Sexual Functioning in Adolescents With Major Depressive Disorder: A Prospective Study

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ABSTRACT

Objective: To examine the association between sexual functioning, depression and anxiety severity, and selective serotonin reuptake inhibitor (SSRI) use in adolescents.

Methods: From September 2010 to December 2014, 15- to 20-year-old participants, either unmedicated or within a month of beginning SSRI treatment, completed the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), and Changes in Sexual Functioning Questionnaire (CSFQ) at baseline and every 4 months for up to 2 years. The *DSM-IV-TR* was used to determine presence of psychiatric disorders. Data regarding use of medications and hormonal contraception were collected. Polymorphisms of the *HTR2A* and *ABCB1* genes were genotyped. Linear mixed-effects regression models examined the association between depression and anxiety symptom severity, SSRI use, and sexual functioning, accounting for relevant covariates.

Results: A total of 263 participants (59% female, mean ± SD age = 18.9 ± 1.6 years, 70% with major depressive disorder) contributed to this analysis. After adjusting for age, sex, and duration in the study, depression severity, but not anxiety severity, was associated with lower CSFQ total scores ($\beta = -0.13$, $P < .0001$) and lower arousal, orgasm, and pleasure subscale scores (all $\beta = -0.03$, $P < .003$). Higher SSRI doses were associated with lower orgasm subscale scores ($\beta = -0.30$, $P < .03$). Hormonal contraceptive use was associated with higher CSFQ total scores ($\beta = 0.97$, $P < .003$) and higher arousal ($\beta = 0.25$, $P < .009$), desire ($\beta = 0.24$, $P < .001$), orgasm ($\beta = 0.27$, $P < .02$), and pleasure ($\beta = 0.15$, $P < .004$) subscale scores. No significant genetic moderating effect was found.

Conclusions: In adolescents, depression is associated with lower sexual functioning while SSRI use impairs orgasm.

J Clin Psychiatry 2021;82(6):21m13892

To cite: Deumic Shultz E, Mills JA, Ellingrod VL, et al. Sexual functioning in adolescents with major depressive disorder: a prospective study. *J Clin Psychiatry*. 2021;82(6):21m13892.

To share: https://doi.org/10.4088/JCP.21m13892

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Sexual functioning is an important facet of life, with difficulties or dysfunction causing distress and reducing quality of life. However, little is known about sexual functioning in adolescence and emerging adulthood[1] despite its being a major developmental transition period.

As teens explore their sexual life, they are learning about what works and what does not. In fact, in 15- to 24-year-old French adolescents, 48% of females and 23% of males reported having impairment in at least one area of sexual functioning.[2] Similarly, in a recent 2-year prospective study of 16- to 21-year-olds,[3] 47% of female and 41% of male adolescents reported having a distressing sexual problem. Thus, understanding the extent and nature of sexual dysfunction in this age group is critical, given that sexual activity and functioning are continuing to develop and mature. Notably, the implications extend beyond sexual satisfaction as positive sexual self-concept has been associated with improved physical and psychological well-being.[4]

Even less is known about sexual functioning in adolescents with major depressive disorder (MDD). Although impaired sexual functioning is not a defining symptom of depressive episodes, it is quite prevalent, affecting more than 40% of adult women and 30% of men with MDD.[5] Even in nonclinical samples, depression severity and sexual functioning are correlated, with desire being more affected than arousal or orgasm.[6,7] In the only study[8] that, to our knowledge, examined sexual functioning in adolescents and young adults, the presence of a major depressive episode (MDE) was associated with lower sexual functioning overall as well as in the facets of desire, arousal, and orgasm more specifically. Furthermore, males exhibited increasing impairment with worsening depression severity.

Importantly, the association between MDD and sexual functioning is complex and is potentially confounded by antidepressant use. A recent review of the literature[9] revealed that 35% of patients treated with SSRIs endorsed orgasmic dysfunction and 10% endorsed a sexual arousal disorder compared to 10% and 6%, respectively, reported in both the bupropion and placebo groups. However, while sexual adverse

Clinical Points

- The association between depression, anxiety, and sexual functioning is complex, potentially confounded by selective serotonin reuptake inhibitor (SSRI) use. There is limited research in adolescence and young adulthood despite its being a major developmental transition period.
- In otherwise medically healthy 15- to 20-year-old participants within a month of starting an SSRI or who were unmedicated were enrolled in a 2-year prospective study, depression severity rather than anxiety severity was associated with worsening sexual functioning, while SSRI use was implicated in worsening orgasmic function.
- Clinicians should ask adolescents and young adults about their sexual functioning (eg, desire, interest, arousal, orgasm) at baseline and during depression treatment and address the concerns when they arise.

drug reactions (ADRs) to antidepressants have been studied extensively in adults,[6,10] only two studies examined this concern in adolescents. The first study[11] reported no cases of sexual dysfunction among 2,264 adolescents treated with SSRIs. Notably, that analysis used medical and pharmacy claims, well known to be constrained by underreporting of ADRs.[12] Moreover, the rates of sexual dysfunction are substantially lower in studies relying on spontaneous reporting compared to those that formally assess for it.[13] The second study[8] consisted of a cross-sectional examination and also found no association following exposure to SSRIs lasting less than 1 month.

Moreover, studies in adults have investigated whether variants in genes related to antidepressant pharmacokinetics and pharmacodynamics moderate the emergence of sexual ADRs. In particular, there has been interest in the ATP-binding cassette, subfamily B, member 1 gene (*ABCB1*), which encodes for the drug efflux transporter p-glycoprotein (Pgp). Pgp is an efflux transporter expressed at the blood-brain barrier that functions to remove substrates, impacting their bioavailability in the brain. Substrates include commonly prescribed antidepressants such as citalopram, paroxetine, and sertraline.[14] Genetic variants in the *ABCB1* gene have been found to predict antidepressant response in patients receiving "Pgp-substrate" medications.[15] Relatively common polymorphisms exist that may impact the substrate specificity of the Pgp protein.[16] For example, Bly et al[17] found that women with the rs1128503 TT genotype of the *ABCB1* gene who received a Pgp-substrate antidepressant reported significantly lower sexual functioning as captured by the Changes in Sexual Functioning Questionnaire (CSFQ) than did those with the CT or CC genotypes. Additionally, given that serotonin (5-HT) contributes to sexual arousal in females and modulates sexual functioning in males,[18,19] pharmacogenetic studies have also examined variants in genes involved in 5-HT signaling. For instance, Bishop et al[18] found that adults treated with SSRIs with the GG genotype of the −1438 G/A variants of the 5-HT_{2A} receptor gene (*HTR2A*) were significantly more likely to report impaired sexual arousal than their GA and AA genotype counterparts. To our knowledge, however, no such studies have been conducted in adolescents. Understanding the role genetic variants may play in the emergence of SSRI-induced sexual ADRs can impact treatment planning, particularly as treatment-induced sexual dysfunction affects quality of life,[20] potentially impeding treatment adherence.[21]

Thus, the purpose of this analysis was to examine sexual functioning in older adolescents with MDD over a 2-year period as an extension to our previous cross-sectional study and investigate the possible moderating effect of functional *ABCB1* variants (C3435T [rs1045642], C1236T [rs1128503], and G2677A/T [rs2032582]) and an *HTR2A* variant (rs6311) on SSRI-induced sexual dysfunction. We hypothesized that depressive symptom severity would be associated with worse sexual functioning and that individuals with a greater number of T alleles in the *ABCB1* gene and carriers of the GG genotype of the *HTR2A* gene would report increased SSRI-induced sexual ADRs.

METHODS

Participants

Between September 2010 and December 2014, 15- to 20-year-old participants were enrolled in an observational study[22,23] examining the skeletal effects of SSRIs. Participants were either unmedicated or within a month of beginning SSRI treatment. Use of other psychotropics led to exclusion, with the exception of benzodiazepines (n = 6 at intake), trazodone (n = 4 at intake), α_2 agonists (n = 1 at intake), and psychostimulants (n = 3 at intake). Exclusionary criteria included substance dependence, eating disorders, pregnancy, significant medical or surgical history, chronic use of medications potentially affecting bone metabolism (eg, corticosteroids), and plans to move out of state in the following year. The study was approved by the local Institutional Review Board. Adult participants and the parent/guardian of minor participants provided written informed consent to the study, and the minor participants provided written assent.

Procedures

Participants completed a baseline visit, at which time demographic data were collected, and returned for follow-up visits every 4 months for up to 2 years. They were contacted by phone monthly between in-person visits. At each encounter, data regarding the use of medications, including psychotropics and hormonal contraception (for females), as well as alcohol usage were collected. Adherence was based on self-report and pharmacy records. SSRI doses were converted into a common unit, whereby 1 unit was equivalent to a daily dose of 20 mg of fluoxetine, paroxetine, or citalopram; 50 mg of sertraline; or 10 mg of escitalopram.[22,23] At every in-person visit, participants also completed the Beck Depression Inventory-II (BDI-II)[24] and the Beck Anxiety Inventory (BAI).[25]

Psychiatric diagnoses, following the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text

Revision,[26] incorporated information from a review of the medical records, the symptom rating scales, the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children IV (DISC-IV),[27] and an unstructured interview by a child psychiatrist. Sexual functioning was assessed using the 14-item CSFQ.[28] This self-completed questionnaire uses a 5-point Likert scale to measure the 5 dimensions of sexual functioning (ie, pleasure, desire-frequency, desire-interest, arousal, and orgasm), with higher scores corresponding to better sexual functioning.[28]

Genomic DNA from white blood cells (98.4%) or saliva (0.8% [0.8% missing information regarding source]) was extracted using Puregene (Gentra Systems; Minneapolis, Minnesota) or Oragene Kit (DNA Genotak; Kanata, Ontario, Canada). After DNA sample yield and purity were established through spectrophotometry and polymerase chain reaction (PCR) amplification, DNA samples were diluted to 20 ng/μL and stored at −20°C. PCR primers and determination of *ABCB1* variants (C3435T [rs1045642], C1236T [rs1128503], and G2677A/T [rs2032582]) and *HTR2A* variant (rs6311) genotypes followed. Established PCR products were visualized by electrophoresis on 1.8% agarose gels stained with ethidium bromide. PCR products were then sequenced using a Pyrosequencer (PyromarkMD) using standard protocols.

Data Analysis

The BDI-II total score excluded the sexual interest item to avoid inflating the association with sexual functioning. Because depression and anxiety are often comorbid and because little information is available about the potential impact of anxiety on sexual functioning, we examined the independent effects of the BDI-II and BAI scores. Given the repeated, albeit variable, number of observations per study participant, linear mixed-effects regression models were fitted to examine the associations between depressive and anxiety symptom severity and SSRI dose, on the one hand, and sexual functioning, on the other.[29] All models included adjustment for age (years) at study entry, duration of time in the study,[30] and sex. Participant-specific random intercepts and slopes were modeled assuming an unstructured covariance matrix. Maximum likelihood (ML) methods were used for estimation, which yields unbiased estimates under the assumption that the missing data mechanism is ignorable.[31] Model assumptions of linearity, homogeneity of variance of the residuals, and normality of the residuals and random effects were checked using appropriate residual plots.[29]

Given that hormonal contraceptive use is associated with both depression[32] and sexual functioning,[33] we repeated the analyses accounting for use of hormonal contraception in females. In addition, the moderating effect of genetic variants was examined, using the same overall models. SSRIs were grouped based on existing literature regarding their potential activity as Pgp substrates in vivo.[14]

Previous research[34] has shown that the *ABCB1* variants are in linkage disequilibrium and that presence of a T allele in 1 or more of the 3 variants genotyped is associated with reduced Pgp expression, which may result in increased drug toxicity. Furthermore, previous research[35] has also shown the presence of at least 2 T alleles to be associated with differences in medication response for Pgp substrates. Therefore, participants were divided based on the presence of < or ≥ 2 T alleles. To optimize statistical power, sertraline, citalopram, and escitalopram were combined in a single group as all 3 are Pgp substrates.[15] Subsequently, 6 haplotype/SSRI groups were created based on the combination of *ABCB1* haplotype groups and SSRI groups. To examine the potential moderating effect of *ABCB1* haplotype on sexual ADRs, a haplotype/SSRI group by SSRI dose interaction term was added to the model. To minimize type 1 error, the moderating effect of the genetic variants was examined only

Table 1. Baseline Demographic and Clinical Characteristics of the Participants[a]

Characteristic	Participants (N = 263)
Age, mean (SD), y	18.9 (1.6)
Female	156 (59)
Race	
White	233 (89)
African American	12 (5)
Ethnicity	
Hispanic	22 (8)
Non-Hispanic	241 (92)
Hormonal contraception[b]	77 (49)
Progesterone	2 (1)
Combination	54 (35)
Other	21 (13)
SSRI	
Citalopram/escitalopram	50 (19)
Fluoxetine	37 (14)
Sertraline	32 (12)
Paroxetine	4 (2)
Baseline SSRI dose, mean (SD), unit/d[c]	0.4 (0.6)
Major depressive disorder	185 (70)
Generalized anxiety disorder	79 (30)
Social anxiety disorder	72 (27)
Panic disorder	18 (7)
BAI score, mean (SD)	8.5 (8.7)
BDI-II score, mean (SD)	11.2 (10.5)
CSFQ score, mean (SD)	
Total	45.9 (11.2)
Desire subscale	6.0 (2.0)
Interest subscale	8.0 (2.6)
Arousal subscale	10.0 (3.0)
Orgasm subscale	9.6 (3.8)
Pleasure subscale	3.1 (1.3)
ABCB1 haplotypes[d]	
No T	54 (21)
1 T	37 (14)
2 T	16 (6)
> 2 T	156 (59)
HTR2A variants[e]	
GG	197 (84)
AG	37 (16)
AA	0 (0)

[a]Values are shown as n (%) unless otherwise noted.
[b]Analysis restricted to female participants.
[c]One SSRI unit was equivalent to 10 mg of escitalopram; 20 mg of fluoxetine, citalopram, or paroxetine; and 50 mg of sertraline.
[d]*ABCB1* haplotypes: haplotypes created based on the number of T alleles in 3 variants of the ATP-binding cassette, subfamily B, member 1 gene.
[e]Genotyping of this variant of the *HTR2A* gene failed in 29 cases.
Abbreviations: BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory-II, CSFQ = Changes in Sexual Functioning Questionnaire, SSRI = selective serotonin reuptake inhibitor.

Table 2. Parameter Estimates (95% Confidence Limits) for BDI-II Score, BAI Score, and SSRI Dose From Linear Mixed-Effects Regression Models Predicting Sexual Functioning[a,b]

Model	Total CSFQ Score	Arousal Subscale	Desire Subscale	Interest Subscale	Orgasm Subscale	Pleasure Subscale
Model 1						
BDI-II	**−0.13 (−0.19, −0.07)**	**−0.03 (−0.05, −0.01)**	−0.01 (−0.02, 0.01)	−0.01 (−0.03, 0.00)	**−0.03 (−0.05, −0.01)**	**−0.03 (−0.04, −0.02)**
SSRI	−0.22 (−0.95, 0.51)	0.06 (−0.16, 0.28)	0.03 (−0.13, 0.20)	0.06 (−0.15, 0.26)	**−0.30 (−0.54, −0.05)**	−0.01 (−0.12, 0.11)
Model 2						
BAI	**−0.12 (−0.18, −0.05)**	**−0.02 (−0.04, −0.00)**	−0.01 (−0.02, 0.01)	−0.01 (−0.03, 0.00)	**−0.03 (−0.05, −0.00)**	**−0.02 (−0.03, −0.01)**
SSRI	−0.30 (−1.03, 0.43)	0.03 (−0.19, 0.26)	0.03 (−0.14, 0.19)	0.05 (−0.15, 0.26)	**−0.32 (−0.56, −0.07)**	−0.04 (−0.16, 0.08)
Model 3						
BDI-II	**−0.11 (−0.18, −0.04)**	**−0.03 (−0.05, −0.00)**	−0.01 (−0.02, 0.01)	−0.01 (−0.03, 0.01)	**−0.03 (−0.05, −0.00)**	**−0.03 (−0.05, −0.02)**
BAI	−0.04 (−0.12, 0.04)	−0.00 (−0.03, 0.02)	−0.00 (−0.02, 0.02)	−0.01 (−0.03, 0.01)	−0.01 (−0.04, 0.02)	0.01 (−0.01, 0.02)
SSRI	−0.20 (−0.93, 0.53)	0.06 (−0.16, 0.28)	0.03 (−0.13, 0.20)	0.06 (−0.15, 0.27)	**−0.29 (−0.54, −0.04)**	−0.01 (−0.13, 0.11)
Model 4						
BDI-II	**−0.11 (−0.21, −0.02)**	**−0.03 (−0.05, −0.00)**	−0.01 (−0.03, 0.01)	−0.00 (−0.03, 0.02)	**−0.03 (−0.06, 0.00)**	**−0.03 (−0.05, −0.01)**
BAI	−0.02 (−0.13, 0.08)	0.00 (−0.03, 0.03)	0.01 (−0.02, 0.03)	−0.00 (−0.03, 0.02)	−0.01 (−0.04, 0.03)	0.01 (−0.01, 0.03)
SSRI	−0.22 (−1.14, 0.70)	0.05 (−0.22, 0.32)	−0.08 (−0.28, 0.12)	0.11 (−0.13, 0.35)	−0.26 (−0.58, 0.05)	0.00 (−0.14, 0.15)
Contraceptive	**0.97 (0.34, 1.60)**	**0.25 (0.06, 0.44)**	**0.24 (0.10, 0.38)**	0.09 (−0.08, 0.25)	**0.27 (0.05, 0.49)**	**0.15 (0.05, 0.26)**

[a]The base model included age, sex, and time in the study.
[b]Boldface indicates statistical significance.
Abbreviations: BAI = Beck Anxiety Inventory-II, BDI = Beck Depression Inventory-II, CSFQ = Changes in Sexual Functioning Questionnaire, SSRI = selective serotonin reuptake inhibitor.

in models where SSRI dose was significantly associated with sexual functioning.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc; Cary, North Carolina) with a significance level of $P \leq .05$.

Table 3. Number (%) of Participants by the ATP-Binding Cassette, Subfamily B, Member 1 Gene Haplotype, and Medication, at Baseline

Variable	<2T	≥2T
Sertraline/citalopram/escitalopram	31 (12)	59 (22)
Fluoxetine	14 (5)	22 (8)
No selective serotonin reuptake inhibitor	46 (17)	91 (35)

RESULTS

Participant Characteristics

Of 279 participants enrolled in the study, 263 contributed to this analysis, after excluding those with a psychotic disorder, bipolar disorder, autism spectrum disorder, or a genetic condition and those with invalid CSFQ data. Table 1 summarizes the demographic and clinical characteristics of the participants.

Sexual Functioning, Depression, Anxiety, and SSRI Dose

After adjusting for age ($\beta = 0.1297$, $P \leq .0003$), sex ($\beta = 0.3220$, $P < .006$), and time ($\beta = 0.1456$, $P < .005$) in the study, higher BDI-II scores were associated with lower CSFQ total scores ($\beta = -0.13$, $P < .0001$) as well as lower scores on the arousal ($\beta = -0.03$, $P < .003$), orgasm ($\beta = -0.03$, $P < .002$), and pleasure ($\beta = -0.03$, $P < .0001$) subscales (Table 2, Model 1). In contrast, higher SSRI doses were associated only with reduced orgasm subscale scores ($\beta = -0.30$, $P < .03$; Table 2, Model 1). The presence of a possible non-linear effect was explored through the inclusion of both spline and quadratic terms in the model and their interaction with the BDI-II score. The addition of these terms did not improve model fit or provide evidence of a non-linear trend in the data.

Comparable findings were observed with the BAI score, albeit the parameter estimates were smaller than with the BDI-II (Table 2, Model 2). When both the BDI-II and BAI scores, along with the same other covariates, were concurrently entered into the models, only the BDI-II score remained significantly associated with sexual functioning ($\beta = -0.11$, $P < .003$; Table 2, Model 3). Notably, accounting for SSRI adherence did not alter the findings, and linear mixed-effects model assumptions were satisfied (results available from the authors upon request).

When individual SSRI agents were examined (Supplementary Table 1), potentially significant differences emerged only with regard to the pleasure ($P < .03$) and desire subscales ($P = .08$). In both instances, the use of citalopram/escitalopram was associated with lower scores compared

to sertraline (β = −0.44, $P < .02$, for pleasure and β = −0.53, $P < .04$, for desire, respectively) and fluoxetine (β = −0.53, $P = .005$, for pleasure and β = −0.53, $P < .05$, for desire, respectively).

Sexual Functioning, Depression, and Hormonal Contraceptive Use

When the analyses were restricted to females and hormonal contraceptive use was accounted for, the association of depression severity with sexual functioning was not altered (β = −0.11, $P < .02$). However, contraceptive use was independently associated with higher total scores on the CSFQ (β = 0.97, $P < .003$) as well as on the arousal (β = 0.25, $P < .009$), desire (β = 0.24, $P < .001$), orgasm (β = 0.27, $P < .02$), and pleasure (β = 0.15, $P < .004$) subscales (Table 2, Model 4).

Moderating Effect of Genetic Variants on Sexual Functioning

Genotype and allele distributions for the *HTR2A*-1438 G/A SNP are presented in Table 1. The allele frequencies for the candidate gene loci did not deviate from Hardy-Weinberg equilibrium ($\chi^2_1 = 1.72$, $P = .19$).

After adjusting for age, sex, time in the study, BDI-II score, and SSRI dose, neither the main effect of the *HTR2A* variants nor their interaction effect with SSRI dose had significant association with the orgasm subscale of the CSFQ (both $P > .10$).

Table 3 shows the number of participants per haplotype groups (ie, < 2T vs. ≥ 2T) in each medication group at baseline. After adjusting for the same covariates, while higher SSRI doses remained related to lower orgasm subscale scores on the CSFQ (β = −1.31; 95% confidence limits, −2.33, −0.29), neither the main effect of the *ABCB1* haplotype/SSRI grouping nor its interaction effect with SSRI dose was significantly associated with the orgasm subscale (both $P > .20$). These results remained unchanged after accounting for adherence and after restricting the sample to non-Hispanic White individuals ($P > .30$).

DISCUSSION

This study expands on our previous work[8] examining the association between depression, SSRI use, and sexual functioning by using a prospective design. Overall, we confirmed that depressive symptom severity, but not that of anxiety, was associated with lower sexual functioning. In contrast to our earlier cross-sectional data, we found that SSRI use was associated with specific impairment in orgasm. Finally, we found no consistent moderating effects of *HTR2A* genetic variant rs6311 or *ABCB1* haplotypes on sexual functioning in participants treated with SSRIs.

In adults, more severe depression is associated with decreased sexual functioning. To our knowledge, this association has not been prospectively examined in adolescents. Importantly, we found that depression was associated with lower functioning in the arousal, orgasm, and pleasure aspects of the sexual cycle. This finding contrasts with our cross-sectional work, which showed a relationship with impairment in desire, but not pleasure. Several factors may account for this discrepancy, including methodological differences or the way the CSFQ captures these two facets—pleasure is measured using a single item whereas desire is measured using 5 items, including frequency and interest.[28] The items related to frequency of sexual activity do not take into account other possible causes of less frequent sexual activity, including pain during intercourse, which has also been shown to hinder sexual functioning.[2] Some studies[36] indicate that for late adolescents, sexual pleasure is a large motivator for engaging in sexual activity, including "hook-ups," which may not be optimally captured with a single questionnaire item.

Similar to findings in adults,[10] this investigation found SSRI use was associated with impairment in orgasm in our adolescent participants, which was not surprising given their successful use in treating premature ejaculation[37] due to serotonin's physiologic role in mediating orgasm.[19,38] Of note, the association between SSRI use and lower orgasm subscale scores was not seen in the female-restricted analysis, most likely due to the smaller sample size, given that the slope estimates were only minimally different (Table 2, Model 4). In addition, preliminary analyses suggest that differences between citalopram and escitalopram, on the one hand, and sertraline and fluoxetine, on the other, may exist, with the two former medications more adversely affecting the pleasure and desire facets of sexual functioning. Whether these findings are due to differences in pharmacokinetics and pharmacodynamics is unclear, as this research is still evolving, partly due to the fact that there are no specific therapeutic ranges established for this class of medication. This is especially true for sexual dysfunction, as the mechanism underlying potential differences between agents remains unknown.[39]

Performance anxiety has been suggested as a possible cause for poor sexual functioning.[40,41] However, we found no independent relationship between anxiety symptom severity and sexual functioning, consistent with our earlier finding.[8] Importantly, anxiety may have variable effects on sexual arousal, with potential facilitation through increased attention to sexual cues[41] or via misinterpretation of anxious arousal as sexual arousal given the overlap of bodily sensations.[42] One shortcoming of those studies, however, is their failure to account for comorbid depression, as we did.

Hormonal Contraception

Our results indicate that hormonal contraceptive use is associated with better CSFQ scores. This finding is consistent with the baseline findings in this cohort[8] and overlaps with the results from Ott et al,[43] who found a reduction in sexual interest in adolescents who discontinued oral contraceptive pills. Of note, hormonal contraception use is associated with greater sexual problems and less frequent sexual activity in adult women.[44] While this difference may be related to biological variances, it may also be due to alleviation of

anxiety about unwanted pregnancy in adolescents who are initiating sexual activity.[45] Further examination is warranted given evidence implicating hormonal contraceptive use by adolescents in the emergence of depression.[32]

Genetics

Several recent reviews[46–48] have examined the opportunities and challenges offered by pharmacogenomics in general and as they relate to child and adolescent psychiatry and SSRI use. In contrast to some published reports,[49] we found no association between the *HTR2A* (rs6311) variant and sexual functioning. This divergence may be due to differences in study design, including whether the participants were actively depressed when sexual functioning was assessed or had had sexual dysfunction prior to initiating antidepressant treatment.[18] Moreover, racial and ethnic composition of the participants may play a role, given the variability in *HTR2A* variants' moderating effect on treatment response based on racial/ethnic backgrounds.[50] Similarly, we found no significant moderating effect of the *ABCB1* haplotype.

Limitations

There are several limitations to this study. First, the CSFQ has been validated in adults, but not adolescents. The CSFQ defines sexual activity broadly beyond intercourse, including masturbation and fantasizing, and some studies[51] show that adolescents' specific definition of sex can vary widely. Thus, collecting specific information regarding sexual activity would have allowed better interpretation of the results. In addition, the BDI-II and BAI may not be the optimal scales to capture, respectively, depression and anxiety symptom severity in youths.[52] This fact may account for the lack of an independent association between anxiety severity and sexual functioning. Our study population consisted primarily of White individuals, which reflects the local population. However, the impact of MDD on sexual functioning should also be examined in more diverse populations, given differences in sex initiation across races/ethnicities.[53,54] In addition, adolescence is a time during which individuals begin to explore not only their sexuality, but also their identity. Our study does not take into account gender identity differences and the impact they may have on sexual exploration. Finally, larger studies are likely needed for well-powered pharmacogenetic analyses examining additional variants, particularly of the *CYP2D6* and *CYP2C19* genes, given their potential associations with other side effects in youths, often via a dose-dependent effect.[55] Future studies should also be adequately powered to explore differences between individual SSRIs.

In sum, in this longitudinal study, we confirm that depression severity is associated with impaired sexual functioning in both male and female adolescents. Moreover, the SSRI effect appears limited to orgasm. As adolescents mature, sexual functioning features more prominently in their lives, requiring clinicians to attend to this important facet of development. Given the propensity of adolescents to avoid spontaneously reporting on their sexual functioning,[13] it is imperative that providers initiate discussions about this topic. Proper assessment may result in treatment implications, including avoiding treatment nonadherence by reducing the dose, switching medications, or even discontinuing psychotropic agents in favor of nonpharmacologic interventions.[56]

Submitted: January 18, 2021; accepted April 30, 2021.

Published online: October 5, 2021.

Potential conflicts of interest: The authors have no conflict of interest to report.

Funding/support: This work was funded by the National Institute of Mental Health (R01MH090072) and the National Center for Research Resources (2UL1TR000442-06).

Role of the sponsor: The funding providers had no role in the conduct and publication of this study.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Previous presentation: This study was presented as a poster at the American Academy of Child and Adolescent Psychiatry's 64th Annual Meeting; October 23–28, 2017; Washington, DC.

Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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Supplementary Material

Article Title: Sexual Functioning in Adolescents With Major Depressive Disorder: A Prospective Study

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DOI Number: https://doi.org/10.4088/JCP.21m13892

List of Supplementary Material for the article

1. Table 1 — Number of participants prescribed individual selective serotonin reuptake inhibitors or no SSRIs per study visit

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Supplementary Table 1: Number of participants prescribed individual selective serotonin reuptake inhibitors or no SSRIs per study visit							
	Baseline	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24
Citalopram	52	25	18	11	9	6	3
Fluoxetine	35	23	19	12	7	4	4
Sertraline	34	27	20	13	11	9	6
Paroxetine	4	3	3	3	2	1	0
No SSRI	138	150	147	148	124	104	73