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EXPERT OPINION

Sexual dysfunction associated with major depressive disorder and antidepressant treatment

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Introduction: There is a well-established relationship between sexual functioning and quality of life. Depression can cause sexual dysfunction (SD) and its treatment can often lead to restoration of sexual functioning. Use of antidepressants has also been associated with SD, with implications for treatment compliance and creation of further distress for the patient.

Areas covered: This review evaluates available information regarding SD related to both depression and antidepressant treatment, including literature up to June 2014. It includes eligible published studies that investigated antidepressant-associated SD (AASD).

Expert opinion: Depression and SD have a bidirectional association. When screening for depression, baseline sexual functioning should be assessed with validated rating scales. If sexual side effects develop with antidepressant treatment, management options include waiting for spontaneous remission, decreasing the medication dose, switching to an alternative drug or adding an augmentation agent or antidote. Research suggests that bupropion and newer antidepressants exhibit a more favorable SD profile compared with other antidepressants, especially selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors. Bupropion, mirtazapine and buspirone have been studied as augmentation agents/antidotes or substitution agents in management of AASD. Future studies validating genetic factors could enable personal genotyping to guide individualized treatment and also facilitate the development of enhanced therapeutic guidelines to avoid or manage AASD.

Keywords: antidepressant associated sexual dysfunction, major depressive disorder, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, sexual dysfunction, treatment emergent sexual dysfunction

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1. Introduction

Major depressive disorder (MDD) is a chronic illness that causes significant morbidity in the US and worldwide, with a lifetime prevalence of up to 15% of the population in industrialized countries [1,2] and 16.2% in the US, according to the National Health and Nutrition Examination Survey [3-5]. The condition has wide-ranging effects not only for an individual's mental health, but serves also as a risk factor for worse outcomes related to medical comorbidities, misuse of substances and poor psychosocial functioning. The decreased interest and pleasure in activities that is a core symptom of depression often applies to sexual function. In fact, patients with depression have a higher occurrence of sexual dysfunction (SD) than the general population [3,6-10].

Recent editions of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV and DSM-5) [11,12] and the 10th Edition of the International

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Article highlights.

- Sexual functioning is often affected by a person's mood. Depression can impair sexual interest and response, and cause dysfunction. Treatment of depressed mood can often improve these symptoms.
- Treatment with antidepressants, however, can itself induce sexual dysfunction (SD). There are both intra- and inter-class variations among antidepressants with regard to effect on sexual functioning. This variation is largely dependent on receptor affinity profile and genetics.
- When treating depression, awareness of associated SD is important and must first begin with baseline screening of sexual function prior to starting any medication regimen. Regular monitoring of sexual function using validated scales is recommended as a part of any treatment plan.
- If SD is present before initiation of pharmacotherapy, providers should consider patient preference and start with an agent with a relatively lower risk of SD. If SD emerges during pharmacological treatment, this side effect can be managed by various strategies, including reduction of medication dose, switching to an alternative agent or adding an antidote, among others.

This box summarizes key points contained in the article.

Classification of Diseases-10 [13] identified SD as a syndrome comprising pathologies affecting each of the following phases: desire, arousal and orgasm, plus sexual pain. All three active phases of the sexual response can be impaired in the presence of depression [6,14-16]. The condition is extremely common across all populations. In the US alone, estimates of the prevalence of SD range from between 10 – 52% in males and 25 – 63% in females [17].

Depression is not always the cause of SD, as SD itself can lead to depression. A recent systematic review demonstrated a bidirectional association between depression and SD, with depression accounting for a 50 – 70% increased risk of developing SD and SD increasing the risk of developing depression by 130 – 210% [18]. Sexual difficulties are extremely common among those with untreated depression. In the ELIXIR study in 2003, it was found that 65% of unmedicated depressed patients suffered SD compared with 71% of those treated with antidepressants [7]. A more recent study observed a higher prevalence rate of 86% among depressed patients not receiving antidepressant treatment versus 73% in those taking these medications [19]. This may suggest that adequate treatment of the disease could promote improved sexual functioning. SD, which is observed during the initial phases of antidepressant therapy, seems to improve in a small percentage of patients after several months [20]. It is important to be aware that the sexual problems can stem from the disease itself, and adequate treatment may correlate with renewed sexual functioning.

Although this bidirectional association could signify that treatment of depression leads to an improvement of SD, this is not always the case. Initiation of antidepressant therapy such as with selective serotonin reuptake inhibitors (SSRIs) may cause or worsen SD [7,21,22]. One review from 2000 that combined results from multiple research studies revealed that 40% of patients treated with antidepressants suffer some form of sexual impairment [23]. In a cross-sectional study involving > 6000 adults with MDD treated with antidepressant monotherapy, the subgroup of 798 patients without other potential causes of SD showed an average prevalence of SD of 24% with a range of 7 – 30% [24]. A 2009 meta-analysis concurred that SD occurred more frequently with use of most antidepressants compared with placebo [25]. Antidepressants in general seem to universally affect all three sexual response phases. However men and women reported adverse effects in different phases, with men more frequently reporting problems with desire and orgasm, whereas women more frequently reporting decreased arousal [26].

Frequency of antidepressant-associated SD (AASD) differs to some extent based on drug mechanism of action. A large prospective study that followed > 1000 patients indicated that among classes of antidepressants, SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) correlated with the highest incidence of SD [20], ranging between 57 and 72%. The same study suggested that use of other antidepressant classes results in a lower incidence of sexual side effects: with 5-HT2 blockers, incidence varied between 8 and 24%, whereas with mono-amine oxidase inhibitors (MAOIs) the rate approached 4%. Similar outcomes were observed in a 2002 study [24]. SSRI and SNRI use again corresponded with the highest frequency of dysfunction, whereas bupropion sustained-release (SR) formulation demonstrated a prevalence of only 7%. Meta-analysis of several studies by Serretti and Chiesa suggests that citalopram, fluoxetine, paroxetine, sertraline and venlafaxine were most likely to induce SD (with prevalence rates between 70 and 80%); fluvoxamine, escitalopram, duloxetine, phenelzine and imipramine were associated with lower incidence rates (25 – 45%) but higher than that of placebo; and finally amineptine, agomelatine, bupropion, mirtazapine, moclobemide and nefazodone conferred the lowest rates (5 – 25%) [25].

Why is it relevant to evaluate SD in the treatment of depression? First, there is a well-established relationship between sexual functioning and quality of life [20,21,27,28], and sexual functioning is important to people regardless of mood state [3,29]. Second, in depressed patients, SD can be an added source of distress, thereby prolonging or worsening their illness [8,28]. Finally, AASD can lead to noncompliance with treatment including medication discontinuation, thereby interfering with recovery [3,20,21,28,30,31]. In a survey of patients who discontinued antidepressant treatment, side effects including SD were the most frequently cited reason for nonadherence [32]. Adherence rates related to treatment with antidepressants display a wide variation, from 8.4% [33] to over 97% [34] across different study populations.

Barriers exist that may limit attention to a patient's level of sexual function; these include patients' hesitancy to

spontaneously report occurrence of this adverse event, physicians' false belief that depression is the only cause of the SD and limited knowledge of symptom management [3,20]. One of the main problems in the evaluation of SD in depressed patients is physicians' belief that patients will spontaneously report the dysfunction. Patients can be hesitant to initiate a discussion for multiple reasons, including cultural differences, resulting in sexual problems that go on undetected [8,35]. For example, in the ELIXIR study, patients that were directly questioned about SD were twice as likely to report problems (69%) compared with reliance on spontaneous reports (35%) [7]. Montejo-Gonzales *et al.* [31] demonstrated a fourfold difference in reporting in a clinical study of 344 patients, with 58% acknowledging SD upon direct and systematic questioning, versus 14% who spontaneously reported dysfunction. Attempts to quantify frequency of AASD are further hindered by physicians' inability to accurately detect its occurrence. Physicians consistently underestimate the prevalence of SD experienced by patients. A study conducted by Clayton *et al.* reported that prior to prescribing antidepressants, physicians predicted that 20% of patients would suffer sexual side effects as a result of the medication. In reality, prevalence rates determined after treatment were almost twice that amount, nearing 37% [26].

In the short-term treatment of depression, SD may not be as significant of a problem as patients' focus on other acute side effects, and in anticipation of improvement of their depression. This is not the case with longer-term treatment of depression, where tolerance of sexual side effects declines as patients' priorities may change [14,35].

2. Search strategy

We conducted a systematic literature search using PubMed, Ovid MEDLINE and Cochrane Databases with information available up to June 2014. Keywords utilized included 'major depressive disorder' or 'MDD', 'sexual dysfunction', 'antidepressant associated sexual dysfunction' or 'AASD', 'selective serotonin reuptake inhibitors' or 'SSRIs', 'serotonin and norepinephrine reuptake inhibitors' or 'SNRIs', 'treatment emergent sexual dysfunction' or 'TESD'. Eligibility criteria included; i) articles dealing with human subjects, age 18 years or older; ii) articles directly addressing SD related to depression and antidepressant treatment, including naturalistic case studies, case reports and clinical trials (e.g., randomized, single-blind and open-label studies); iii) articles describing physiology of sexual function; and iv) articles dealing with animal studies whose findings could be easily translated to humans.

3. Risk factors

The frequency of SD is affected by multiple risk factors that may confound estimation of prevalence in patients taking antidepressants. Incidence varies according to demographic conditions, including age, education history, marital situation and employment status. For example, sexual side effects are more common in older individuals and those with lower education levels [26,36], whereas reduced rates are exhibited by patients who are married and employed full time [26].

Numerous chronic medical conditions – such as neurological disease, diabetes, chronic pain, cancer and ischemic heart disease – impact sexual function [37]. Sexually transmitted diseases and excess use of alcohol and illicit substances can alter the neurocircuitry of the sexual cycle and thus lead to SD. Increasing age is an independent risk factor for both depression and SD [37,38]. In women, menopause results in structural anatomic changes that may lead to dyspareunia. Disfigurements such as mastectomy or burns may impact one's sexual self-perception. Medications other than antidepressants, including antipsychotics, lithium, mood stabilizers, thiazide and potassium-sparing diuretics, β-blockers and histamine (H_2) blocking antiulcer drugs, affect different stages of the sexual response through various mechanisms. Previous or current sexual abuse and unwanted sexual relationships may also play a role [39-43].

4. Pathophysiology

The sexual response is the result of a combination of psychosocial and organic factors. These factors not only vary between different individuals but within the same individual in different settings. The sexual tipping point model created by Perelman is based on this mind/body balance and postulates that there is a threshold for expression of any sexual interest or activity in humans. This threshold varies between and within different situations/experiences based on the balance between physical and psychological factors at a certain point in time (modulating excitation versus inhibition) [44].

4.1 Anatomical and biochemical mechanisms

The sexual response involves a complex interplay between neurogenic, psychogenic, vascular and hormonal factors orchestrated by the brain. Functional neuroimaging studies elucidate brain regions and neuronal networks involved in sexual activity. It has been suggested that the functional anatomy of sexual behavior closely resembles that of other pleasure or rewarding experiences [45]. The main anatomical areas involved are the hypothalamus, limbic system and cortex [46].

Sexual response can be looked at in terms of its different phases or components. The components include the autonomic nervous system, emotions, motivation and cognition/attention. Different brain regions are activated with each of the phases and components. The desire phase is linked with activations of the hypothalamus, ventral striatum, amygdala, insula and orbitofrontal cortex; meanwhile, arousal and orgasm are associated with decreased amygdala and ventromedial cortex activity. The refractory phase is linked to increased activation in the amygdala, hypothalamus and orbitofrontal cortex [45]. The autonomic component is mediated by the hypothalamus, cingulate cortex and insula [47,48]. The amygdala and cingulate cortex are at the center of the emotional/affective response [45].

The ventral striatum is largely responsible for the motivational aspect [47,49], whereas the orbitofrontal and medial temporal cortex regulate the cognitive aspect of sexual processing [48,50,51].

At the molecular level, the autonomic nervous system, the hypophyseal-pituitary-adrenal axis, sex hormones and neurotransmitters act synergistically during the sexual response cycle [52]. The initial phase of sexual response, libido, is predominantly controlled by dopamine. Arousal of genital tissue resulting in erection in men and genital swelling and lubrication and swelling in women is controlled by acetylcholine and nitric oxide. Finally, orgasm, accompanied by ejaculation in men, is regulated by serotonin, norepinephrine and prolactin, and is associated with oxytocin release. Excess serotonin (5-HT) at the 5HT-2 and 5HT-3 receptors, meanwhile, inhibits ejaculation and orgasm. SD also results from increased serotonin affecting 5HT-2 and 5HT-3 receptors; decreased dopamine; blockade of cholinergic and α-1 adrenergic receptors; inhibition of nitric oxide synthetase; and elevation of prolactin levels.

4.2 Drug-specific effects

Antidepressant agents are known to affect all three areas of the sexual response cycle; the specific phase affected and degree of symptom severity are influenced by the type and number of receptors targeted by individual medications. In addition, these factors are impacted by the medications' net effects on receptors, including serotonin, norepinephrine, dopamine, histamine and acetylcholine. The overall impact may also be dose dependent. Data on the effects of individual antidepressants are limited.

Within the sexual response cycle, serotonin has been found to decrease sexual desire and arousal overall. However, response differs based on receptor subtypes. Stimulation of 5HT-2C and 5HT-1A may facilitate erection and ejaculation, respectively, whereas stimulation of 5HT-2A is thought to have negative effects on sexual function [53].

4.2.1 *Selective serotonin reuptake inhibitors*

Neuroimaging suggests that diminished sexual arousal and desire with SSRIs are likely related to central nervous mechanisms and, to a much lesser extent, to peripheral mechanisms [54]. Primary central effects of SSRIs are inhibitory, potentially via decreased dopamine release in the mesolimbic system [55] and suppression of spinal ejaculatory centers [56]. Comparative studies between SSRIs generally have not shown an intra-class difference related to the effects on sexual function [57].

Vilazodone is a novel SSRI that acts on the 5-HT transporter and as a partial against at both presynaptic and postsynaptic 5-HT1A receptors. Its mechanism of action suggests that it might have a more favorable profile relative to sexual function [58].

4.2.2 *Serotonin and norepinephrine reuptake inhibitors*

Although high incidence rates of AASD are also observed with dual-acting antidepressants [20], an increase of central norepinephrine seems to facilitate sexual arousal and orgasm.

Among SNRIs, venlafaxine seems to carry the highest risk of sexual side effects. Venlafaxine is a more potent 5-HT reuptake inhibitor than noradrenergic reuptake inhibitor, especially at low doses. One study examining venlafaxine versus bupropion and another examining venlafaxine versus agomelatine indicated that venlafaxine was associated with more sexual side effects than both comparators [58,59].

Desvenlafaxine is the major metabolite of venlafaxine and so exhibits a similar receptor affinity profile. An integrated analysis of all short-term randomized controlled studies using desvenlafaxine indicated that the most common self-reported SD associated with desvenlafaxine treatment involved erectile dysfunction in men and anorgasmia in women [60]. A more recent study using the Arizona Sexual Experiences Scale (ASEX) scale, comparing desvenlafaxine (50 and 100 mg per day) and placebo, found no statistically significant difference between active treatment groups and placebo in rates of SD [61]. The contrasting results may be attributed to the difference in assessment methods (self-report versus validated questionnaire).

Duloxetine is an SNRI with greater affinity for 5-HT and noradrenergic reuptake transporters than venlafaxine, and activates both receptor types in a balanced ratio. A comparative study of duloxetine versus escitalopram showed that treatment-emergent AASD was significantly higher for escitalopram compared with both duloxetine and placebo, with no significant difference between duloxetine and placebo. Duloxetine was associated with less effect on sexual function compared with that of an SSRI. This may be due to its more favorable 5-HT/noradrenergic ratio [62].

4.2.3 *Tricyclic antidepressants*

Studies on SD related to tricyclic antidepressants are scarce. A double-blind comparative study between amitriptyline and sertraline revealed a lower incidence of SD with amitriptyline [63]. However, other data suggest that amitriptyline carries a rate of SD higher than placebo, presumably because of its anticholinergic effect [64]. Clomipramine has been reported to cause anorgasmia or delayed orgasm in 90% of treated subjects [65].

4.2.4 *Mono-amine oxidase inhibitors*

Similarly, studies on MAOI-related SD are scarce. Moclobemide does not differ from placebo in rates of SD [25]. An early study suggested increased sexual desire with moclobemide compared with the tricyclic antidepressant, doxepin; however, this study did not include a direct comparison of moclobemide with placebo, so the increased sexual desire should be interpreted with caution [66].

A meta analysis of the transdermal MAOI selegiline, showed no improvement of function at a dose of 6 mg/24 h [67].

4.2.5 *Other antidepressants*

Trazodone, a serotonin transporter inhibitor plus 5HT2A- and 5HT2C-receptor antagonist, does not have detrimental effects on sexual functioning [68,69] and has been demonstrated

to improve erectile performance in men and lubrication in women in a sample of patients with SSRI-induced SD [70].

Mirtazapine is the first noradrenergic and specific serotonergic antidepressant that enhances central noradrenergic and 5HT-1 transmission, while simultaneously blocking 5HT-2 and 5HT-3 receptors. These mechanisms account for the drug's lack of associated SD. Mirtazapine thus serves as a useful treatment augmentation tool or alternative antidepressant agent [71,72].

The selective dopamine and norepinephrine reuptake inhibitor bupropion is associated with a rate of SD comparable to placebo, seen in < 10% of the patients exposed [58,73]. Several randomized controlled clinical studies observed a low rate of SD when bupropion was compared with SSRIs including fluoxetine [74] and sertraline [34,75,76]. This effect is believed to be largely accounted for by bupropion's effect on central dopamine levels/function. This parallels the occurrence of drug-induced hypersexuality in patients with Parkinson's disease that are treated with dopamine agonist medications [77]. Other studies have shown that blocking of central dopamine receptors exerts an opposite effect and induces SD [78].

Reboxetine is a selective norepinephrine reuptake inhibitor with little effect on 5-HT or dopamine reuptake. This drug's association with SD is comparable to placebo [79]. Some evidence suggests that this is more pertinent to female patients and the reasons for this are unclear [80].

4.3 Genetic predictors

AASD varies in severity and does not affect everyone receiving treatment. These observations prompted investigation of possible genetic variants that can influence the risk of SD. Initial studies looked at serotonin receptors, serotonin transporter genes, glutaminergic genes, cytochrome p450 genes, drug efflux transporter genes and others. Many of these studies were limited by sample size and warrant replication in larger populations for further validation.

Specific single-nucleotide polymorphisms (SNPs) of interest have been identified. One distinct 5-HT2A receptor SNP, 5-HT2A-1438 GG, appears to correlate with lower scores of sexual arousal compared with alternate genotypes [81]; a more recent Malaysian study failed to replicate this finding but was limited by sample size [82]. A larger study linked SD with a particular insertion/deletion variant within the promoter region of the *SLC6A4* serotonin transporter gene; this effect was most striking in female patients that were concurrently prescribed oral contraceptives [83]. Research has also demonstrated a connection between SNPs of glutaminergic genes and an array of sexual problems, including decreased libido, erectile dysfunction and difficulty achieving orgasm [84]. A genome-wide association study performed in Japan showed that 11 SNPs clustered in the intronic region of the MDGA2 gene were associated with SSRI-/SNRI-induced SD [85]. Interestingly, the MDGA2 gene is expressed in the central and peripheral nervous system and is associated with neuroticism [86].

Other studies have reported a relationship between genetic variation within the cytochrome P450D6 gene and SD from paroxetine use [87].

A recent study investigated variants of the ABCB1 gene, which encodes a drug efflux transporter on the blood–brain barrier, and postulated that variants with decreased function—thereby leading to higher antidepressant concentration in the central nervous system—may increase the risk of SD. This theory seemed to hold true for one particular genetic variant, rs1128503, which was linked with SD in individuals receiving an SSRI that served as a transporter substrate [88].

5. Assessment

The use of structured scales has been incorporated into many recent clinical antidepressant trials in order to measure SD as an adverse event. These scales are not exclusively limited to research, however, and can assist clinicians providing direct patient care with improved detection of SD, thereby possibly improving patient treatment adherence and lowering the risk of depression recurrence [3]. An adequate assessment involves evaluation of sexual function prior to initiation of treatment, and also periodically during treatment, in order to monitor for change in sexual functioning associated with treatment, for example, development of antidepressant-associated SD [8]. As previously mentioned, patients' spontaneous report of SD is unreliable; therefore, the use of validated and specific questionnaires that encompass multiple aspects of sexual functioning is warranted [7,21].

Measures available for clinical use include the ASEX [89], the Changes in Sexual Functioning Questionnaire (CSFQ) [90], the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) [91] and the Sex Effects Scale [92,93]. These scales demonstrate adequate psychometric properties, including validity and reliability, as well as sensitivity to change, that enables monitoring of sexual function before and during antidepressant therapy [94]. The Food and Drug Administration has supported the use of the ASEX and the CSFQ following an analysis of sexual function assessments in recent registration trials for antidepressant medications [95]. In a survey of 29 'expert' psychiatrists in the area of AASD, Balon and Segraves [96] found that most physicians (90%) routinely conduct an initial assessment of sexual functioning via interview-based discussion prior to treatment. However, only 24% of practitioners employ formal questionnaires as part of the evaluation, mostly commonly the CSFQ (10.3%).

The evaluation of SD must include a comprehensive assessment of patient factors, including age, relationship(s), use of alcohol or other substances, as well as comorbid psychiatric and medical conditions [3]. Therefore, depressed patients should be routinely screened for SD. Conversely, patients that present with sexual symptoms should routinely be assessed for depression [18,97]. According to the World Health

Organization, sexual health is "a state of physical, emotional, mental, and social well-being in relation to sexuality. It is not merely the absence of disease, dysfunction or infirmity" [98]. As such, a biopsychosocial model can be helpful in both the evaluation and management of SD. The condition is subjective and can be influenced by cultural and social factors, such as people's expectations or desired level of sexual functioning and what is considered 'normal' [57,99,100]. A detailed psychosexual history [20] can reveal more information regarding symptom onset (primary versus secondary SD), settings in which symptoms occur (generalized versus situational), and potential contributing social relationship factors (or inversely, how relationships are affected by SD).

6. Management

Although studies examining the pharmacological treatment of AASD are limited, several approaches for its management have been proposed. Some strategies include choosing an antidepressant with a low incidence of SD (bupropion, mirtazapine), dose reduction, waiting for spontaneous remission (adaptation/tolerance), drug holiday, medication switching or augmentation, addition of an antidote, as well as others.

6.1 Dose reduction

AASD is often related to the dose of antidepressant medication. Thus, consideration of dose reduction to the minimal therapeutic dose is often a first-line approach. This method can also be beneficial for patients experiencing other adverse side effects with medication use. Decreased medication dose, however, can result in reemergence of depressive symptoms and does not guarantee immediate restoration of sexual function [101].

6.2 Adaptation

Adaptation, or waiting for spontaneous remission of the dysfunction, presumably occurs via the development of tolerance. A disadvantage to this strategy is that it may require a long wait, which patients may not tolerate [102], thereby increasing the risk of noncompliance with treatment. The ELIXIR study [7] found that in as many as 42% of the 4557 patients, physicians waited for spontaneous remission of the SD. This is likely an ineffective strategy, particularly in patients who report significant impact of their SD, given that as few as 5 – 10% of patients actually experience remission [20,26]. Although the physiopathology of adaptation is unknown, researchers have observed that patients who developed tolerance responded successfully to antidepressant treatment, suggesting that the spontaneous remission might be a marker for the down-regulation of serotonin receptors and an increased threshold for SD. When compared with treatment responders, nonresponders to antidepressant treatment had greater levels of SD across all domains [103,104].

6.3 Drug holiday

Rothschild [105] conducted a study with 30 outpatients who reported AASD to evaluate the outcome of a mandated drug holiday. Patients were instructed to discontinue the prescribed SSRI (sertraline, paroxetine or fluoxetine) after their Thursday morning dose and resume dosing on Sunday at noon, with sexual activity scheduled at the end of that period, over four consecutive weekends. Patients taking sertraline and paroxetine reported an improvement in sexual functioning, but not those taking fluoxetine, presumably because of its longer half-life. Of note, there was no significant worsening of depressive symptoms after temporary discontinuation of the antidepressants. Disadvantages to this strategy include the potential for treatment noncompliance if patients decide to skip other days as well. In addition, drug discontinuation symptoms could occur with short-acting SSRIs [26,102], not measured in this study.

6.4 Switching or augmentation strategy

A meta-analysis by Serretti *et al.* presented a hierarchy of antidepressants in terms of the impact on sexual function. Sertraline was indicated to be the worst offender followed by venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram and fluvoxamine [25]. Overall rates of SD across all drug types varied between 25.8 and 80.3%. It is important to note that this meta-analysis incorporated studies that utilized different rating scales to assess sexual function, varying medication doses, and also those with small sample sizes; furthermore, they employed dissimilar research methodologies, including those that were open-label, double-blind, cross-sectional and retrospective.

SNRIs and SSRIs correlate with a higher rate of SD compared with other antidepressants such as bupropion [24]. Mirtazapine, agomelatine, vilazodone, vortioxetine, moclobemide and amineptine are some other antidepressants considered to have a favorable SD profile [3,25,103,106-108]. Nefazodone use in the US declined dramatically secondary to its risk of hepatotoxicity, and so has not been included in any studies over the course of the past 10 years.

6.5 Individual drug effects (note that no medication has an indication for treatment of AASD)

6.5.1 Bupropion

Bupropion has often been suggested for a substitution or augmenting strategy in an attempt to minimize risk of AASD. Gartlehner *et al.* pooled several randomized controlled trials and demonstrated that bupropion antidepressant use corresponded to a lower rate of SD compared with escitalopram, fluoxetine, paroxetine and sertraline [109]. Several head-to-head longitudinal studies have shown bupropion to have a more favorable SD profile compared with other antidepressants [26,58,59,92,110]. Similarly, in a study that evaluated patients without risk factors for SD except MDD, patients

on citalopram and venlafaxine XR had a sixfold increased risk of developing SD compared with those on bupropion XL [24]; patients taking paroxetine and sertraline had a fivefold greater risk and those on fluoxetine, a fourfold greater risk versus bupropion. A double-blind, randomized controlled trial comparing sexually active patients prescribed either bupropion XL or venlafaxine XR observed that by as early as the second week, sexual function assessment scores remained unchanged for patients on bupropion XL, but significantly declined in those receiving venlafaxine XR. This implies a negative effect of venlafaxine XR on sexual function compared with bupropion XL [58]. A separate head-to-head comparison between bupropion XL and escitalopram demonstrated a higher SD rate in patients on escitalopram compared with bupropion XL [110].

In one double-blind, randomized controlled trial examining the use of bupropion SR as an adjunct to the existing treatment regimen in female patients already prescribed an SSRI [111], women that received both SSRI and bupropion SR showed a statistically significant improvement in their sexual function based on the Female Sexual Function Index compared with those receiving SSRI and placebo. An improvement in sexual desire level, lubrication, orgasm and overall sexual satisfaction was also observed in this group. A separate placebo-controlled study reported that use of bupropion SR as augmentation agent correlated with significant improvement on the CSFQ in the frequency of sexual activity and desire compared with placebo [112]. Of note, the recovery in sexual functioning observed with bupropion SR appears to be dose dependent [111,113].

6.5.2 *Mirtazapine*

Mirtazapine can also serve as a substitution or augmentation agent. Patients who switched from an SSRI to mirtazapine for up to 6 weeks were less likely to experience reemergence of SD [72]. A naturalistic study in which patients with depression were tracked for 6 months while receiving mirtazapine demonstrated resolution of SD by the 6th month of follow-up [114]. The efficacy of augmentation strategies with mirtazapine has been investigated through several studies. Ozmenler *et al.* evaluated the effect of using mirtazapine as an augmentation agent in patients with residual SD despite the remission of depressive symptoms with antidepressant therapy [115]. The patients remained on their antidepressant, 36.4% remaining on paroxetine, 27.3% on sertraline, 21.2% on citalopram and 15.1% on fluoxetine. After treatment with mirtazapine for 6 – 8 weeks, 42.4 – 48.5% of the patients reported an overall decrease in the rate of SD [115]. There was also a concomitant decrease in the Hamilton Rating Scale for Depression score, signifying therapeutic benefit for depressive symptoms.

6.5.3 *Buspirone*

Buspirone has been proposed as having a favorable SD profile; however, there is a paucity of randomized-controlled studies to support this theory. A placebo-controlled trial with patients who received buspirone as an adjunct for citalopram- or paroxetine-resistant MDD indicated an improvement in sexual function compared with those on adjunctive placebo [116]. A more recent study by Michelson *et al.* evaluated buspirone as an augmentation agent: in this study, women who had been successfully treated with fluoxetine but had experienced concomitant SD showed an overall improvement in sexual function with buspirone augmentation (though this difference was not statistically significant compared with placebo) [117].

6.5.4 *Vilazodone*

A pooled analysis of three studies on vilazodone: Two 8-week placebo-controlled studies (one used the ASEX and the other used the CSFQ) and one 52-week open-label study (utilized the CSFQ) assessed sexual function in patients with MDD. At baseline, half of men and 2/3 of women had SD. Sexual function improved on average in both vilazodone and placebo groups. In men, there was a low-moderate magnitude effect size favoring placebo over vilazodone (Cohen's D-value = -0.33); by contrast, the low magnitude effect size of 0.23 in women suggests a small benefit for vilazodone versus placebo. Treatment emergent SD was spontaneously reported by 8% of patients receiving vilazodone and < 1% by those receiving placebo ($p < 0.001$). This study is limited by the lack of a comparator antidepressant with known SD to confirm assay sensitivity. These data suggest that vilazodone may have a small adverse impact on sexual function in adults with MDD, possibly more so in men [118].

6.5.5 *Vortioxetine*

In a pooled analysis of seven randomized-controlled, short-term studies (six studies on MDD and one study on generalized anxiety disorder), vortioxetine was not significantly different from placebo in risk of treatment emergent SD in patients without baseline SD, as measured by the ASEX. Vortioxetine was also equivalent to placebo in risk of worsening symptoms of SD in patients with baseline SD. The aforementioned findings were applicable to doses of vortioxetine ranging from 5 to 20 mg/day. Assay sensitivity was demonstrated by use of duloxetine in five of the studies, which demonstrated statistically significantly higher rates of TESD compared with placebo and vortioxetine at both 5 and 10 mg/day [119].

In a separate study of patients with well-treated MDD and experiencing SSRI (citalopram, paroxetine and sertraline)-induced SD, patients were abruptly switched to either 10 – 20 mg/day of vortioxetine or 10 – 20 mg/day of escitalopram in a random fashion. Sexual function was evaluated using the CSFQ self-report over 8 weeks. Vortioxetine was shown to be statistically significantly superior to escitalopram in improving TESD in this population, as measured by the total CSFQ score, 4 of 5 subscales, and all three phases of the sexual response cycle. Antidepressant treatment efficacy was maintained with both agents [120].

6.6 Antidotes

Both clinical and bench research studies have evaluated the use of PDE-5 inhibitors like sildenafil, tadalafil and vardenafil as possible antidotes to AASD. Animal studies that have measured erectile dysfunction via intracavernous pressure after administration of SSRIs have demonstrated a reversal of the decreased intracavernous pressure—and therefore presumed improved sexual functioning—with the use of PDE-5 inhibitors [121]. Sukoff Rizzo *et al.* (2008) conducted a study in rats with a decreased number of penile erections while on fluoxetine. They were exposed to yohimbine, apomorphine and sildenafil; only sildenafil was found to be effective in restoration of sexual function [122]. Clinical research studies support these animal findings. For example, a randomized-controlled trial by Nunberg *et al.* demonstrated that male subjects with SSRI-associated SD who received sildenafil experienced a statistically significant improvement in sexual satisfaction and overall function [123]. In a subsequent study in 2008 by Nurnberg *et al.*, women with AASD who received sildenafil suffered significantly fewer adverse sexual events, including delayed orgasm and inadequate lubrication, compared with those who received placebo, although sexual desire was unchanged [124].

Exogenous testosterone has been an optional management strategy for SD. A 6-week, double-blinded, placebo-controlled trial on 100 men with a diagnosis of MDD taking an antidepressant who had a low or low-normal testosterone level showed an improvement in ejaculatory ability with the use of exogenous testosterone [125]. Women, especially those in the late reproductive years, can have low testosterone levels, which likely impairs sexual functioning. Insufficient testosterone production can result in reduced conversion to estrogen, and in turn lead to diminished sexual desire and function. Exogenous testosterone has been shown to result in an improvement in the frequency of sexual activity and sexual satisfaction in premenopausal women with a low libido [14].

Other medications that have been investigated for the management of AASD include reboxetine, mianserin, amantadine and nefazodone [118,126].

6.7 Other strategies

Lorenz and Meston [127] conducted a study evaluating the effect of exercise on sexual arousal in females receiving SSRI antidepressant therapy via measurements of heart rate using an electrocardiogram and genital arousal using a vaginal photoplethysmograph. Results revealed enhanced genital arousal by photoplethysmograph in women who exercised either 5 or 15 min prior to sexual stimuli, but interestingly, self-reported sexual arousal did not appear to improve with exercise. In a more recent study using a randomized crossover design [128], researchers examined women with AASD who were assigned to complete 3 weeks of exercise immediately before sexual activity or 3 weeks of exercise separate from sexual activity (with crossover to the other arm of the study after the initial 3 weeks). They found that sexual desire significantly improved with exercise immediately before sexual activity. Scheduling regular sexual activity, although not exercise, significantly improved orgasm function.

A variety of other agents have been studied in the management of AASD. Many of these are based on traditional remedies utilized in various cultures worldwide and are available without prescription as 'supplements' to enhance sexual function. For example, Maca root (*Lepidium meyenii*) is a plant indigenous to the Andes region in South America. Despite many animal experiments suggesting its ability to enhance spermatogenesis and fertility, randomized controlled trials in humans have provided limited evidence for its effectiveness in improving sexual function [129]. Dording *et al.*. [130]. did perform a study with a small sample showing significant improvement in sexual functioning based on formal questionnaire results. Data with *Ginkgo biloba* use have been inconclusive [131-136]. Additional treatments under investigation include S-adenosylmethionine [137], saffron [138] and acupuncture [139], among others.

7. Conclusion

Depression can negatively impact the level of sexual functioning in many patients. Treatment of MDD often can improve sexual symptoms; however, antidepressant medications themselves have been associated with sexual side effects. It is important to assess for sexual symptoms, as they can lead to treatment nonadherence and/or discontinuation. Patients often do not spontaneously report treatment emergent SD. Therefore, a more accurate evaluation would include direct inquiry by the treating provider and the use of validated rating scales.

Biological factors, including anatomic, genetic and neurotransmitter effects, combine with environmental and psychosocial factors to modulate both excitatory and inhibitory processes related to sexual functioning. Therefore, a treatment plan for SD should consider all these aspects [102]. Many options for management of AASD include waiting for spontaneous remission, decreasing antidepressant dose to the minimal effective dose, specifically choosing medications at drug initiation that are associated with a lower rate of SD, adding an augmenting agent or antidote, as well as other strategies. Pharmacological interventions may be complicated by psychosocial factors. A psychosocial assessment may identify the need for other interventions, such as counseling, couples' or family therapy, sensate focus and sexual education [140-142]. Promotion of a healthy lifestyle, cultivation of patients' sense of well-being and maintenance of overall health are also essential to any treatment plan.

8. Expert opinion

Depression can result in SD; the reverse is also true. When screening for depression, it is important to assess baseline

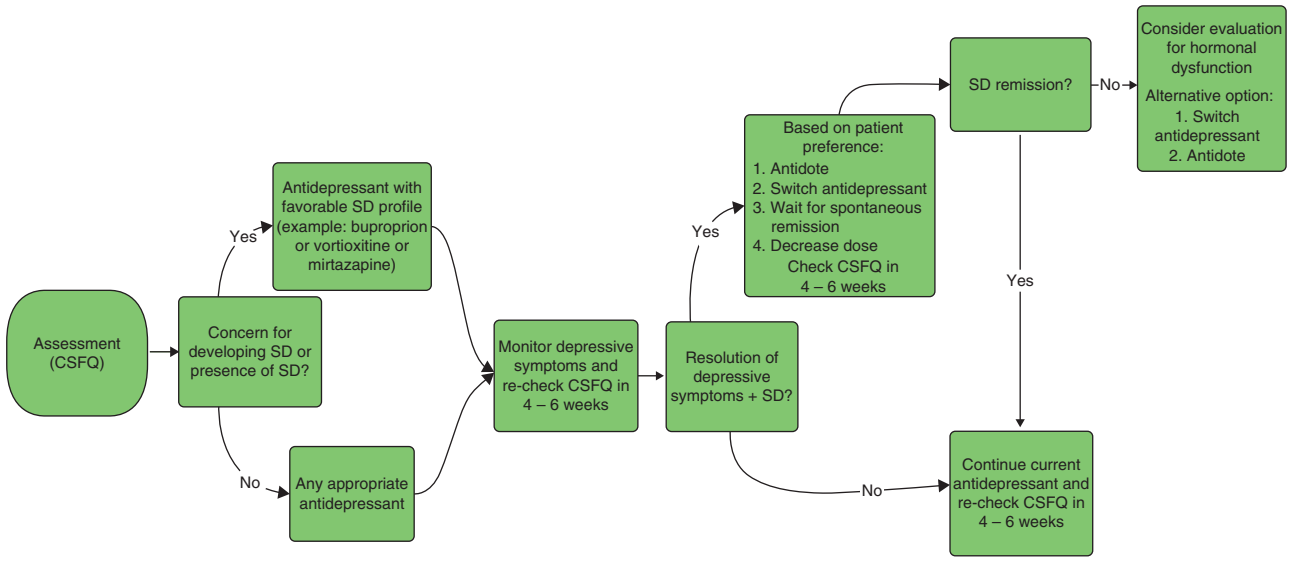

Figure 1. Suggested therapeutic guidelines for management of AASD.
AASD: Antidepressant-associated sexual dysfunction; CSFQ: Changes in sexual functioning questionnaire; SD: Sexual dysfunction.

sexual functioning, taking into consideration patients' demographic factors, medical and psychiatric comorbidities, and other medications. The use of validated rating scales (ASEX, CSFQ) not only allows for more accurate information about sexual functioning in individual patients compared with spontaneous self-report, but also allows a form of comparison for the same patient once antidepressant treatment is initiated.

In this article, we have presented a review of the relevant literature regarding management of SD related to antidepressant use. We have also discussed the pathophysiology and the growing body of evidence indicating the importance of genetic factors in determining response to treatment as well as increased risk of TESD. The role of individualized treatment in the management of SD cannot be overemphasized. For a sexually active patient with a first episode of depression, for example, TESD may result in treatment nonadherence and potentially a worsening of depression by stopping antidepressant therapy. Conversely, for a patient who has failed multiple antidepressants, and an effective antidepressant results in SD, the focus should be on quality of life via management options such as use of antidotes or augmentation strategies to minimize side effects without sacrificing efficacy.

As a general guideline, we recommend that if the initial evaluation reveals pre-existing SD or the patient's preference regarding minimal/no effect of treatment on their sexual function, antidepressants associated with lower risk of sexual side effects (mirtazapine, bupropion, vortioxetine) should be selected. If, on the contrary, screening does not indicate prior SD, or sexual functioning is not a priority for the patient, antidepressant options should be based on general treatment guidelines and patient preference.

Once treatment is initiated, SD should be monitored periodically (every 4 – 6 weeks) over the course of treatment, ideally with use of validated measures that can allow a pre/post-treatment comparison. In the event of emergence of SD, options for management include (in order of preference given available evidence) adding an augmentation agent or antidote, change to an antidepressant with low risk of SD, waiting for spontaneous remission or decreasing the dose of the medication. If the previously mentioned strategies are not effective, changing the antidepressant is the best option, especially if depressive symptoms are not in remission; Consideration should be given to the need for evaluation of hormonal dysfunction. We would recommend against use of drug holidays as these can result in symptoms of medication withdrawal or the reemergence of depressive symptoms and/or promote medication noncompliance with skipping of scheduled doses.

We reviewed promising studies regarding low incidence of SD with vilazodone and vortioxetine, suggesting an alternative as a first-line antidepressant agent when risk of SD is to be minimized, they may have merit as an augmenting agent.

Recent key findings include the bidirectional nature of depression and SD (related neuroendocrine processes), and drug class effects on sexual functioning associated with the mechanism of action.

There is increasing evidence that genetic factors may contribute to the inter-individual variability in AASD. If larger studies are able to validate the currently limited data involving candidate genes, personal genotyping that helps guide individualized treatment could become a reality. Additionally, this would facilitate the development of enhanced therapeutic guidelines to avoid or manage AASD (**Figure 1**).

Certainly, more research is needed that allows better understanding of the individual variability of

antidepressant-associated SD, but also specific antidepressants' effect on sexual functioning. One important limitation in previous studies has been the lack of consistent methods to assess sexual function; the FDA's recommendation on the use of two validated measures (ASEX, CSFQ) can perhaps remedy this. Greater standardization in methodology, measurement and data analysis may lead to an increased number of improved management options in MDD. Other barriers to overcome include the reluctance of providers to proactively address SD in depression and its treatment, and the difficulty for patients in communicating their concerns.

Future research must seek genetic and physiological markers and mechanisms for TESD, and identify alternative, effective management strategies to ensure remission of symptoms of MDD while maintaining/restoring the individual's quality of life.

Declaration of interest

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