found between depression and cortisol secretion, and between gender and cortisol secretion in the study by Forbes et al. (2004) may be due to the younger age of both depressed and control groups (12.5 and 10 years respectively) (Forbes et al., 2004). Although, Dorn et al. (1996) found a greater ACTH response to CRH stimulation test among boys which was irrespective of their depression status (Dorn et al., 1996), it is difficult to compare their findings to those of the present study

because of the different mechanism of action of CRH; CRH acts primarily by releasing ACTH, whereas mCPP acts on central 5HT receptors. In summary, findings related to the effect of gender on cortisol secretion are mixed and require further examination.

Limitations of the present study include a small sample size, saline and mCPP infusions were administered on the same day, lack of normal controls, the effect of menstrual cycle could not be fully examined due to the small number of females in the LSSB group who were in their secretory phase of the cycle, the effect of other comorbid diagnoses was not examined, past history was not recorded that would clarify if the participants had experienced previous depressive episodes, interval between suicidal behaviors and actions and when study procedures were completed was not recorded, and whether there were any symptoms suspicious for bipolar depression (predominantly irritable mood, SSRI induced hypomania or worsening in response to antidepressants). Furthermore, the relatively small sample size may also be a factor in our finding of cortisol hypersecretion limited to males. Strengths of the study are that participants were homogenous in terms of a non-psychotic depression diagnosis (possibly due to stringently applied exclusion criteria for psychotic disorders), on measure of pubertal development, were free of psychotropic medications at the time of the study, and were screened out if there was a positive history of substance abuse and/or alcohol. The subjects included in the present study were adolescents who were mid to late pubertal (Tanner stage 3), thus constituting a relatively homogenous group in terms of their pubertal development. Puberty is important because of the association between cortisol secretion (Forbes et al., 2006), particularly in adolescent males (Di Luigi et al., 2006).

The main clinical implication of our finding is that among depressed adolescent males, episodic cortisol hypersecretion may be a biomarker of more severe suicidal ideation and behavior experienced during the previous six months. Although, clinical application of the method used in the present study may be limited because the pharmacological probe that we used required intravenous administration, alternative orally administered probes may be explored. Future studies should also examine the precise timing of cortisol disturbance among adolescents who are both suicidal and depressed. Because of its cross-sectional design, the present study is unable to answer whether cortisol hypersecretion preceded, accompanied, or followed depression or whether these findings have predictive implications (illness-recurrence, suicidal acts or completed suicide). Moreover, because of the absence of a control group, these findings could not be compared with non-depressed males. These questions can only be answered by larger scale and longer term studies that would compare depressed adolescents with normal and/or psychiatric controls, while including adolescents with different symptom profiles and comorbid diagnoses.

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Fig. 1.

Decline in plasma cortisol in subject-groups (LSSB & HSSB) based on SSB scores (spectrum of suicidal behaviors).

Fig. 2.
Change in plasma cortisol AUC in subject-groups (LSSB & HSSB) based on SSB scores (spectrum of suicidal behaviors) following saline and mCPP infusions.

Fig. 3.

Plasma cortisol among males based on SSB groups at multiple time points (repeated measures) during mCPP infusion.

Table 1

Demographic and clinical characteristics: groups based on spectrum of suicidal behavior scale (SSB) and gender.

	Low SSB SSB < 3 (n = 21)	High SSB SSB 3 (n = 23)	Females (n = 29)	Males (n = 15)	p
Age	15.6 ± 2 years	15.3 ± 1 years	15.5 ± 1.6	15.2 ± 2	0.52
Gender (%)	F = 13 (62)	F = 16 (70)			0.59
Race (%)	Caucasians = 17 (81)	Caucasians = 20 (87)	Caucasians = 25 (68)	Caucasians = 12 (32)	0.9
~ Tanner stage					
3	0	3 (13)	3 (11)	0	0.1
4	6 (35.3)	10 (43.5)	8 (30)	8 (62)	
5	11 (64.7)	10 (43.5)	16 (59)	5 (38)	
Menstrual phase:					0.03 ^{*,a}
Proliferative	10 (91)	6 (43)	16 (64)		
Secretory	1 (9)	7 (50)	8 (32)		
Pre-pubertal	0 (0)	1 (8)	1 (4)		
Hospitalized	7/21(33)	18/22 (82)	16/28 (57)	9/15 (40)	1.0
Co-morbid dysthymia	1/15 (7)	8/23 (35)	6/23	3/13	0.6
Co-morbid any anxiety disorder	1/13 (6.7)	7/21 (33.3)	5/23	3/13	0.6
Co-morbid disruptive behavior disorder	4/15 (26.7)	6/21(28.6)	5/23	5/13	0.2
GAF score	54±12	42±14	49.5± 14.7 ^{*,a}	45.1±11.2	0.3
^a Baseline CDRS-r	45±11	59±17	52.8±15.7 ^{*,a}	50.4±16.4	0.3
Baseline sleep problems	3.3±1.3	4.1±1.2	3.9±1.3	3.4±1.4	0.3
CBCL externalizing score	57±12	64±12	60.7±12.2	60.5±13.1	0.9
CBCL internalizing score	62 ±10	68 ±9	64.5±10.2	65±8.8	0.8
CBCL total problem score	59±12	67±10	63±11	62.7±13.3	0.9

~ Tanner: 3 = dark, coarse pubic hair; 4 = adult but decreased distribution; 5 = adult distribution of pubic hair.

^a Baseline sleep problems was derived from CDRS-R.* $p < 0.05$.** $p < 0.01$.† $p < 0.10$.