Neuropsychiatr Invest. 2022;60(4):91-98

Original Article
10.5152/NeuropsychiatricInvest.2022.22007

The Effect of Treatment Continuation on Sexual Function of Men and Women with Anxiety Disorders: A Prospective Clinical Study

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ABSTRACT

Objective: The human sexual response is a complex physiological process that involves different neural, paracrine, autocrine, and endocrine mechanisms. Previous studies have revealed complex associations between sexual dysfunction, mood symptoms, and treatment with antidepressant drugs. Identify the incidence of antidepressant treatment-emergent sexual dysfunction or the effect of treatment continuation on sexual function.

Methods: This study examined the effects of treatment persistence on sexual dysfunction in 35 patients with anxiety disorders (23 females, 12 males). The study was conducted in a naturalistic setting and utilized well-validated measures.

Results: Cross-sectional findings indicated a point prevalence of sexual dysfunction of 57.1% at baseline, 75.1% at week 6, and 39.3% at week 12. The longitudinal analysis found worsening of sexual function at week 6 (but improvement in anxiety symptoms) and improvement of well-being and sexual function with 12 weeks of treatment continuation.

Conclusion: This study provides preliminary results on the relationship between sexual dysfunctions and anxiety symptoms. Further research in this area is needed to confirm these preliminary results.

Keywords: Sexual dysfunction, anxiety, treatment persistence

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Received: April 11, 2022
Accepted: October 12, 2022
Publication Date: November 12, 2022

INTRODUCTION

The human sexual response is a complex physiological process. The widely accepted 5-stage sexual response model (Masters & Johnson and Lief model)[1,2] involves different neural, paracrine, autocrine, and endocrine mechanisms. It is proposed that libido is stimulated by dopamine,[3] inhibited by serotonin, and threshold-adjusted by androgens.[4] Arousal and the plateau phase are respectively triggered and maintained by parasympathetic signals. Both central and peripheral regulation of penile erection/vaginal lubrication involves several neurotransmitters and systems. Orgasm is related to sympathetic neurons, and resolution represents a return to the base phase, during which different molecular mechanisms are involved both centrally and peripherally to facilitate detumescence.[5,6] The most common sexual dysfunctions in men are erectile dysfunction, affecting between 10%[7] and

Cite this article as: Elnazer HY. The effect of treatment continuation on sexual function of men and women with anxiety disorders: A prospective clinical study. *Neuropsychiatr Invest.* 2022;60(4):91-98.

16% [8] and premature ejaculation affecting 14% of men.[7] The most common sexual dysfunction in women is hypoactive sexual desire disorder with a prevalence of 16%-46%.[9]

Recognition rates of sexual dysfunction in primary medical care are low.[10-12] Lack of communication of sexual difficulties was reported in 50%-73% of patients with enduring mental illnesses.[13] This was also found to be more pronounced in females (80%).[14] Relying on spontaneous reporting of sexual dysfunction could—potentially—mislead the clinician to assume the lack of sexual difficulties.

Mood disorders typically follow a chronic, waning, and remitting course. Symptoms of depression commonly co-exist with symptoms of anxiety which are associated with sexual dysfunction.[15,16] The presence of 12 months' mood disorders was found to have a significant association with poor sexual satisfaction.[17] Pharmacological management of anxiety disorders typically utilizes antidepressants as first line of treatment.[18] Sexual difficulties are commonly reported adverse effects of antidepressant medications.[19] Their estimated prevalence depends on the utilized method of data collection, with a low prevalence when relying on spontaneous reports and higher proportions while using confidential questioning or questionnaires.[20] Antidepressants can cause sexual dysfunction by disturbing cholinergic/adrenergic balance, antagonism of peripheral alpha-2 adrenoceptors, inhibition of nitric oxide, and increased serotonergic availability.[21] Some studies also reported increased levels of prolactin associated with antidepressants treatment.[22,23] An animal study found serotonin reuptake inhibitor (SSRI)-mediated sexual dysfunction to be due to reduced nitrous oxide via increasing nicotinamide adenine dinucleotide phosphate oxidase activity.[24] Other mechanisms may also be involved in erectile dysfunction associated with SSRI; central sensitization of 5HT receptors can produce an inhibitory effect on the parasympathetic system. Peripherally, increasing levels of the available serotonin through inhibiting reuptake in the platelets can produce vasoconstriction at the cavernous bed, via 5HT1B, 5HT1D, and the non-receptor mechanism of serotonylation, therefore leading to erectile dysfunction.[25]

The common phenomenon of sexual dysfunction associated with antidepressant treatment[18,20] suggests some overlap in mechanisms underlying response to antidepressant treatment with mechanisms underlying sexual functioning. Also, affective symptoms were reported to reduce compliance with pharmacological treatment of sexual dysfunction. It has proven difficult to accurately identify the incidence of antidepressant treatment-emergent sexual dysfunction (encompassing both the worsening of pre-existing problems and the development of new sexual difficulties in previously untroubled patients). However, studies on the prevalence of sexual dysfunction in patients who were prescribed either SSRI or serotonin-noradrenaline reuptake inhibitor (SNRI) indicated that between 27% and 65% of females and 17% and 57% of males experienced either a worsening of pre-existing difficulties or the emergence of new sexual difficulties in the early weeks of treatment.[19,26,27] It is worth noting that some antidepressants can have a therapeutic effect in some patients with sexual dysfunction. Patients with persistent premature ejaculation can benefit from treatment with either clomipramine or SSRIs.[28] Dapoxetine was found to be effective at 60 mg daily, in increasing intravaginal ejaculation latency.[29] High daily doses of trazodone (150-200 mg) were also found to be beneficial in treating psychogenic erectile dysfunction.[30]

A meta-analysis (of studies with different designs, n = 14) found that treatment-emergent sexual dysfunction was not more common than with placebo for the antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine, or nefazodone: by contrast and other antidepressants had significantly more negative impact than placebo, affecting all phases of sexual function. The study found that sexual dysfunction was associated with the following antidepressants, in decreasing order of impact: sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine, with sexual dysfunction rates ranging from 25.8% to 80.3%.[31] A more recent meta-analysis (n = 58, randomized controlled trials and 5 observational studies) found relative disadvantages for paroxetine and venlafaxine, and relative advantages for bupropion, but there were only minor differences between antidepressants.[3,4] The relationship between anxiety disorders and sexual dysfunction and dissatisfaction has not been explored extensively. Little is known about the prevalence of sexual dysfunction in patients with anxiety disorders or its association with demographic and other clinical factors.[32]

Commonly adopted approaches including dose reduction, drug holiday, and switching of antidepressants have been instigated only modestly.[33] These measures could risk symptomatic relapse and discontinuation symptoms.[34] Adjuvant treatments have little supporting evidence from placebo-controlled investigations. Some studies have found some benefits with bupropion, olanzapine, topical testosterone gel, and aripiprazole.[35] Phosphodiesterase 5 (PDE-5) inhibitors were found to be efficacious (for both males and females) in resolving sexual dysfunction with antidepressants.[36-38]

This study was set to examine the effect of antidepressant persistence on sexual dysfunction.

METHODS

Ethics

This project received the required ethical approvals from Hampshire Research Ethics Committee (REC reference: 16/SC/0038); UK Health Research Authority (HRA) (IRAS project ID: 170365); and Medicinal Health Research Authority (MHRA) (EudraCT number: 2016-000337-48).

Participants

The inclusion criteria were given as follows: age 20-60 years; participants who had the primary diagnosis of an anxiety disorder or anxiety-related disorder, defined according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria (American Psychiatric Association 2013);[39] and were competent to provide written consent. Patients were excluded from the study if they did not have a primary diagnosis of an anxiety disorder, were unable to provide written, informed consent, have clinically significant alcohol or substance use in the previous 3 months, were pregnant and breastfeeding, were diagnosed with any acute physical health condition, or have been prescribed medication which is deemed to influence sexual function (beta-adrenoreceptor antagonists, centrally acting alpha agonists, diuretics, alpha-adrenergic drugs, and angiotensin II receptor antagonist).[40]

Procedure

Participants who offered informed consent were assessed at baseline (week 0), after 6 weeks of being stabilized on their usual treatments (week 6), and assessments were repeated after further 6

weeks (at week 12). Some potential participants dropped out following the initial explanation of the study (53 males [39%], 82 females [61%]: mean age, 34 years). The attrition rate from expressing interest in taking part to provide informed consent was 76%. Reasons for dropping out were as follows: feeling too unwell to take part in the study (22% [too anxious 21%, too depressed 1%]); concerns about time commitments (15%); the lack of financial compensation/reward (14%); not feeling comfortable talking about sexual life (10%); and no reason given (39%).

Patients were assessed using the Arizona Sexual Dysfunction Scale (ASEX),[41] Hospital Anxiety and Depression Scale (HADS),[42] Clinical Global Impression of Illness Severity (CGI-S),[43] Warwick–Edinburgh Mental Well-Being Scale,[44] Emotional Quality of the Relationship Scale (EQR), Sexual Activity and Satisfaction Scales (SAS),[45] and Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA).[46] Treatment adherence was determined by patient report and tablet count. Blood samples were collected from participants (with their consent) for the analysis of prolactin levels at baseline (week 0), week 6, and week 12.

The Arizona Sexual Dysfunction Scale (ASEX)

Arizona Sexual Dysfunction Scale was developed in 2000, by McGauhey and colleagues. It comprises 5 items, which quantify sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. It has well-documented reliability and validity and is concise and easy to administer in clinical settings. Possible total scores range from 5 to 30, with higher scores indicating greater sexual dysfunction. Arizona Sexual Dysfunction Scale designates "sexual dysfunction," with a total score of 19 or more; any single item with a score of 5 or more; or any 3 items with a score of 4 or more. The ASEX has been used in many cross-sectional prevalence studies and in randomized controlled trials of pharmacological treatment, but there is some uncertainty about its utility in other clinical settings. The ASEX scale appears to have excellent internal consistency and scale reliability and strong test–retest reliability. Furthermore, ASEX scores appear to correlate well with factors and related items on other validated questionnaires for assessing sexual dysfunction. Arizona Sexual Dysfunction Scale has very high sensitivity and specificity and very high positive and negative predictive values.[41]

Warwick–Edinburgh Mental Well-Being Scale (WEMWBS)

Warwick–Edinburgh Mental Well-Being Scale was developed in 2006 by Tennant and colleagues. The scale consists of 14 positively worded items for assessing a population's mental well-being. The items are all worded positively and cover both feeling and functioning aspects of mental well-being. The top 15% of scores range from 60 to 70 and the bottom 15% from 14 to 42. The scale has good content validity and a Cronbach's alpha of 0.91. Warwick–Edinburgh Mental Well-Being Scale has a high correlation with mental health and well-being but lower correlations with overall health. Its distribution is near normal and the scale did not show ceiling effects. It discriminated between population groups in a way that is largely consistent with the results of other population surveys. Test–retest reliability at 1 week was high (0.83). Social desirability bias was lower or similar to that of other comparable scales.[44]

Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale was developed by Zigmond and colleagues in 1983. This questionnaire comprises 7 questions for anxiety and 7 questions for depression. Anxiety and depression questions are interspersed within the questionnaire; these are scored separately. Each item has a possible score of 0-3. A total score of 8-10 indicates a borderline case and a score of 11-21 indicates a probable case.

The mean correlation between HADS-A and HADS-D is 0.56. The mean Cronbach's alpha for HADS-A is 0.83 and 0.82 for HADS-D. An optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both HADS-A and HADS-D. The sensitivity and specificity for both HADS-A and HADS-D of approximately 0.80 are very similar to the sensitivity and specificity achieved by the General Health Questionnaire (GHQ-28). Correlations between HADS and BDI; GHQ-28; Clinical Anxiety Scale; Spielberger's State-Trait Anxiety Inventory; Symptom Checklist (SCL-90) and subscales of Anxiety and Depression Montgomery Asberg Depression Rating Scale, were in the range 0.49-0.83.[42]

Clinical Global Impression (CGI)

The Clinical Global Impression was developed for use in National Institute of Mental Health-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. This is an assessment of the clinician's view of the patient's global functioning prior to and after initiating a treatment. It provides an overall clinician-determined summary measure that considers all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI comprises 2 parts; one item measures the severity of psychopathology (CGI-S) and the second measures change from the initiation of treatment (CGI-I). Each domain has a possible score of 1-7. Clinical Global Impression ratings are positively correlated with self-reported and clinician-administered measures in patients with social anxiety. The CGI-I was found to be highly correlated ($r=0.71$), with measures of change from Health of the Nation Outcomes Scales, the Michigan Hand Outcomes Questionnaire, and Depression Anxiety Stress Scales-2. The limitations of this simple and short scale are its poor distribution properties, and a presumably restricted significance of change ratings has been recognized.[43]

Emotional Quality of the Relationship Scale (EQRS)

Emotional Quality of the Relationship Scale was developed in 1988. This scale measures affection, emotional intimacy, communication, and satisfaction with these areas of the relationship as a whole. It has 7 sub-domains and items are scored on a 4-point ordinal scale ranging from 4 (very great) to 1 (very poor). Scores are summed resulting in a composite score that ranges from a minimum score of 7 to a maximum of 28. Higher scores indicate that the emotional quality of the relationship is stronger. Internal consistency of the EQR is high ($\alpha=0.85$). The EQRS is significantly ($P < .01$) and moderately correlated with the Sexual Behavior Scale ($r=0.45$); HADS ($r=-0.38$), and the Quality of Life Visual Analog Scale ($r=0.37$). No cut-points or normative data have been established.[45]

Sexual Activity and Satisfaction Scales (SAS)

This is a sub-scale of the EQRS which was developed by Kreuter and colleagues in 1996, to investigate sexual activity and satisfaction in patients with spinal injury and their partners. The first item investigates the frequency of sexual activity, with or without intercourse, which is scored on the scale from 1 to 8; the second and third items investigate sexual satisfaction and satisfaction of the relationship as

a whole, each is scored on the scale of 1-4. Higher scores indicate greater sexual activity and satisfaction. Internal consistency is high for the SAS scale (Cronbach's $\alpha = 0.87$). In patients with spinal injury, SAS was found to be correlated with EQRS $r = 0.57$. No cut-points or normative data have been established.[45]

Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQUESA)

Oxford Questionnaire of Emotional Side Effects of Antidepressant was developed by Price and colleagues in 2001. This scale was developed to measure emotional symptoms present in patients treated with antidepressants.[46] It has 26 items; each has a possible score of 1-5. Oxford Questionnaire of Emotional Side Effects of Antidepressant items is sub-classified into 4 dimensions: not caring (NC), emotional detachment (ED), reduction in positive emotions (RP), and general reduction in emotions (GR). A further attributional dimension can be scored: antidepressant as a cause (AC). Reduction in positive emotions and not caring may be closely related to the phenomenon of depression as well as to the phenomenon of antid epressant-associated emotional blunting, whereas the 2 remaining dimensions (GR and ED) are less closely related to depression. For participants whose gold standard response increased by 1 or more, the mean increase in OQUESA total score was 2.81, but this did not reach statistical significance (mean increase: 2.81, 95% CI: 5.72 to −0.99, $t = 1.96$, $df = 36$, $P = .058$. For participants whose gold standard response did not change, the total score increased by 0.980, which was not statistically significant (mean increase: 0.980, 95% CI: −1.06 to 3.01, $t = 0.956$, $df = 98$, $P = .342$).[46]

Enzyme-Linked Immunosorbent Assay for Serum Prolactin Levels

An 8-10 mL sample of venous blood was collected by venipuncture into a serum separator tube vacutainer (gold top, with gel as a separator) under sterile conditions by trained staff and as per the National Health Service standards. Blood samples were sent to the University Hospital of Southampton pathology laboratory for analysis. The sample was obtained from blood cells and serum supernatant after centrifugation (1750 g for 10 minutes). A human prolactin standard is provided to generate a standard curve for the enzyme-linked immunosorbent assay. We used the commercially available kit from R&D system (Minneapolis, Minn, USA). The kit has a reported high sensitivity and excellent specificity for detection of human prolactin. No significant cross-reactivity or interference between human prolactin and analogs was observed. The kit manufacturer reported a standard curve range of 15.6-1000 pg/mL, sensitivity of 12.5 pg/mL, inter-assay coefficients of variability (CV%) of <10%, and intra assay CV of <8%. Standards or diluted samples (10% bovine serum albumin) were pipetted into a clear microtiter plate coated with a monoclonal antibody to capture the prolactin present. After 2 hours of incubation, the plate is washed (with 25× concentrated solution of buffered surfactant with preservative), and a peroxidase-conjugated prolactin polyclonal antibody is added. The plate is again incubated for 2 hours and washed (4 times). Anti-G substrate of 200 µL (stabilized tetramethylbenzidine) is then added to the plate, which reacts with the bound prolactin antibody conjugate. After a third, 30 minutes incubation, the reaction is stopped by adding 50 µL of the stop solution (2N sulphuric acid), and the intensity of the generated color is detected in a microtiter plate reader capable of measuring at 450 nm.

StatisticalAnalysis

As per protocol, participants underwent tests at baseline (before treatment), 6 weeks, and 12 weeks of treatment. Some participants preferred not to provide answers to some questionnaires at baseline but collaborated on other tests. Data were analyzed using International Business Machines' Statistical Package for the Social Sciences® Statistics 26.0. At each test point, data were analyzed for mean psychometric scores and at baseline and mean ASEX sub items scores at week 6 and week 12. Canonical multivariate correlation analyses and predictability analyses were used to assess correlations.

RESULTS

In total, 35 participants consented to take part in this study; 12 (35%) were males and 23 (65%) were females (mean age: 32.46 years, standard error of mean [SEM]: 2.175). All participants had English as their first language: 29 were White British, 4 Asian British, and 1 Black British. Twenty participants (57%) were professionally active at the time of enrolment, and 25 participants (71%) reported being in a stable relationship at the time of enrolment. Nineteen participants (54.3%) were within the range of healthy body mass index (18.5-24.9), but 13 (37.1%) were overweight and 3 (8.6%) were underweight (Table 1). Participants received 6 weeks of treatment from their usual clinician. At week 6, 19 patients (57.7%) had undergone treatment with an SSRI; 6 patients (18.3%) with an SNRI; 3 patients with a noradrenergic and specific serotonergic antidepressant (NASSA) (9%); 2 patients (6%) with cognitive behavioral therapy (CBT); and a single patient with a β-blocker (3%): 2 patients (6%) had not undergone any treatment by the week 6 review and undergone further 6 weeks of treatment (n = 27) by week 12.

Arizona Sexual Dysfunction Scale Performance Properties

Arizona Sexual Dysfunction Scale reliability analysis found statistically significant mean inter-item correlations (Table 2) at baseline (week 0) (0.757, minimum: 0.655, maximum: 0.877, range: 0.222 variance: 0.004); at week 6 (0.548, minimum: 0.3, maximum: 0.745, range: 0.445 variance: 0.016); and at week 12 (0.741, minimum: 0.642, maximum: 0.798, range: 0.155 variance: 0.003). Cronbach's alpha was 0.939 at baseline (week 0); 0.853 at week 6; and 0.934 at week 12. Factor analysis found a relatively larger Eigen value for the first ASEX item (sexual desire) (Table 3).

Pre-Treatment/Baseline Findings

The mean scores and SEM on rating scales at baseline (week 0) were as follows: WEMWBS: 27 (SEM: 1.81); HADS-A: 15.42 (SEM: 0.88); HADS-D: 13 (SEM: 0.82); EQRS: 18.4 (SEM: 1.04); SAS: 7.88 (SEM: 0.58); CGI-S: 4.56 (SEM: 0.22). OQUESA-GR: 15.5 (SEM: 1.17); OQUESA-RP:

Table 1. Participants' Demographics

Gender	Males 35%		Females 65%	
BMI	37.1% overweight,		54.3% within healthy range	8.6% underweight
Professional activity	Active 57%		Off work 43%	
Relationship	Stable/long term 71%		Non-long-term 29%	
Ethnicity	White British 82.9%	Asian British 11.5%	Black British 2.8%	non-disclosed 2.8%

BMI, body mass index.

Table 2. ASEX Scores Paired Sample Correlations

		Females			*Males*		
		N	Correlation	Sig.	N	Correlation	Sig.
Pair 1	ASEX-1 W0 & ASEX-1 W6	22	0.472	.026	11	-.032	.926
Pair 2	ASEX-1 W6 & ASEX-1 W12	18	0.649	.004	9	.721	.028
Pair 3	ASEX-2 W0 & ASEX-2 W6	22	0.646	.001	11	.134	.695
Pair 4	ASEX-2 W6 & ASEX-2 W12	18	0.784	.000	9	.624	.072
Pair 5	ASEX-3 W0 & ASEX-3 W6	22	0.704	.000	11	.276	.412
Pair 6	ASEX-3 W6 & ASEX-3 W12	18	0.666	.003	9	.557	.119
Pair 7	ASEX-4 W0 & ASEX-4 W6	22	0.664	.001	11	-.239	.479
Pair 8	ASEX-4 W6 & ASEX-4 W12	17	0.774	.000	9	.409	.275
Pair 9	ASEX-5 W0 & ASEX-5 W6	22	0.398	.067	11	-.014	.966
Pair 10	ASEX-5 W6 & ASEX-5 W12	18	0.672	.002	9	.321	.400
Pair 11	ASEX-Total W0 & ASEX-Total W6	22	0.603	.003	11	-.001	.998
Pair 12	ASEX-Total W6 & ASEX-Total W12	18	0.785	.000	9	.522	.150

ASEX, Arizona Sexual Experience Scale; ASEX-1, sex drive subscale; ASEX-2., sexual arousal subscale; ASEX-3, erection/vaginal lubrication subscale; ASEX-4, orgasm subscale; ASEX-5, orgasm satisfaction subscale; W0, baseline; W6, week 6 testing; W12, week 12 testing.

22.18 (SEM: 0.75); OQUESA-ED: 15.09 (SEM: 3.17); and OQUESA-NC: 18 (SEM: 1.27).

The ASEX total mean score for male participants (n = 12) at baseline (week 0) was 14.17 (SEM: 2.25). Arizona Sexual Dysfunction Scale item mean scores were as follows: item 1 (sex drive), 3.8 (SEM: 0.56); item 2 (arousal), 3.8 (SEM: 0.56); item 3 (erection), 2.75 (SEM: 0.48); item 4 (ability to reach orgasm), 2.58 (SEM: 0.4); and item 5 (orgasm satisfaction), 2.67 (SEM: 0.48). The ASEX total mean score for female participants (n = 23) at baseline (week 0) was 19.09 (SEM: 1.33). Arizona Sexual Dysfunction Scale item mean scores were as follows: item 1 (sex drive), 3.83 (SEM: 0.3); item 2 (arousal), 3.83 (SEM: 0.3); item 3 (vaginal lubrication), 3.7 (SEM: 0.33); item 4 (ability to reach orgasm), 4.17 (SEM: 0.26); and item 5 (orgasm satisfaction), 3.78 (SEM: 0.33).

Categorization of sexual dysfunction in the study sample using ASEX criteria identified 20 participants (57.1%) with sexual dysfunction: 5 (25%) males and 15 (75%) females. The 15 participants who were not classified as having sexual dysfunction were more balanced in gender (7 males [46.7%], 8 females [53.3%]).

Canonical multivariate correlation analysis of multiple-X multiple-Y correlation found a statistically significant correlation between ASEX total mean score and CGI-S mean score ($P = .048$) and HADS-D mean

Table 3. ASEX Total Variance Analysis

		Initial Eigenvalues		Extraction Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
Baseline						
1 Sex drive	4.029	80.579	80.579	4.029	80.579	80.579
2 Arousal	0.472	9.440	90.019			
3 Erection/vaginal lubrication	0.223	4.465	94.484			
4 Ability to reach orgasm	0.175	3.494	97.978			
5 Orgasm satisfaction	0.101	2.022	100.000			
	Extraction method: principal component analysis					
Week 6						
1 Sex drive	3.200	63.993	63.993	3.200	63.993	63.993
2 Arousal	0.865	17.297	81.290			
3 Erection/vaginal lubrication	0.457	9.146	90.436			
4 Ability to reach orgasm	0.262	5.232	95.668			
5 Orgasm satisfaction	0.217	4.332	100.000			
	Extraction method: principal component analysis					
Week 12						
1 Sex drive	3.965	79.305	79.305	3.965	79.305	79.305
2 Arousal	0.421	8.430	87.735			
3 Erection/vaginal lubrication	0.250	4.995	92.730			
4 Ability to reach orgasm	0.212	4.242	96.972			
5 Orgasm satisfaction	0.151	3.028	100.000			
	Extraction method: principal component analysis					

ASEX, Arizona Sexual Experience Scale.
Scores: 1 extremely easily, 2 very easily, 3 somewhat easily, 4 somewhat difficult, 5 very difficult, 6 never

score ($P=.01$) and a statistically significant inverse correlation with WEMWBS mean score ($P=.00$) and SAS mean score ($P=.01$). These correlations remained statistically significant after adjusting for age and gender, using logistic regression partial correlation. After further adjustment for EQRS and SAS, ASEX total mean score had statistically significant correlations with HADS-D mean score ($P=.00$). After further adjustment for EQRS and SAS, ASEX total mean score had statistically significant correlations with HADS-D mean score ($P=.00$) and with OQUESA-ED ($P=.00$). After further adjustment for HADSD, no statically significant correlations between ASEX and any of the tested parameters were found.

Effects of 6 Weeks of Treatment

By week 6, 33 participants received 6 weeks of treatment with: 57.7% with an SSRI; 18.3% with an SNRI; 9% with NASSA; 6% with CBT; and 3% with a β-blocker; 6% did not receive treatment. The mean psychometric scores at week 6 were as follows: WEMWBS: 33.30 (SEM: 1.75); HADS-A: 13.70 (SEM: 0.73); HADS-D: 10.82 (SEM: 0.68); EQRS: 20.08 (SEM: 0.93); SAS: 7.77 (SEM: 0.59); CGI-S: 4.27 (SEM: 0.23); CGI-I: 2.69 (SEM: 0.16); OQUESA-GR: 16.30 (SEM: 0.75); OQUESA-RP: 18.97 (SEM: 95); OQUESA-ED: 11.06 (SEM: 0.87); OQUESA-NC: 16.10 (SEM: 0.86); and OQUESA-AC: 14.48 (SEM: 25). The mean scores of HADS-A and HADS-D decreased from baseline (week 0) to week 6. Paired sample *t* test found non-statistically significant changes in mean psychometric scores for anxiety symptoms (HADS-A) ($P=.069$) and depression symptoms (HADS-D) ($P=.338$).

The mean ASEX total score for male participants (n = 11) at week 6 was 18.27 (SEM: 1.73). Arizona Sexual Dysfunction Scale subitem scores were as follows: item 1 (sex drive) 4.27 (SEM: 0.36); item 2 (arousal) 3.64 (SEM: 0.34); item 3, (erection) 2.91 (SEM: 0.27); item 4 (ability to reach orgasm) 4.18 (SEM: 0.46); and item 5 (orgasm satisfaction) 3.64 (SEM: 0.54).

The mean ASEX total score for female participants (n = 22) at week 6 was 21.14 (SEM: 1.12). Arizona Sexual Dysfunction Scale subitem scores were as follows: item 1 (sex drive) 4.64 (SEM: 0.28); item 2 (arousal) 4.09 (SEM: 0.28); item 3, (vaginal lubrication) 3.73 (SEM: 0.31); item 4 (ability to reach orgasm) 4.55 (SEM: 0.24); and item 5 (orgasm satisfaction) 4.14 (SEM: 0.32).

At week 6, 75.1% of the participants were found to have sexual dysfunction (as defined by ASEX criteria), compared to 57.1% at baseline (week 0). Canonical multivariate correlation analysis of multiple-X multiple-Y between ASEX scores at baseline (week 0) and week 6 found statistically significant correlations for the mean scores of ASEX total ($P=.02$), item 2 (arousal) ($P=.01$), and item 4 (ability to reach orgasm) ($P=.00$). Pearson's correlation analysis found that ASEX-total score at week 6 was positively and significantly correlated with ASEX total score at baseline (week 0) ($r=0.407$, $P=.019$). Regression analysis found positive predictability of ASEX total score at week 6 from ASEX total score at baseline (week 0).

Arizona Sexual Dysfunction Scale total mean score increased from baseline (week 0) to week 6, with a mean change of 3.15 (SEM: 1.22, $P=.01$). Some ASEX item scores changed significantly from baseline (week 0) to week 6: item 1 (sexual drive) 1.061 (SEM: 0.298, $P=.001$) and item 4 (ability to reach orgasm) 0.82 (SEM: 0.28, $P=.01$). The changes in other items were non-significant: item 2 (arousal) 0.45 (SEM: 0.26, $P=.10$); item 3 (erection/vaginal lubrication) 0.18 (SEM: 0.25, $P=.47$); item 5 (orgasm satisfaction) 0.64 (SEM: 0.34, $P=.07$). Analysis by gender found a statistically significant increase in mean scores for female participants: ASEX total score: 2.23, SEM: 1.09 ($P=.03$) and item 4 (ability to reach orgasm): 2.215, SEM: 0.2 ($P=.04$).

Effect of 12 Weeks of Treatment Persistence

By week 12 testing, 27 participants had continued their treatment for further 6 weeks. The mean psychometric scores at week 12 were as follows: WEMWBS: 39.85 (SEM: 2.691); HADS-A: 11.37 (SEM: 0.968); HADS-D: 8.52 (SEM: 0.826); EQRS: 20.95 (SEM: 1.014); SAS: 8.32 (SEM: 0.599); CGI-S: 3.26 (SEM: 0.211); CGI-I: 2.43 (SEM: 0.249); OQUESA-GR: 14.84 (SEM: 1.061); OQUESA-RP: 15.54 (SEM: 1.112); OQUESA-ED: 10.38 (SEM: 0.967); OQUESA-NC: 14.58 (SEM: 1.126); and OQUESA-AC: 11.57 (SEM: 1.110).

The mean ASEX total score at week 12 for male participants (n = 9) was 16.89 (SEM: 2.42). Arizona Sexual Dysfunction Scale item scores were as follows: item 1 (sex drive) 3.67 (SEM: 0.62); item 2 (arousal) 3.11 (SEM: 0.51); item 3 (erection) 3.22 (SEM: 0.57); item 4 (ability to reach orgasm) 4 (SEM: 0.58); and item 5 (orgasm satisfaction) 3.22 (SEM: 0.68). The mean ASEX total score at week 12 for female participants (n = 18) was 17.44 (SEM: 1.45). ASEX item scores were as follows: item 1 (sex drive) 3.78 (SEM: 0.33); item 2 (arousal) 3.44 (SEM: 0.37); item 3, (vaginal lubrication) 3.39 (SEM: 0.34); Item 4 (ability to reach orgasm) 3.53 (SEM: 0.3); and Item 5 (orgasm satisfaction) 3.33 (SEM: 0.3).

At week 12, 39.3% of the participants were found to have sexual dysfunction (as defined by ASEX criteria), compared to 75.1% at week 6 and 57.1% at baseline (week 0).

Canonical multivariate correlation analysis of multiple-X multiple-Y correlation found statistically significant correlation between ASEX total mean score and HADS-A total mean score ($P=.042$); SAS total mean score ($P<.0001$); CGI-S total mean score ($P=.001$); and OQUESA-RP total mean score ($P=.002$). Adjusting for age, ASEX total mean score continued to be correlated with SAS total mean score ($P=.01$).

Arizona Sexual Dysfunction Scale mean scores decreased from week 6 to Week 12 with a change in ASEX by 2.44 (SEM 1.22, $P=.01$). Paired *t*-sample test found statistically significant decrease from week 6 in item 1 (sexual drive) 2.94 ($P=.07$); item 2 (arousal) 2.56 ($P=.017$); and item 4 (ability to reach orgasm) 3.06 ($P=.005$). Analysis by gender found a statistically significant decrease in female participants with a change in item 1 (sexual drive) 2.27, SEM: 0.27 ($P=03$); item 5 (orgasm satisfaction) 2.15, SEM: 0.26 ($P=.046$); ASEX total 2.77, SEM: 0.0 ($P=.1$). Paired sample correlations for ASEX scores at baseline (week 0), week 6, and week 12 found that ASEX scores were significantly correlated in female participants, except for item 5 (orgasm satisfaction) (Table 3).

Prolactin Levels

Plasma prolactin level evaluation by enzyme-linked immunosorbent assay was found to be within normal range (57.5-276 mu/L for males and 57.5-561 mu/L for females) at concentrations given as follows: baseline (week 0) (male [n = 1], female [n=6]); week 6 (male [n = 8], female [n = 18]); and week 12 (male [n = 6], female [n = 16]). Paired *t* test analyses found changes in mean plasma prolactin concentrations from baseline (week 0) to week 6 and to week 12 and did not meet statistical significance.

DISCUSSION

More than half of the participants struggled with sexual dysfunction at baseline (57%). There was a significant correlation between sexual dysfunction (ASEX scores) and depressive symptoms (HADS-D) with emotional detachment (OQUESA-ED). This continued to be statistically significant after adjusting for age, gender, and quality of relationship. The findings suggest no statistically significant correlation between HADS-A and ASEX scores. There was worsened sexual function (ASEX) after 6 weeks of treatment. 75.1% were found to have sexual dysfunction. Overall sexual function and ability to reach orgasm were particularly worse in females after 6 weeks of treatment.

This study found similar prevalence of baseline sexual dysfunction to previous studies.[19,26,27] The severity of depressive symptoms was correlated with the severity of sexual dysfunction. This might suggest that baseline sexual dysfunction is more closely related to symptoms of depression than symptoms of anxiety. Treatment-emergent sexual dysfunction in this study sample was somewhat higher than in some previously published studies.[19,26,27] A potential explanation could be that patients with anxiety symptoms are more susceptible to experiencing escalation of anticipatory anxiety while starting a new treatment might in turn influence their sexual function.

At week 12, there was improved sexual function (ASEX): improved overall sexual function, sexual drive, and orgasm satisfaction were more statistically significant in females. The severity of anxiety symptom (CGI-S) was improved with treatment continuation. These findings are in line with previous studies which found that treating symptoms with antidepressant to remission reduced sexual dysfunction.[36]

Study Limitations

The study findings are limited by the small sample size. Other potential weaknesses of the current study include lack of blindness to the treatment groups (assessment bias).

This study shows that patients with anxiety disorders who suffer sexual dysfunction are likely to struggle with dysfunction in more than 1 sexual domain. Findings suggest initial improvement in anxiety symptoms but worsened sexual function with 6 weeks of treatment. Persistence with treatment for 12 weeks resulted in further improvement in anxiety symptoms and improvement of sexual function (particularly in female patients).

Sexual dysfunction was correlated with the severity of anxiety symptoms and inversely correlated with mental well-being. Clinicians might educate patients regarding their course of treatment and what they might expect. Investigating sexual dysfunction in this patient group, as an integral part of overall clinical assessment, can provide the patient with a better opportunity for effective management of their anxiety symptoms; sexual function, and overall well-being enhancement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hampshire Research Ethics Committee (Date: 28/11/2017, REC reference:16/SC/0038.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author declare that they have no competing interest.

Funding: The author declared that this study has received no financial support.

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