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Association of testosterone levels and future suicide attempts in females with bipolar disorder

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Abstract

Background—Considerable evidence suggests that testosterone may play a role in the pathophysiology of mood disorders in females. This is the first prospective study to examine whether blood testosterone levels predict suicide attempts in females with bipolar disorder.

Methods—Females with a DSM-IV diagnosis of a bipolar disorder in a depressive or mixed episode with at least one past suicide attempt were enrolled. Demographic and clinical parameters were assessed and recorded. Plasma testosterone was assayed using a double antibody radioimmunoassay procedure. Patients were followed up prospectively for up to 2.5 years.

Results—At baseline, testosterone levels positively correlated with the number of previous major depressive episodes and suicide attempts. Cox proportional hazards regression analysis found that higher baseline testosterone levels predicted suicide attempts during the follow-up period.

Limitations—A limitation of the study is that the sample size is modest. Another limitation is that we did not have a bipolar nonattempter or healthy volunteer control group for comparison.

Conclusion—Testosterone levels may predict suicidal behavior in women with bipolar disorder.

Keywords

bipolar; female; testosterone; suicide

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Contributors: Leo Sher designed the study and managed the literature searches and analyses. Leo Sher, Maria A. Oquendo, J. John Mann, Michael F. Grunebaum, Gregory M. Sullivan, Ainsley K. Burke, and Thomas B. Cooper contributed to the implementation of the study. Leo Sher undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Introduction

The lifetime prevalence of bipolar I disorder has been found to be around 1% for both men and women (Kessler et al., 1994). Bipolar disorder is potentially fatal as a result of accidents and increased mortality associated with comorbid substance use and medical illnesses, but its highest lethality relative to the general population results from suicide (Bostwick and Pankratz, 2000; Mitchell and Malhi, 2004; Oquendo et al., 2004; Tondo et al., 2003). Lifetime rates of attempted suicide may be higher in bipolar disorder than major depressive disorder (ranges of 26–29% versus 14–16%) (Chen and Dilsaver, 1996). Rates of completed suicide in bipolar disorder are also high, about 10–20% lifetime (Goodwin and Jamison, 1990). A meta-analysis of suicide studies in psychiatric disorders found that the suicide rate for bipolar disorder was 15 times that of the general population (Harris and Barraclough, 1997). No gender difference has been found in terms of completed suicide rates for bipolar disorder, unlike the general population in which suicide rates of males are three to four times those of women (Barnes and Mitchell, 2005). Completed and attempted suicide occurs predominantly during the depressed phase of the illness (Ferrier, 1999; Isometsa et al., 1994; Lopez et al., 1999; Holma et al., in press). Female bipolar patients can spend about a third of their lives in the depressed phase of the disease, which is associated with a higher risk of suicide (Judd et al., 2002). Finding a biological predictor of suicide attempts in female patients with bipolar disorder is, therefore, of potential value in predicting suicide.

Considerable evidence suggests that testosterone may play a role in the pathophysiology of mood disorders in females (Dalton, 1981; Baischer et al., 1995; Vogel et al., 1978; Eriksson et al., 1992; Weiner et al., 2004; Fava et al., 1989; Shulman et al., 1992; van de Poll et al., 1992; Crammer, 1986; Dewis et al., 1986; Burd et al., 2001). An association between blood or saliva testosterone levels and depressive symptoms in women was observed by several groups (Dalton, 1981; Baischer et al., 1992; Vogel et al., 1978; Eriksson et al., 1992; Weiner et al., 2004; Fava et al., 1989; Shulman et al., 1992; van de Poll et al., 1992). Some studies also found that administration of testosterone reduces symptoms of depression and anxiety in women (Crammer, 1986; Dewis et al., 1986; Burd et al., 2001). An association between blood free testosterone and premenstrual syndrome was also observed (Dalton, 1981; Eriksson et al., 1992). It is worth noting that symptoms of premenstrual syndrome are sometimes similar to symptoms of bipolar disorder (Studd, 2012).

This is the first prospective study to examine whether blood testosterone levels predict suicide attempts in females with bipolar disorder. We hypothesized that testosterone may be related to the course of bipolar illness and suicidal behavior in female patients with bipolar disorder. We examined whether testosterone is related to the course of illness at baseline and whether blood testosterone levels predict suicide attempts on follow-up.

Methods

Subjects

Participants were recruited through a combination of emergency department referrals, referrals from other outpatient services, and self-referral in response to advertisements. All participants provided written informed consent as approved by the New York State

Psychiatric Institute Institutional Review Board. To be included, patients had to have a DSM-IV diagnosis of a bipolar disorder based on the Structured Clinical Interview for DSM-IV; be in a depressive or mixed episode; have at least one past suicide attempt; and be 18 to 75 years of age. We limited this study to previous suicide attempters in order to have a higher risk group for suicide attempt on follow-up and thus sufficient power to allow detection of a relationship to testosterone and clinical variables. Exclusion criteria were lack of capacity to provide informed consent; pregnancy or lactation; active medical problems, including substance use disorders requiring detoxification. We used the female subsample of subjects included in our previous research report (Sher et al., 2012) and included prospective observational data.

Clinical evaluation

Axis I and II pathology was assessed at baseline with the Structured Clinical Interview for DSM-IV Axis I and II Disorders. Current severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Lifetime aggression and impulsivity were assessed with the Aggression History Scale (Brown-Goodwin, revised; Brown and Goodwin, 1986) and the Barratt Impulsivity Scale, respectively (Barratt, 1965). Hostility (lifetime) was rated with the Buss-Durkee Hostility Inventory (Buss and Durkee, 1957). The Scale for Suicide Ideation (SSI) was used to measure the severity of suicidal ideation (Beck et al., 1979), and hopelessness during the previous week was measured with the Beck Hopelessness Scale (BHS) (Beck et al., 1974). A lifetime history of all suicide attempts, including number of attempts and the method of the attempt, was recorded on the Columbia Suicide History Form (Oquendo et al., 2003). A suicide attempt was defined as a self-destructive act that was committed with some intent to end one's life. The Medical Lethality Rating Scale was used to measure the degree of medical damage caused by each suicide attempt (Beck et al., 1975). The scale was scored from 0 to 8 (0=no medical damage, 8=death), with anchor points for different suicide attempt methods. The degree of suicide intent for the worst attempt was rated with the Suicide Intent Scale (Beck et al., 1974). Reasons for living were evaluated using the Reasons for Living Inventory (Linehan et al., 1983). Patients were followed up prospectively for up to 2.5 years. Interviewers were Masters or PhD-level psychologists. Inter-rater reliability was good to excellent (ICC 0.71 – 0.97).

Testosterone assay

Plasma testosterone was assayed using a double antibody¹²⁵I radioimmunoassay procedure (MP BIOMEDICALS Costa Mesa, California). All assays were run in duplicate with an eight point standard curve encompassing 0.1–10ng/ml. Three quality control low, medium and high levels were run with each batch assay. Inter and intra assay coefficient of variation were < 8% and <10% respectively.

Statistical analyses

Pearson's correlations were used to test the relation between testosterone levels and clinical parameters. Cox proportional hazards regression was used to analyze the time to the first suicide attempt (Leon et al., 1990). Collinear covariates were not included in the model. The SPSS 19 statistical program was used to perform statistical analyses.

Results

Fifty-one women were enrolled into the study. Demographic and clinical characteristics of study participants are presented in Table 1. At baseline, testosterone levels positively correlated with the number of past major depressive episodes and suicide attempts but negatively with the Reasons for Living Scale scores (Table 2). We did not find a correlation between testosterone levels and Brown Goodwin lifetime aggression scale scores, the number of manic episodes, current severity of suicide ideation, depression or hopelessness.

The mean interval of prospective observation between the enrollment in the study and the first suicide attempts was 458.5 ± 311.6 days. The Cox proportional hazards regression analysis demonstrated that higher baseline testosterone levels predicted suicide attempts during the follow up period: HR=1.69, Wald=6.575, df=1, p=0.01, which means an increase in the testosterone level by 0.1 ng/ml (10 ng/dl) increases the probability of suicide attempt 16.9 times.

Discussion

Testosterone and suicidality

We have observed, for the first time, that higher testosterone levels predict suicide attempts in women. We have also found that testosterone levels positively correlated with lifetime number of suicide attempts and negatively correlated with Reasons of Living scores.

Prior studies of the relation between testosterone and suicidal behavior were mostly focused on male populations and produced contradictory results. Tripodianakis et al. (2007) compared testosterone levels in males admitted to hospital wards after a suicide attempt with testosterone levels in healthy males in the same age range and found that attempters had significantly lower testosterone levels compared to controls, and that the attempters who used violent methods had lower testosterone levels compared to the non-violent attempter subgroup. Markianos et al. (2009) examined testosterone levels in a group of male psychiatric patients who had attempted suicide by jumping, compared with a group of male subjects who were hospitalized after accidentally falling from a high height, and in healthy controls. Both accident and suicide attempt groups had lower testosterone levels compared to the control group, and there was a trend towards lower testosterone levels in suicide attempters compared to the accident group. Another research group found no difference with regard to plasma testosterone levels between male suicide attempters and male controls (Perez-Rodriguez et al., 2011). No association between testosterone levels and a history of a suicide attempt in the last six months was observed in military veterans with posttraumatic stress disorder (Butterfield et al., 2005). We have previously reported that testosterone levels positively correlated with the number of suicide attempts in bipolar patients (Sher et al., 2012). The discrepancies between the results of the studies of the relation between testosterone and suicidal behavior could be related to variations in sample selection criteria, differences in time intervals between suicide attempts and blood sampling and other factors. Also, control and patient groups were often poorly matched.

The observations that testosterone levels positively correlated with the number of suicide attempts and negatively correlated with Reasons of Living scores are consistent with each other. The Reasons for Living Scale (RFL) was developed to measure life-sustaining beliefs that would prevent someone from engaging in suicidal behavior. The scale has been found to predict suicidal acts in depressed patients and correlates negatively with “clinical suicidality” which includes measures of hopelessness, suicidal ideation, and self-reported depression (Malone et al., 2000).

Testosterone and depression

Possibly, depression mediates the relation between testosterone and suicidality. Our observations that testosterone levels positively correlated with the number of major depressive episodes is consistent with observations that depressed women and women with premenstrual syndrome have increased testosterone levels (Dalton, 1981; Baischer et al., 1992; Vogel et al., 1978; Eriksson et al., 1992). Polycystic ovarian syndrome, a hormonal disorder characterized by chronically augmented testosterone levels is associated with significantly increased depression (Weiner et al., 2004). In women first identified by abnormally elevated androgen levels, self-reported negative moods, such as depression, hostility, and irritability, were increased (Fava et al., 1989; Shulman et al., 1992; van de Poll et al., 1992). While some research suggests that elevated levels of androgens may be related to menstrual cycle-mood disorders and to negative mood states in women, depressed females also may experience relief with the administration of testosterone (Crammer, 1986; Dewis et al., 1986; Burd et al., 2001). It has been suggested that antidepressant effects of testosterone are through actions of 3 α -diol (Edinger and Frye, 2005; Frye and Walf, 2009). Testosterone’s aromatized metabolite, estradiol, can also have antidepressant effects (Frye and Walf, 2009).

Testosterone and aggression

A significant number of studies suggest that testosterone is associated with aggression, both in men and in women (Archer, 1991; Dabbs and Hargrove, 1997; Giammanco et al., 2005). For example, in women prison inmates, higher testosterone levels are associated with higher levels of criminal violence and aggressive dominance (Dabbs and Hargrove, 1997). Based on the clinical and epidemiological findings, some researchers have suggested that there are significant similarities between aggression against the self and aggression against others, that some suicide attempters may share personality traits with violent criminals (Engstrom et al., 1999). We have also observed an association between aggression and suicidal behavior (Oquendo et al., 2004; Sher et al., 2005). For example, we have demonstrated that high aggression predicts suicidal acts (Oquendo et al., 2004). However, we did not find an association between the testosterone levels and Brown-Goodwin aggression scale scores in our sample. This is consistent with the observations by Archer et al. (1998) and Campbell et al. (1997) who did not find correlations between blood testosterone levels and aggression scale scores, and by George et al. (2001) who reported no correlation between the cerebrospinal fluid (CSF) testosterone levels and Brown-Goodwin aggression scale scores. Some studies observed that correlations between testosterone and aggression were low when rating scales were used, but higher when aggressiveness was evaluated by other people in the subject’s environment (Archer, 1991). Rada et al. (1976) argued that rating scales

measure aggressive traits, yet it may be more appropriate to examine evidence of aggressive states and how these fluctuate over time.

Limitations

A limitation of the study is that the sample size is modest. Another limitation is that we did not have a bipolar nonattempter or healthy volunteer control group for comparison.

Conclusion

This is the first prospective study on the relation between suicidal behavior and testosterone in women. It shows that testosterone levels may predict suicide attempts in women. The results are consistent with multiple observations suggesting that testosterone influences mood and behavior in females. The results should be treated with caution until replicated.

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Table 1

Demographic and clinical features of female suicide attempters with bipolar disorder

Variable Name	Mean or (N)	SD or (%)
Demographic features		
Age (yrs)	33.2	9.6
Marital status (married)	(9)	(17.6)
Education (total years)	14.4	2.3
Clinical features		
Hamilton Depression Rating Scale (HDRS)	19.9	6.2
Brown-Goodwin Aggression History Scale	23.1	6.8
Barratt Impulsivity Scale (BIS)	66.9	18.0
Buss Durkee Hostility Scale	44.2	12.6
Beck Hopelessness Scale (BHI)	11.7	5.9
Age at first major depressive episode	15.6	7.8
Age at first manic episode	20.1	7.6
Age at first psychiatric hospitalization	26.6	9.8
Number of depressive episodes	9.0	6.3
Number of manic episodes	6.5	7.0
Number of psychiatric hospitalizations	3.7	4.8
Number of suicide attempts	3.0	2.0
Maximum lethality of suicide attempts	2.7	1.4
Beck Suicidal Ideation Scale	12.4	8.5
Reasons for Living Scale	146.1	44.6
Testosterone level (ng/ml)	0.4	0.2

Table 2

Correlations of testosterone levels with demographic and clinical features of female suicide attempters with bipolar disorder

Variable Name	Correlations		
	r	p	N
Demographic features			
Age (years)	-.002	.986	51
Education (total years)	-.384	.005	51
Clinical features			
Hamilton Depression Rating Scale	.027	.850	50
Brown-Goodwin Aggression History Scale	.126	.395	48
Barratt Impulsivity Scale (BIS)	.138	.360	46
Buss Durkee Hostility Scale	-.057	.715	44
Beck Hopelessness Scale (BHI)	.000	.997	45
Age at first major depressive episode	-.193	.268	35
Age at first manic episode	-.048	.793	32
Age at first psychiatric hospitalization	-.138	.460	31
Number of depressive episodes	.353	.014	48
Number of manic episodes	.077	.605	47
Number of psychiatric hospitalizations	.055	.728	43
Number of suicide attempts	.408	.003	51
Maximum lethality of suicide attempts	.098	.504	49
Beck Suicidal Ideation Scale	.133	.425	38
Reasons for Living Scale	-.373	.014	43