Testosterone Levels and Androgen Receptor Gene Polymorphism Predict Specific Symptoms of Depression in Young Men

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ABSTRACT

Background: Testosterone (T) has been hypothesized to modulate the expression of depressive symptoms in men; however, support for this proposition is mixed.

Objective: To investigate bioavailable T, measured from saliva, and androgen receptor gene (AR) polymorphism (the number of glutamine [CAG] repeats in exon 1 of AR) and their relation to discrete symptoms of depression in 150 men aged 17 to 27 years who varied in mood status from depressed to nondepressed.

Methods: Participants completed the Center for Epidemiologic Studies Depression Scale and the Patient Health Questionnaire-9. Principal components analysis of the scales identified 5 factors: Negative Affect, Social/Evaluative, Cognitive, Sleep, and Appetite.

Results: Across the sample as a whole, higher ratings on sleep symptoms of depression were predicted by lower T concentrations and shorter CAG lengths. The association between T, CAG length, and sleep symptoms was confirmed among the subgroup of men who reported moderate to severe depression. In this subgroup, CAG repeats and T concentrations also emerged as significant predictors of negative affect scores, with the number of CAG repeats making the primary contribution.

Conclusions: These findings suggest that androgens may influence specific symptoms of depression in men. (Gend Med. 2012;9:232–243) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: activational effect, AR polymorphism, gonadal hormone, mood, sex steroid.
INTRODUCTION

Major depressive disorder is characterized by disturbances in serotonergic, dopaminergic, and noradrenergic brain pathways and by a constellation of symptoms that includes affective, motivational, appetitive, and cognitive changes. Some evidence suggests that testosterone (T) may be associated with depressive symptomatology in men, although the association remains controversial. In middle-aged to older adults, studies have found lower T concentrations in men with depression compared with matched controls1–3 (cf. reference 4) or found significant associations between T concentrations and severity of depression,1,5 particularly if free or bioavailable T is used as the index of T activity. The association may extend to subthreshold depression or dysthymia.6,7 Conversely, symptoms phenotypically similar to major depression, including dysphoria, irritability, fatigue, and loss of libido, commonly occur in conjunction with hypogonadism (low T concentration) in younger and older men.6,8,9 Reduced T concentrations may precede and predict the onset of symptoms of depression, which suggests that they might constitute a risk factor for development of depressive changes.9 For example, Shores et al10 found that men identified as having clinical hypogonadism were at increased risk of major depression over a two-year follow-up period.

Treatment data are equivocal regarding any effect of T therapy in major depression. However, randomized controlled trials have suggested that the administration of T can effectively ameliorate mood in some men with hypogonadism7,11 and, potentially, can serve as an adjuvant to antidepressant therapy in subsets of men with refractory depression or dysthymia12,13 (but see references 14 and 15). Administration of exogenous T has little effect on mood in eugonadal men who are not depressed16,17; however, pharmacologically induced hypogonadism precipitated depressive symptoms in a subset (~10%) of healthy young men with no history of psychiatric illness,18 and following supraphysiologic dosages of T, elevation in mood (hypomanic changes) and increased energy were reported in 10% to 15% of healthy men who had no evidence of depression.19 However, not all studies have detected an association between low T concentration and depressive affect, or evidence of any therapeutic response to T supplementation. Reasons for the variability in findings might include differences in ages and symptoms of depression, but are not well understood.

Genetic variation in the androgen receptor (AR) is one factor that could conceivably influence outcomes. Testosterone acts in the brain by binding to ARs and also through metabolic conversion to its aromatized metabolite 17β-estradiol. The AR is encoded by a single gene, AR, carried on the X chromosome. Polymorphisms in AR, specifically the variable length of a polyglutamine repeat sequence in exon 1, confer differences in transactivational activity20,21 and AR expression.22,23 Short glutamine (CAG) repeat length is associated with increased transcription of androgen-responsive target genes.24 In principle, therefore, it is possible that not only differences in circulating T concentrations, but also individual differences in AR CAG length, by influencing the responsivity of the AR, may be associated with depressive symptoms in susceptible groups of men.

Length of the AR CAG repeat has been associated in previous studies with susceptibility to prostate cancer, cardiovascular risk, and other androgen-dependent characteristics.24 Risk of major depressive disorder or dysthymia also may be correlated with the AR genotype, possibly in combination with T concentration; however, CAG repeat length has seldom been considered, and findings have been mixed. In middle-aged to elderly men, Seidman et al25 found that men identified as having clinical hypogonadism were at increased risk of major depression over a two-year follow-up period.

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used, in which items intentionally undersample somatic or vegetative symptoms of depression that can arise in elderly populations as a result of concurrent medical illness. Schneider et al. found that CAG repeat length was a positive predictor of depressive symptoms on the Patient Health Questionnaire-9 in outpatient groups of men with psychiatric symptoms or men with “aging male symptoms.” Häkönen et al. found a positive correlation between CAG length and endorsement of items assessing “depressed mood” and “wish to be dead” in a sample of Finnish men unselected for depression.

Two studies have examined AR CAG repeat length in adolescent samples. Vermeersch et al. found an interaction between T and CAG length; free T was inversely associated with depressive symptoms in nondepressed adolescent boys, but only in boys with long, not short, CAG repeat lengths. Su et al. found that boys with first-episode major depression had significantly shorter CAG repeat lengths than did controls. Severity of depression, measured using the Beck Depression Inventory, was inversely correlated with CAG repeat length in the adolescent patients.

On the whole, existing data tentatively support a reciprocal relationship between T activity and the emergence of depressive symptoms, although some work suggests that low T concentration may be associated with depression only in AR CAG subgroups that fall at the low or high end of the normal range, not in all men.

The objective of the present study was to investigate the associations between depressive symptoms, CAG repeat length, and levels of bioavailable T, measured in saliva, in a sample of young university-aged men with a wide range in mood status. The T concentration in saliva closely reflects the bioavailable fraction of T in serum, providing a direct index of the T that is available to interact with tissue. In addition, although findings from a few previous studies suggest that CAG length may relate to depressive symptoms, the present study is the first to evaluate whether specific symptoms (eg, affective, somatic) that accompany depression are differentially related to T and AR CAG repeat length.

METHODS

Participants

Study participants were 150 young men aged 17 to 27 years (mean [SD], 18.75 [1.65] years), recruited from the University of Western Ontario (London, ON, Canada), who ranged in mood status from nondepressed to clinically depressed. Participants did not have any chronic medical conditions, as determined by self-report. In participants with preexisting depression, the diagnosis had been made by an independent medical practitioner; however, no participants were using antidepressant agents at the time of the present study. Participants were excluded if they had any medical condition that can influence T metabolism or if they used medications, including antidepressants, that may alter T concentrations. Also excluded were participants with a history of neurologic or endocrine disorders or who were receiving treatment for affective disorders other than depression. All participants gave written informed consent. Reimbursement was provided in the form of either course credit or monetary compensation.

Procedure

The present study was part of a larger investigation of associations between T biomarkers, cognition, and affect. Participants were tested individually in a quiet room between 1:00 PM and 7:00 PM to control for circadian variation in T concentration. T concentrations are most steady in the afternoon and early evening, a time that is thus recommended for studies in which individual differences in T are the focus of investigation. On arrival, DNA sampling was performed to determine AR genotype (CAG repeat length). Two saliva specimens were then collected for measurement of T, one immediately after the DNA sampling and a second approximately 75 minutes later. T concentrations from the 2 specimens were averaged to yield a single mean value. When collected under controlled conditions, there is an excellent correlation \( r = 0.85 \) between a single timepoint measurement of T and the mean of 7 samples obtained over 1 year or longer. For details of specimen collection and analysis, see Testosterone Measurement.
Depression Scales

Participants completed 2 self-report questionnaires that inquired about depressive symptoms, the Center for Epidemiologic Studies Depression Scale (CES-D) and the Patient Health Questionnaire-9 (PHQ-9). Both instruments have proven reliability and validity in general population samples.

The CES-D is a 20-item scale. Participants rated the extent to which they had felt a particular way in the past week (e.g., “I felt sad”) on a 4-point scale ranging from “rarely” to “most of the time.” Responses were summed across the 20 items. On the basis of established clinical cut-off points, scores of 0 to 15 indicate nondepressed levels of depressive symptoms, scores of 16 to 22 indicate mild levels of depressive symptoms, and scores of ≥23 indicate moderate to severe depression. Internal consistency of the CES-D, as measured using the Cronbach α, ranges from 0.85 in community samples to 0.90 in psychiatric samples. The CES-D demonstrates moderate to high concurrent validity with other measures, including the Symptom Checklist-90 and the Hamilton Rating Scale for Depression. In factor analytic studies, the CES-D factor structure ranges between 2 and 5 factors.

The PHQ-9 is a 9-item scale on which participants rated the extent to which they had been bothered by symptoms during the past 2 weeks (e.g., “Feeling tired or having little energy”) on a 4-point scale ranging from “not at all” to “nearly every day.” Responses were summed to yield a total score. Scores of 0 to 4 indicate nondepressed levels of depressive symptoms, scores of 5 to 9 indicate mild levels of depressive symptoms, and scores of ≥10 indicate moderate to severe depression. Internal consistency of the PHQ-9 is excellent, with correlations ranging between 0.86 and 0.89. The scale has a sensitivity of 98% and specificity of 80% for identification of major depressive disorder, and demonstrates good concurrent validity with other measures of depression. An advantage of the PHQ-9 is that symptoms are rated over a two-week timeframe, corresponding to the diagnostic interval in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision).

DNA Genotyping

To minimize saliva impurities, participants abstained from eating, drinking fluids other than water, smoking, chewing gum, or brushing their teeth for 30 minutes before sample collection. Before the first saliva sample was obtained, participants rinsed their mouths with water. For DNA collection, participants collected about 2 mL of saliva into a sterile Oragene-DNA vial (DNA Genotek, Inc, Kanata, Ontario, Canada). Once collected, the whole saliva was mixed with 2 mL of Oragene-DNA stabilizing solution. Saliva sampling produces a higher DNA yield than either mouthwash or buccal swab methods, and better quality DNA than the buccal swab method.

Genotyping was performed by The Center for Applied Genomics at The Hospital for Sick Children in Toronto (Canada). In brief, 50 ng of DNA was extracted from the saliva samples, and the CAG repeat region of the AR gene was amplified using polymerase chain reaction with one primer labeled with 6-FAM dye for visualization (5'-CTTTCCAGAATCTGTTCCAG-3') and a second unlabeled primer (5'-GAAGGTTGCTGTTCCTCATC-3'). Amplified fragments were run through capillary electrophoresis, and were read using an ABI3730XL DNA Analyzer (Applied Biosystems, Inc, Foster City, California) to separate the polymerase chain reaction products according to size. Quantification of the length of the CAG repeat region from each sample was accomplished using GeneMapper software (version 3.5; Applied Biosystems). Repeat numbers were confirmed by sequencing a subset of samples with alleles of different lengths. Genotyping could not be performed in 19 men (12%) because of limited quality or quantity of DNA available.

Testosterone Measurement

Four milliliters of whole saliva was collected into a polystyrene culture tube pretreated with sodium azide, using an inert gum (Trident; Cadbury Adams Canada Inc, Toronto, Ontario) to stimulate saliva flow. Gum interferes with the quantification of T in some assays, but is inert in the technique.
used here. Saliva contains only that fraction of the total T that is not bound to sex hormone–binding globulin, and, therefore, represents the fraction that is metabolically active or “bioavailable.” Specimens were stored at −20°C until analysis.

The saliva was analyzed in duplicate via radio-immunoassay. A $^{125}$I Coat-A-Count kit for testosterone (Siemens Healthcare Diagnostics, Inc, Deerfield, Illinois) was modified for saliva according to an established laboratory protocol. The antiserum is highly specific for T, showing cross-reactivity with dihydrotestosterone <5% and negligible cross-reactivity with other steroids. The intra-assay coefficient of variation averaged <7%. Assay sensitivity was 7.5 pg/mL.

**Statistical Analyses**

Total scores on the CES-D and PHQ-9 were computed. In addition, the individual items were entered into a principal components analysis to objectively identify the symptom domains sampled by the 2 scales. The resulting symptom components were used as criterion variables in multiple regression analyses to determine the degree to which individual’s symptom scores could be predicted from CAG repeat length and T concentrations. All analyses were performed using SPSS for Windows (version 18.0; SPSS, Inc, Chicago, Illinois). Exploratory regression analyses were run initially for the sample as a whole, followed by confirmatory regressions restricted to the most depressed subgroup. At the exploratory step, a separate regression analysis was performed for each of the 5 symptom components found in the principal components analysis. Type I error was controlled by adopting $\alpha = 0.01$ as the criterion for significance. Because previous studies have suggested that T concentrations may not predict mood scores within the normal range, the Negative Affect component was singled out for analysis in the depressed subgroup a priori, and was expected to correlate with T activity on the basis of previous literature. All other symptom components were analyzed in the depressed subgroup only on a confirmatory basis, that is, if they were significant in the analyses for the sample as a whole.

**RESULTS**

**Testosterone and CAG Repeat Length**

Consistent with other studies in young men, salivary T concentrations ranged from 51.98 to 196.10 pg/mL (mean [SD], 105.54 [28.64] pg/mL; $n = 149$). One male participant, who had a mean T concentration in the female range, was excluded from all statistical analyses involving T. CAG length ranged from 12 to 33 repeats (22.10 [3.09]). The normal length of the CAG repeat sequence ranges between 9 and 35 repeats, with an average of 20 to 22 repeats. To determine whether T concentrations might homeostatically compensate for carrying a gene with a longer or shorter repeat sequence, a Pearson correlation coefficient between CAG repeat length and T levels was calculated. The correlation of $r = −0.03$ was nonsignificant, as in other studies.

**PHQ-9 and CES-D Symptom Ratings**

To quantify symptom severity, the total scores on the PHQ-9 and CES-D were examined. The number of participants in the nondepressed, mild, and moderate-to-severe symptom categories on each scale, and the mean T level for each category, are shown in the Figure. There was no significant group difference in T, either for the PHQ-9 ($F(2, 144) = 0.24; P = 0.79$) or the CES-D ($F(2, 144) = 0.61; P = 0.55$), when the subgroups were defined on the basis of total scores.

**Depressive Symptom Components**

To create a more refined measure of depressive symptoms, individual item responses on the PHQ-9 and CES-D were entered into a principal components analysis with varimax rotation. A 5-component structure was found to provide the best fit to the data. The defining loadings used to identify each component are given in Table I. On the basis of the pattern of item loadings, the 5 components were identified as Negative Affect, Social/Evaluative, Concentration, Sleep, and Appetite.
Multiple regression analyses were performed using each depressive component as a criterion variable and using CAG repeat length and T concentration as predictor variables, to determine whether T and CAG length, either separately or in combination, contributed to the variance in depressive symptoms. Because some studies have suggested that T concentrations might influence symptoms only in men with long or short CAG alleles, an interaction term was included as a potential predictor, but was not significant in any of the regression analyses. A forced-entry regression model was applied to enable the relative influence of T and CAG length to be simultaneously evaluated.

For the sample as a whole, T concentration and CAG length significantly predicted sleep-related symptoms of depression \(F(2, 126) = 6.42; R^2 = 0.09; P = 0.002\), and together explained approximately 9% of the variance in the Sleep scores. Lower T concentration \((\beta = -0.19; P = 0.03)\) and shorter CAG repeat length \((\beta = -0.24; P = 0.005)\) were associated with higher scores on the sleep-related items. For the Negative Affect, Social/Evaluative, Concentration, and Appetite components, the regressions did not reach the \(\alpha = .01\) criterion for significance, and T concentration and CAG length explained <5% of the variance.

In men who reported moderate to severe symptoms on either the PHQ-9 or CES-D \((n = 29)\), the association between CAG length, T concentration, and sleep was confirmed \(F(2, 23) = 4.79; R^2 = 0.29; P = 0.02\), with both T concentration \((\beta = -0.37)\) and CAG repeat length \((\beta = -0.38)\) serving as significant predictors (Table II). In this depressed subgroup, CAG repeat length and T concentration were also significant predictors of Negative Affect \(F(2, 23) = 3.65; R^2 = 0.24; P = 0.04\), as hypothesized, with number of CAG repeats making the primary contribution \((\beta = 0.48)\). Longer repeat lengths were associated with greater Negative Affect. In addition, CAG length and T concentration jointly predicted the total score on the PHQ-9 \(F(2, 23) = 4.20; R^2 = 0.27; P = 0.03\), T concentration \((\beta = -0.43; P = 0.02)\), and CAG repeats \((\beta = 0.30; P = 0.10)\).

**DISCUSSION**

The present investigation is the first to demonstrate associations between salivary T and AR polymorphism and specific symptom domains of depression. T concentration and CAG repeat length were significant predictors of sleep-related symptoms, in the sample as a whole and in particular in men who reported moderate to severe levels of depressive symptoms. In the depressed subgroup, T concentrations and CAG repeat lengths also significantly predicted negative affect, together accounting for 24% of the variance in the Negative Affect scores. A longer CAG repeat length, signify-
ing a less effective AR, was predictive of greater negative affect.

That the associations were clearer in the subgroup of men who self-reported being depressed is not entirely surprising. Nondepressed participants, who were included in the full-sample analysis, had low scores on the 2 clinical screening instruments administered, and the resulting restriction of range in the depression scores in this subgroup may have attenuated any correlation that might have been present. Conversely, greater variability in scores was found in men actively experiencing depressive affect, enabling significant associations to be revealed. That these associations were found in young men is significant. Very few studies have investigated androgenic influences on depressive symptoms in young men, in whom the average T concentration is at its highest during the male lifespan. Associations between T concentration and depressive symptoms may be easier to detect in middle-aged or elderly men, provided that appropriate measures of depression are used, because T concentration declines with age, whereas higher T concentrations ordinarily present in endocrinologically healthy young men may afford a protective influence on mood.

In the present data, significant associations were found for only 2 domains: Negative Affect and

Table I. Defining items from the PHQ-9 and CES-D and their loadings on the 5 extracted principal components

<table>
<thead>
<tr>
<th>Component</th>
<th>Defining Items</th>
<th>Item Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Affect</td>
<td>“Feeling down, depressed, or hopeless”</td>
<td>0.818</td>
</tr>
<tr>
<td></td>
<td>“I felt depressed”</td>
<td>0.792</td>
</tr>
<tr>
<td></td>
<td>“I felt sad”</td>
<td>0.766</td>
</tr>
<tr>
<td></td>
<td>“I felt I could not shake off the blues even with help from my family or friends”</td>
<td>0.719</td>
</tr>
<tr>
<td>Sleep</td>
<td>“My sleep was restless”</td>
<td>0.761</td>
</tr>
<tr>
<td></td>
<td>“Trouble falling or staying asleep, or sleeping too much”</td>
<td>0.708</td>
</tr>
<tr>
<td></td>
<td>“Feeling tired or having little energy”</td>
<td>0.472</td>
</tr>
<tr>
<td>Concentration</td>
<td>“I had trouble keeping my mind on what I was doing”</td>
<td>0.736</td>
</tr>
<tr>
<td></td>
<td>“Trouble concentrating on things, such as reading the newspaper or watching television”</td>
<td>0.704</td>
</tr>
<tr>
<td>Social/Evaluative</td>
<td>“People were unfriendly”</td>
<td>0.775</td>
</tr>
<tr>
<td></td>
<td>“I felt that people disliked me”</td>
<td>0.749</td>
</tr>
<tr>
<td></td>
<td>“Moving or speaking so slowly that other people could have noticed”</td>
<td>0.657</td>
</tr>
<tr>
<td></td>
<td>“I talked less than usual”</td>
<td>0.505</td>
</tr>
<tr>
<td>Appetite</td>
<td>“I did not feel like eating; my appetite was poor”</td>
<td>0.817</td>
</tr>
<tr>
<td></td>
<td>“Poor appetite or overeating”</td>
<td>0.714</td>
</tr>
</tbody>
</table>

CES-D = Center for Epidemiologic Studies Depression Scale; PHQ-9 = Patient Health Questionnaire-9.

Table II. Multiple regression model for predicting Negative Affect and Sleep components in men with moderate to severe depressive symptoms

<table>
<thead>
<tr>
<th>Component</th>
<th>R</th>
<th>R²</th>
<th>Predictor</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Affect</td>
<td>0.49 (P=0.04)</td>
<td>0.24</td>
<td>CAG length</td>
<td>0.48</td>
<td>2.61</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Testosterone</td>
<td>−0.15</td>
<td>−0.82</td>
<td>0.42</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.54 (P=0.02)</td>
<td>0.29</td>
<td>CAG length</td>
<td>−0.38</td>
<td>−2.19</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Testosterone</td>
<td>−0.37</td>
<td>−2.08</td>
<td>0.048</td>
</tr>
</tbody>
</table>

CAG = numbers of glutamine.
Sleep. Individual’s scores on each of these symptom domains were extracted from a principal components analysis of the CES-D and PHQ-9 items. Factor analytic studies of the CES-D typically identify a negative affect component and a social/evaluative factor, as in the present study, whereas sleep- and appetite-related symptoms often merge into a single “somatic” factor. A concentration factor is not commonly observed, although cognitive complaints are common in depression.

Cognitive complaints may, however, be especially salient in a university population, in whom everyday cognitive demands are high.

In agreement with Härkönen et al and Schneider et al, who studied outpatients using the PHQ-9, we found that longer CAG genotypes were associated with higher levels of depressive affect. Few data are currently available on CAG length and depression; however, low T itself is associated with major depressive disorder, and may even constitute a risk factor for symptom development. In studies of T, direction of causation is often difficult to establish because dysregulation of the hypothalamic-pituitary-adrenal axis commonly occurs in major depression and, through feedback mechanisms, can lower the production of T. In our data, variance in depressive affect was linked to variation in CAG genotype, not T concentrations per se. In the group who exhibited moderate to severe depressive symptoms, a longer CAG genotype, suggestive of reduced capacity of AR to respond to T, was strongly associated with the level of experienced negative affect (β = 0.48). This observation supports an inverse association between negative affect and level of T activity. Because CAG genotype is a fixed trait of individuals, the association cannot be explained by a causal effect of depression itself on the biological marker.

For sleep, our findings, both in the sample as a whole and in the men who reported significant depressive symptoms, only partly overlap those for negative affect. T concentrations were negatively associated with the sleep symptoms of depression; however, contrary to expectation, shorter CAG repeat lengths corresponded to higher sleep symptom ratings. This may denote a difference in mechanism (see later in discussion). The direction of the CAG result will need to be verified via a replication study and, ideally, future work that uses objective measures of sleep. It has been well established that differences may exist between subjective reports of sleep characteristics and objective, physiologic measurements obtained using polysomnography or other techniques. How various physiologic variables might differentially correlate with T concentration and CAG length in depressed men could be potentially revealing.

Sleep disruption and lethargy have been empirically identified as early emerging symptoms in patients about to experience a depressive episode, and numerous studies have found a positive association between quantity of sleep and T concentrations in younger and older men. A recent meta-analysis demonstrated that nondepressed individuals with insomnia were at 2-fold greater risk of developing depression than those without sleep difficulties. Of interest, T is an antagonist of 5-hydroxytryptamine-3 (5-HT3) serotonin receptors, a receptor subtype implicated in sleep physiology. Receptor antagonism is associated with improved quality of sleep, whereas receptor agonists delay the onset of REM sleep in humans. Considered together, it is possible that the antagonistic effect of T at 5-HT3 receptors improves sleep, which in turn reduces daytime lethargy.

The negative association between CAG length and sleep identified in the present study is in contrast with the positive association observed for negative affect. A negative correlation could be explained if T acts on sleep via aromatization to 17β-estradiol rather than via direct AR binding. If so, a negative correlation between T concentration and symptom severity, as noted in the present work, would be expected because higher T concentrations provide more biological substrate for metabolic conversion. Because longer CAG repeats in AR are associated not only with reduced AR activity but also with reduced AR proliferation, longer CAG length means fewer ARs for T to bind to, increasing the quantity of T freely available to be aromatized to estradiol. In women, higher estradiol levels are associated with positive effects on both mood and vigor; however, in men, the importance of estradiol conversion is unknown.
and thereby represents a potential direction for future investigation. Of interest, 17β-estradiol has been identified as a functional antagonist at 5-HT$_3$ receptors, and the antagonism by T at the 5-HT$_3$ receptor is believed to be independent of nuclear receptor binding.

CONCLUSIONS

The present study found that bioavailable T concentrations, polymorphism in the AR gene, or both, significantly predicted ratings of affective and sleep symptoms derived from the PHQ-9 and CES-D. The genotype-hormone association demonstrated is not unlike that observed in other conditions such as Alzheimer's disease, in which the APOE genotype has been suggested to interact with the sex hormone estradiol to influence the risk or rate of cognitive decline in women. To the extent that CAG length influences the capacity of T to generate a biological response, polymorphism in the AR gene may represent an independent risk factor for depression in men, perhaps one that assumes increasing importance as T concentration declines with aging, altering ligand availability.

ACKNOWLEDGMENTS

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Both authors contributed to the design of the study, statistical analysis, and interpretation of the data. Ms. Sankar collected the data in partial fulfilment of the requirements for her MSc thesis, and wrote the first draft of the manuscript. Both authors contributed to and have approved the final manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES


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