Antidepressant-Associated Sexual Dysfunction in Patients with Depression: A Meta-Analysis of Sexual Functioning Data Collected via Prospective Questionnaire

Paula Jacobsen

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ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION
IN PATIENTS WITH DEPRESSION: A META-ANALYSIS OF SEXUAL FUNCTIONING
DATA COLLECTED VIA PROSPECTIVE QUESTIONNAIRES

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

PROGRAM IN RESEARCH METHODOLOGY

BY
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CHICAGO, IL
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ACKNOWLEDGEMENTS

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ABSTRACT

Sexual functioning is associated with symptoms of depression, which occurs at rates much higher than that in the general population. Treatment of depression and remission of depressive symptoms can improve sexual functioning; however, antidepressants and other medications may cause or worsen sexual functioning. Assessment of sexual dysfunction in the past has predominantly relied on the patient spontaneously reporting problems with sexual functioning to their physician or other medical professional. Due to the sensitive nature of the topic, patient reporting is typically low and does not reflect the actual prevalence of sexual dysfunction. This research assessed the rate and level of antidepressant treatment-associated sexual dysfunction as assessed by validated questionnaire in published and unpublished data.

Studies eligible for inclusion were randomized, double-blind, placebo-controlled trials evaluating the antidepressant effect in patients with acute major depression. Studies must have included approved antidepressants evaluating doses in the therapeutic range and include a validated questionnaire to assess sexual functioning, i.e., the ASEX or CSFQ. The studies must have included sufficient data to calculated mean standardized effect sizes and/or odds ratios for developing sexual dysfunction.

The initial search yielded 320 records. After review for eligibility and completeness, the searched yielded 17 studies for inclusion in this meta-analysis. Sexual dysfunction odds ratios and standardized mean effect sizes for antidepressant versus placebo were calculated. Where available, odds ratios and mean effect sizes were also calculated by sex.
The odds of developing sexual dysfunction with paroxetine, escitalopram and duloxetine were significantly worse than placebo. Evaluation by gender indicated that for women the odds of developing sexual dysfunction with desvenlafaxine was also significantly worse than placebo. Standardized mean effect sizes indicated significantly worse sexual functioning versus placebo for escitalopram and paroxetine with both sexes combined. Significant differences were also found for men taking vilazodone. Conclusions of this meta-analysis are limited by the number of studies included. For some antidepressants there was only one study that qualified. Not all studies provided data by sex. Gender effects are apparent with some antidepressants, so this data is of particular interest when evaluating the risk of developing sexual dysfunction.
CHAPTER ONE
OVERVIEW

Sexual dysfunction is a disruption in the normal sexual response cycle and typically affects the desire, arousal, and/or orgasm phase(s). Sexual dysfunction occurs in approximately one-third of the general population; however, the prevalence increases with certain comorbid conditions. Several factors that contribute to the level of dysfunction are: medical illnesses, such as, obesity, diabetes, cardiovascular disease, sexually transmitted diseases, and urinary tract infection; alcohol consumption; substance abuse; social status; sexual trauma; medications; emotional issues; and psychiatric illness. The particular focus of this work addresses sexual dysfunctioning associated with depression and in response to antidepressant drug treatments, which occur at rates much higher than that in the general population.

Depression is associated with many symptoms that can have a negative effect on intimacy and sexual relationships; i.e., persistent sadness, loss of interest in activities once pleasurable, decreased energy, feelings of worthlessness, and irritability and social withdrawal. Treatment of depression and remission of depressive symptoms can improve sexual functioning; however, antidepressants and other medications may cause or worsen sexual functioning, which is referred to as treatment-induced or treatment-emergent sexual dysfunction. In the literature, there is a wide range reported in the level of sexual dysfunction associated with various antidepressants. Medications with a predominantly serotonergic mechanism of action (MOA), such as the Selective Serotonin Reuptake Inhibitors (SSRIs), are associated with higher rates of sexual dysfunction compared to drugs that primarily exhibit a non-serotonergic MOA. For example,
medications, such as buproprion, which primarily exhibit dopaminergic and noradrenergic effects, are associated with little or no sexual dysfunction. Antidepressants not only differ in the level of impact on sexual functioning, but there are also differences in other tolerability parameters and in efficacy, which vary across individuals, thus making selection of medication therapy multifaceted and to a great extent individualized.

Treatment-associated side-effects often affect medication compliance and may lead to discontinuation of treatment. Lack of medication compliance is a significant issue as this can interfere with the treatment of depression, often resulting in an incomplete response or lack of remission of depressive symptoms. Depression is associated with significant reductions in quality of life, impaired productivity, and reduced overall health, and according to the Centers for Disease Control and Prevention is the 10th leading cause of death in the United States. In addition, sexual dysfunction is a commonly reported side-effect that often results in medication discontinuation.

Assessment of sexual dysfunction in the past has predominantly relied on the patient spontaneously reporting problems with sexual functioning to their physician or other medical professional. Due to the sensitive nature of the topic, patient reporting is typically low and does not reflect the actual prevalence of sexual dysfunction. Several prospective questionnaires have been developed in order to more accurately assess the true levels of dysfunction associated with medication treatment or illnesses. Most of the antidepressant-associated sexual dysfunction data reported in the literature are from individual studies and include active treatment versus placebo, treatment versus active comparator, or both. Comparing across studies to judge the comparative level of sexual dysfunction is difficult due to natural variation across studies, and the use of different assessment tools. A few meta-analyses and other systematic reviews have been
conducted to address the issue of comparisons across antidepressants; however, the body of research has grown, the methods for assessing sexual dysfunction have become more systematic, and new, differentiated antidepressants have entered the market. Therefore, a current meta-analysis would provide useful information in the understanding of antidepressant associated sexual dysfunction.

The purpose of this research is to assess the rate and level of antidepressant treatment-associated sexual dysfunction as assessed by validated questionnaire in published and unpublished data. The inclusion of unpublished data from ClinicalTrials.gov, pharmaceutical websites, The Food and Drug Administration (FDA) summary basis of approval documents and other sources will add further insight into the effects of antidepressants on sexual functioning. The objectives of this analysis are to assess the rates of sexual dysfunction and to assess the level of sexual dysfunction associated with commonly prescribed antidepressants and placebo.

The outcome of this research adds to the body of knowledge available on treatment-associated sexual dysfunction. In the typical clinical setting, it is relatively uncommon for clinicians to proactively question depressed patients regarding their sexual functioning. It is equally unlikely that patients will bring up this topic with their healthcare provider. Usually, the most urgent treatment goals are addressed initially (depressed mood, feelings of hopelessness, worthlessness and any potential suicidal ideation of behaviors) and residual symptoms are often considered as something to tolerate or perhaps deal with later. Unfortunately, the residual symptoms of sexual dysfunction are often left unaddressed and can eventually lead to poor overall treatment outcomes, lack of treatment compliance, remission and recurrence. Both patients as well as healthcare providers are often hesitant to switch medications if the majority of the depressed symptoms appear to be controlled. In part, the reluctance to address sexual
dysfunction is due to the lack of effective and tolerable alternatives for an individual patient, as well as lack of knowledge of the relative sexual dysfunction associated with available antidepressants.

This research will provide a means for healthcare providers to reference the rates of sexual dysfunction, including the recently approved antidepressants, among the second-generation antidepressants. Having these data available as a meta-analysis provides a systematic, standardized and comparative assessment, which is difficult to perform when reviewing individual studies.
CHAPTER TWO

INTRODUCTION

The normal human sexual response cycle is generally described as having four phases: (1) Desire or libido, characterized by an interest in sexual activity, (2) Excitement or arousal, the subjective sense of sexual pleasure accompanied by physiological changes (including penile erection in men, and vaginal lubrication and clitoral engorgement in women), (3) Orgasm, the peaking of sexual pleasure and release of tension, and (4) Resolution, the sense of muscular relaxation and general well-being (Masters & Johnson, 1966; Kaplan, 1979; Levin, 2008). Sexual dysfunction is characterized by a disruption in the normal sexual response cycle and typically affects the desire, arousal, and/or orgasm phase(s) (DSM-IV, 1994). Sexual dysfunction is prevalent and occurs in approximately one-third of the general population. Some estimates report that as many as 43% of women and 31% of men experience some degree of sexual dysfunction (Laumann et al., 1999). Most studies have shown that a greater percentage of women than men report issues with sexual functioning (Montgomery et al., 2002). In both sexes, the most common complaint is decreased libido. In men, erectile dysfunction and premature ejaculation are common complaints; in women, failure to achieve orgasm is often reported. There are several factors that contribute to problems in normal sexual functioning, including medical illnesses (e.g., obesity, diabetes, cardiovascular disease, sexually transmitted diseases, urinary tract infection, etc.), alcohol consumption, substance abuse, social status, sexual trauma, medications, emotional issues and psychiatric illness (e.g., depression or anxiety) (Laumann et al., 1999; Baldwin, 2001; Zajecka, 2001).
Sexual dysfunction is a frequently reported symptom of depression and comparative studies consistently report higher rates of sexual dysfunction in depressed patients compared to the general population. Some studies have reported loss of sexual interest in approximately 70% of depressed patients (Casper et al., 1985). A more recent prospective study (Zurich Cohort Study) of 591 males and females from the general population of Zurich reported the prevalence of sexual dysfunction in depressed patients as 50% versus 24% in non-depressed patients (Angst, 1998). Prior studies had reported on the association of sexual dysfunction and depression, but had not systematically studied this association in untreated patients. Kennedy et al. (1999) conducted a study of 134 men and women with depression who were willing to complete a sexual functioning questionnaire before initiating antidepressant treatment. The results of this study also indicated high levels of sexual dysfunction in patients who were currently experiencing a major depressive episode. Approximately 50% of the women and 25% of the men reported no sexual activity during the preceding month and 50% of women and 42% of men reported a decrease in sexual desire. The most commonly reported issues with arousal in sexually active patients were inability to sustain erection in men (46%) and less sexual arousal in women (50%).

A 2013 review and meta-analysis conducted to assess the bidirectional relationship of depression and sexual dysfunction, evaluated six studies on the risk of depression in patients with sexual dysfunction, and six studies on the risk of sexual dysfunction in patients with depression (Atlantis et al., 2012). The results of this review demonstrated that depressed patients had a 50% to 70% increased risk of developing sexual dysfunction and those with sexual dysfunction had a 130% to 210% increased risk of developing depression, reinforcing other data demonstrating the inter-relatedness of sexual dysfunction and depression.
Pathophysiology of Depression and Sexual Functioning

Depression is characterized by persistent sadness, loss of interest in activities once pleasurable (including sex), decreased energy, feelings of worthlessness, irritability and social withdrawal; symptoms which may adversely affect intimate relationships and create difficulties in sexual relationships (Baldwin, 2001). The three main monoamine systems involved in the pathophysiology of depression are serotonin (5-hydroxytryptamine, 5-HT), noradrenaline (NE), and dopamine (DA). Postmortem, cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging studies in depressed unmedicated individuals have demonstrated decreased 5-HT, NE and DA availability in the central nervous system (Nemeroff, 2008).

Most antidepressants function by increasing availability of serotonin in the brain; many also increase the availability of noradrenaline and/or dopamine. Newer antidepressants (often referred to as second generation), such as the selective serotonin reuptake inhibitors (SSRIs), have many improvements over older antidepressants (e.g., tricyclics), particularly in safety; however, response to SSRIs has been incomplete for many patients. This has led to further development of antidepressants targeting the NE and/or DA systems (e.g., serotonin norepinephrine reuptake inhibitors [SNRIs] or ‘atypical’ antidepressants such as bupropion, nefazodone, mirtazapine, vilazodone, and vortioxetine).

Sexual function is regulated by complex interactions between the endocrine and nervous systems. Among the hormones that may impact sexual function, testosterone, estrogen, and oxytocin appear to have greater roles in facilitation of the desire, arousal and/or orgasm phases of sexual response (Meston & Frohlich, 2000; Anil Kumar et al., 2009; Clayton & Montejo, 2006). Neurotransmitters also appear to have a significant impact on sexual functioning. Data indicate that there is a positive association between DA levels and desire and motivation for sexual
activity; and in men, DA may be linked to penile erection. In men, NE levels positively correlate with arousal and erection during masturbation and sexual activity. Some data have shown that levels of NE increased up to 12-fold at orgasm and returned to baseline within 2 minutes of orgasm. In women, blood plasma levels of NE increased during masturbation, peaked at orgasm and declined after orgasm (Exton et al., 1999). The basis for targeting the DA system to improve efficacy over SSRIs lies in the fact that the inability to experience pleasure is a significant symptom of depression; and pleasure, regardless of the activity (including sexual behavior), is primarily mediated by DA neurons and related neuronal circuits (Nemeroff, 2008).

**Antidepressant Treatment-Associated Sexual Dysfunction**

Treatment of depression and remission of depressive symptoms can improve sexual functioning; however, antidepressants and other medications may cause or worsen sexual functioning, which is referred to as treatment-induced or treatment-emergent sexual dysfunction. Because sexual dysfunction is associated with comorbid conditions, including depression as well as medication treatment, and in many cases the cause-effect relationship cannot be determined, the term *treatment-associated sexual dysfunction* (TASD) is often used to describe this phenomenon. In the Zurich Cohort Study (Angst, 1998), a comparison was performed between depressed patients who received only psychotherapy or treatment with medication (50% received benzodiazepines and 50% received antidepressants) versus those who received no treatment. Approximately 62% of depressed patients who received medication experienced sexual problems as compared to 45% of untreated depressed patients. Interestingly, the group of depressed patients who received psychotherapy alone experienced an equally high rate (63%) of sexual dysfunction.

One meta-analysis of several antidepressants reported between 25% and 80% of people taking antidepressants experience sexual dysfunction, depending on the medication they were
taking (Serretti & Chiesa, 2009). In this analysis, the rate of sexual dysfunction in patients on placebo was 14%, which is lower than the rate of sexual dysfunction in depressed patients reported elsewhere in the literature indicating that the assessment of rates of sexual dysfunction varies widely across studies.

Problems with sexual functioning can begin as early as 7 days after treatment with medication, depending on the antidepressant, and improvement can also occur shortly after discontinuation of treatment (Anita Clayton MD, personal communication). Ideally, this would make the assessment of causality of sexual dysfunction and antidepressant treatment more straightforward given confounding factors are limited.

The understanding of sexual functioning has increased since the introduction of newer antidepressants. Older generation antidepressants were associated with sexual dysfunction, but were not selective in their effects on neurotransmitters (e.g., MAOIs). As SSRIs are selective in that they specifically increase serotonin activity, the relationship between serotonin and sexual response has been further clarified. Medications with a predominantly serotonergic mechanism of action, e.g., the SSRI paroxetine, may be associated with the highest incidence of TASD (~70%) compared to drugs that primarily exhibit a non-serotonergic MOA (Kennedy & Rizvi, 2009). Specifically, increased serotonin activity is associated with decreased libido and impaired ejaculation (Meston & Frohlich, 2000). Often the symptoms of sexual dysfunction are mitigated by a reduction in dose of the antidepressant. Furthermore, some SSRIs have been shown to be useful in the treatment of premature ejaculation by increasing the latency to orgasm (Waldinger et al., 1998).

As discussed above, the level of DA and NE affects the desire, arousal and orgasm phases of the sexual response cycle. Antidepressants that primarily exhibit a non-serotonergic MOA be
associated with fewer sexual side-effects than SSRIs. Some studies show that antidepressants that have noradrenergic and well as serotonergic effects (SNRIs such as duloxetine, mirtazapine, and venlafaxine) are associated with less sexual dysfunction, suggesting that increased noradrenaline may mitigate the deleterious effect of serotonin on sexual dysfunction (Kennedy & Rizvi, 2009). In one study, TASD was significantly lower with the SNRI duloxetine as compared to the SSRI paroxetine (46% versus 61%); however, both were significantly worse than placebo (Delgado et al., 2005). Medications that exhibit dopaminergic as well as noradrenergic actions (e.g., buproprion) have been associated with little or no sexual side-effects, and are often used as add-on therapies to counteract antidepressant-induced sexual dysfunction (Kennedy & Rizvi, 2009). In another study of TASD in patients taking one of several SSRIs or buproprion, rates of sexual dysfunction ranged from 30% for citalopram and venlafaxine to 7% for buproprion (Clayton et al., 2002).

A recently updated review from The Cochrane Collaboration (Taylor et al., 2013) evaluated the effectiveness of various management strategies for sexual dysfunction associated with antidepressants. Twenty-three studies that met the selection criteria were included in the meta-analysis. The strategies evaluated in these studies included the addition of further medication (22 studies) and change in antidepressant medication (one study). Based on this review, most augmentation studies failed to show significant improvements in sexual dysfunction compared to placebo; however, the addition of buproprion improved sexual functioning in men and women, and the addition of sildenafil (Viagra) indicated greater improvement in erectile function over placebo in men.
Impact of TASD on the Treatment of Depression

Treatment-associated side-effects often affect medication compliance and may lead to discontinuation of treatment. One study surveyed 350 depressed patients regarding compliance with antidepressant treatment and reasons for noncompliance and/or discontinuation (Ashton et al., 2005). Of the 350 patients surveyed, 60% had completely discontinued treatment with the most common reasons being lack of efficacy (44%), “didn’t like the way the medicine made me feel” (37%), “lost interest in sex” (23%), “tiredness” (18%) and “weight gain” (16%). Of those currently prescribed an antidepressant (97%), 22% indicated they were noncompliant, with “couldn’t have an orgasm” (20%) and “lost interest in sex” (20%) reported as reasons for noncompliance by those patients. In addition, “lost interest in sex” was reported by 47% of all patients prescribed an antidepressant with “unable to have erection” and “difficulty reaching orgasm” considered to be “extremely difficult to live with” by 25% and 24% of the patients, respectively. Although there are not many studies assessing patient self-reported reasons for noncompliance, sexual dysfunction is a commonly reported side-effect associated with treatment and does lead to medication discontinuation and often switching antidepressants to find one that produces less sexual dysfunction.

Lack of medication compliance is a significant issue as this can interfere with the treatment of depression, leading to lack of, or incomplete response or remission of depressive symptoms. Depression is associated with significant reductions in quality of life, impaired productivity, reduced overall health, and substantial economic burden (World Health Organization, 2012; Bech et al., 2006). Depression is also associated with an increased risk of suicide (Reeves & Ladner, 2010; Stone et al., 2009; Barbui et al., 2009). According to The World Health Organization (WHO), major depression is a leading cause of disease burden in North America.
and the fourth leading cause worldwide as of year 2000. By year 2020, WHO estimates that depression will be the second leading cause of global burden of disease. In the United States, major depressive disorder (MDD) affects 5-7% of people each year, and 13-16% of individuals during their lifetime (Hasin et al., 2005; Kessler et al., 2003; Kessler, Berglund et al., 2005; Kessler, Chui et al., 2005); therefore, lack of treatment compliance due to side-effects, in general, and TASD, specifically, can have significant impact on those suffering from depression.

**Assessment of Sexual Functioning**

Initially, assessment of sexual dysfunction relied on the patient spontaneously reporting sexual functioning-related adverse events. Patient reporting is typically low and does not reflect the actual prevalence of sexual dysfunction. In one study of 344 patients using SSRIs, spontaneously reported sexual dysfunction was 14.2% compared to 58.1% when reported via questionnaire (Montejo-Gonzalez et al., 1997). As a result of the propensity to under-report sexual side-effects, prospective questionnaires were designed in order to obtain a more accurate assessment of sexual dysfunction. Several questionnaires have been developed to assess sexual dysfunction in patients; some are administered via interview (e.g., Psychotropic-Related Sexual Dysfunction Questionnaire [PRSexDQ]), self-reported or by interview (e.g., Arizona Sexual Experiences Scale [ASEX], Changes in Sexual Functioning Questionnaire [CSFQ], Rush Sexual Inventory Scale, and Sex Effects Scale), and are usually available in male and female versions. Most record sexual functioning using categories on a Likert scale, but some assess sexual functioning using anchors on a visual analog scale (VAS). Criteria are often identified that categorize the patient as having normal or abnormal sexual dysfunction and many have subscales that assess the three main phases of the sexual response cycle: desire, arousal, and orgasm.
In one study of 1022 patients that utilized a prospective questionnaire (PRSexDQ) conducted by the Spanish Working Group of Psychotropic-related Sexual Dysfunction, sexual dysfunction associated with antidepressants as a whole was 62.4% for men and 56.9% for women, although women reported greater severity of sexual dysfunction (Montejo, et al., 2001). A meta-analysis of studies exploring antidepressant-related sexual dysfunction was conducted by Serretti and Chiesa (2009). This analysis examined the overall rate of treatment-emergent sexual dysfunction as well as the rates of dysfunction in the sexual response phases of desire, arousal, and orgasm. The authors targeted studies examining antidepressant-related sexual dysfunction in patients without prior sexual dysfunction, and the method of acquiring data was through direct inquiry or patient completed questionnaires. In addition to direct inquiry, various scales were included, but the most common were the ASEX and CSFQ. The literature review for this analysis was performed on published studies through July 2008 using MEDLINE. While this study included useful data on many of the commonly prescribed antidepressants, as the authors note the research is subject to publication bias. In addition, the field of study in TASD has increased over the last several years and more articles have been published on newer antidepressants.

A more recent meta-analysis by Reichenpfader et al. (2014) evaluated the comparative harms of second-generation antidepressants in depressed patients utilizing network analysis. The authors concluded that the comparative risk of sexual dysfunction associated with specific antidepressants could not be precisely determined due in part to the variation of sexual dysfunction adverse events reported across studies for a given antidepressant. The variation seen across studies could have been impacted by the inclusion of data gathered by various methods, including spontaneously reported adverse events. Therefore, a review that includes only sexual dysfunction data from prospective questionnaires may reduce the variation in reporting and
provide a greater distinction in the relative incidence of sexual dysfunction associated with antidepressant treatment.

The purpose of this research is to assess the rate and level of treatment-associated sexual dysfunction as assessed by questionnaire in published and unpublished data (i.e., clinicaltrials.gov, pharmaceutical company websites and The Food and Drug Administration (FDA) summary basis of approval documents were reviewed). Data from these sources are publicly available, but many of the studies are not published in journals. Including these data will add further insight into the effects of antidepressants on sexual functioning.

**Objectives**

The objectives of this research are to assess the rates, and the level of sexual dysfunction associated with commonly prescribed antidepressants versus placebo.
CHAPTER THREE

METHODS

This research is a systematic review and meta-analysis of the rates of treatment-associated sexual dysfunction in depressed patients taking commonly prescribed antidepressants approved in the United States. This analysis evaluated the level of sexual dysfunction in the intent-to-treat population (i.e., all the patients who were enrolled and randomly allocated to treatment in randomized clinical trials, and are included in the analysis and analyzed in the groups to which they were randomized) as well as by sex when data were available.

Data Sources and Search Criteria

The literature search was performed using Ovid® (searching MEDLINE and EMBASE databases), and clinicaltrials.gov. The initial database search included articles published through March 2016. The following terms were used to search titles and abstracts for the following associations using Ovid®: “depression OR MDD”; “antidepressant OR antidepressive agents”; “randomized AND double-blind”; and “sexual dysfunction OR sexual function OR libido.” Each search result linked to include all associations. Clinicaltrials.gov was searched using the following terms: “depression AND antidepressant AND randomized AND sexual.” Only interventional studies and studies with results were included. The Food and Drug Administration (FDA) summary basis of approval documents were reviewed for sexual functioning data via validated questionnaires for the following commonly prescribed antidepressants: duloxetine, venlafaxine, desvenlafaxine, bupropion, escitalopram, sertraline, fluoxetine, vilazodone, and vortioxetine.
Study Selection

Typical Study Characteristics

The typical studies that met the criteria below were randomized, double-blind, placebo-controlled studies of the efficacy or tolerability of at least one approved antidepressant. Many of the studies also included an active-control (an approved antidepressant) in addition to the test antidepressant. The patient population was acute major depressive disorder (MDD) patients who were experiencing a major depressive episode. Eligible studies included a proactive questionnaire assessing patient sexual functioning at baseline prior to study interventional treatment, and at least one timepoint post-treatment. Based on the criteria of the questionnaire, patients were categorized as having normal or abnormal sexual functioning prior to treatment and at one or more post-baseline timepoints. Most studies included a change from baseline total score on the sexual functioning scale. Studies were placebo-controlled to allow comparison of active treatment to no treatment. The primary objective of most studies was efficacy of the antidepressant on depressive symptoms, with sexual functioning being assessed as a tolerability endpoint.

Study Selection Process and Criteria

Two trained reviewers (including the author) independently screened the abstracts and full texts articles for eligibility of studies identified by the initial search criteria. The screening process included two steps: an initial review of the titles and abstracts followed by a review of the full text of studies that meet the initial screening criteria. A third party reviewed any disagreements and resolved.

The following selection criteria were applied.
Studies were included based on the following criteria:

1. Study was randomized, double-blind, placebo-controlled antidepressant interventional study.
2. Study included human patients at least 18 years of age who are being treated for depression.
3. Study included only monotherapy antidepressant interventions (i.e., studies examining combination therapies were excluded to minimize confounding factors).
4. Study assessed sexual dysfunction/functioning through the use of a validated sexual functioning questionnaire.
5. Study evaluated only antidepressants approved by FDA for the treatment of depression.
6. Sexual functioning was assessed at screening/baseline and at least one post-baseline assessment during antidepressant treatment.
7. Study evaluated the safety/tolerability and/or efficacy of an antidepressant.
8. Study evaluated antidepressant doses within the approved efficacious dose range; however, the study could have been positive, negative or failed in terms of efficacy in the treatment of depression.
9. Treatment period of study was at least 6 weeks duration.
10. Publication was in English.

Studies were excluded based on the following criteria:

1. Study identified antidepressant intervention by drug class, but not antidepressant name.
2. Study evaluated patients with sexual dysfunction not related to antidepressants or depression, e.g., study evaluated a comorbid condition associated with sexual dysfunction.
3. Study included patients who had conditions, or were taking medications known to affect sexual functioning, other than depression and antidepressants.

4. Study was reported only in abstract form.

Studies for which both reviewers agreed did not meet selection criteria were excluded.

**Quality Assessment**

The risk of bias was assessed by two independent reviewers (including the author) utilizing the criteria developed by the Cochrane Collaboration (Higgins et al., 2011). An assignment of “low”, “unclear” or “high” risk of bias was applied to the following domains: Sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (see Table 1). Any disagreements on assessments were resolved between the reviewers by consensus.
Table 1. Cochrane Collaboration’s tool for assessing risk of bias

<table>
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<th>Type of bias</th>
<th>Description</th>
<th>Relevant domains in the Collaboration’s ‘Risk of bias’ tool</th>
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<tr>
<td>Selection bias</td>
<td>Systematic differences between baseline characteristics of the groups that are compared</td>
<td>• Sequence generation</td>
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<td>• Allocation concealment</td>
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<td>Performance bias</td>
<td>Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest</td>
<td>• Blinding of participants, personnel and outcome assessors</td>
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<td>• Other potential threats to validity</td>
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<tr>
<td>Attrition bias</td>
<td>Systematic differences between groups in withdrawals from a study</td>
<td>• Incomplete outcome data</td>
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<td></td>
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<td>• Blinding of participants, personnel and outcome assessors</td>
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<tr>
<td>Detection bias</td>
<td>Systematic differences between groups in how outcomes are determined</td>
<td>• Blinding of participants, personnel and outcome assessors</td>
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<td>• Other potential threats to validity</td>
</tr>
<tr>
<td>Reporting bias</td>
<td>Systematic differences between reported and unreported findings</td>
<td>• Selective outcome reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Any important concerns not covered in the other domains of the tool</td>
<td>• Bias due to problems not covered elsewhere</td>
</tr>
</tbody>
</table>

The following data were extracted from the sources: (a) study population and demographic information, (b) participant eligibility criteria, (c) study design, duration and sample size, (d) method of randomization, (e) method of maintenance of blind, (f) intervention and dose, (g) patient disposition (completion, withdrawals, and reason for withdrawal), (h) sexual functioning assessment tool, (i) incidence of sexual dysfunction, (j) sexual functioning assessment tool mean total score, where available, (k) percent patients who have shifted from normal to abnormal sexual functioning, where available, and (l) antidepressant treatment effect. Further details are outlined in the coding manual found in Appendix A.
The author coded the data for all the studies and an independent trained coder coded a 20% sample of the studies meeting criteria. Any discrepancies were discussed and resolved between the author and independent coder.

**Outcome Measures**

**Primary Outcomes**

The primary outcome is the standardized mean effect for sexual dysfunction for each antidepressant versus placebo as assessed by validated sexual functioning questionnaires.

**Secondary Outcomes**

The following secondary outcomes were examined:

1. Odds ratio for developing sexual dysfunction of each antidepressant versus placebo as assessed by validated sexual functioning questionnaires.
2. Assessment of differences by gender, and by phases of the sexual response cycle, where data were available.

**Sexual Dysfunction Assessment Tools**

In clinical research trials, the most frequently used scales for assessing sexual functioning associated with antidepressant use are the Arizona Sexual Experiences Scale (ASEX) and Changes in Sexual Functioning Questionnaire (CSFQ); however, several other scales have been utilized to a lesser extent and reported in the literature. The ASEX and CSFQ scales are summarized below, and examples of each of the scales described below are listed in Appendix B.

**Arizona Sexual Experiences Scale (ASEX)**

The ASEX is a brief self-report or clinician-administered scale with items assessing five core domains of sexual functioning: drive, arousal, penile erection/vaginal lubrication, ability to achieve orgasm and satisfaction from orgasm (McGahuey et al., 2000). Each of the five
questions are rated on a 6-point Likert scale ranging from hyperfunction (1) to hypofunction (6) with a total score range of 5-30. Higher scores indicate worse sexual functioning. The third question differs in the male and female version and relates to penile erection or vaginal lubrication. The ASEX was designed to be simple and easy to use, and to assess sexual activity regardless of the availability of a sexual partner. An ASEX score of $\geq 19$, or any 1-item score $\geq 5$, or any 3-item scores $\geq 4$ indicates a high probability of sexual dysfunction. The reliability and validity of the ASEX was examined in 38 healthy control and 58 psychiatric patients aged 18 years and older. The Cronbach’s alpha coefficient for the ASEX was .9055. The test–retest reliability for the ASEX was also calculated (for patients, $r = .801$, $p < .01$, for controls, $r = .892$, $p < .01$). The validity of the ASEX was tested against another validated questionnaire that included assessment of sexual functioning. Further details on the reliability and validity of the ASEX can be found in McGahuey et al., 2000. Sexual functioning data from the ASEX are typically reported as rates of normal/abnormal sexual functioning and rates of patients developing sexual dysfunction post-treatment. Total score changes over time are also reported; however, this is only possible when all five questions are answered.

**Changes in Sexual Functioning Questionnaire (CSFQ)**

The CSFQ is a self-report or clinician-administered scale that contains 36 items (men) and 35 items (women), which assesses five domains of sexual functioning (sexual desire/frequency, sexual desire/interest, pleasure, arousal, and orgasm), and three phases of the sexual response cycle (desire, arousal and orgasm) (Clayton et al., 1997). The first 21 items apply to both men and women. Items are rated on a 5-point Likert scale where a higher score reflects better sexual functioning. The CSFQ was designed to differentiate between people who have had life-long poor sexual functioning and those who have developed sexual dysfunction after normal
functioning. A shorter 14-item version of this scale, the CSFQ-14, was developed to more efficiently assess the domains of sexual functioning evaluated by the longer version and has demonstrated good construct validity and internal reliability. The reliability and validity of the CSFQ-14 was examined in 6,286 patients evaluated for depression. Cronbach’s alpha coefficient was calculated for the whole sample and for each sex separately. Cronbach’s alpha for the total CSFQ-14 score was .90 for the female version and .89 for the male version. Further details of the reliability and of the validity can be found in Keller et al., 2006.

A score of less than 47 for men and less than 41 for women indicates sexual dysfunction on the CSFQ-14 scale (Keller et al., 2006). The CSFQ-14 is more commonly used than the longer version, and has been the choice for use in clinical trials and other studies reported in the literature. Sexual functioning data per the CSFQ-14 are reported as rates of normal/abnormal sexual functioning, the rate of patients developing sexual dysfunction post-treatment, and total scores or scale subscores changes.

The methods of sexual functioning assessment have varied widely, including by patient interview, reporting of adverse events, and various questionnaires. This varying format of inquiry makes determination of the impact of a given antidepressant on sexual functioning difficult to assess across studies. For example, reports of adverse events only are known to be under-reported and unreliable, and are therefore not helpful in differentiation effects compared to placebo. Structured questionnaires that assess the same construct, i.e., domains related to the sexual response cycle, yield more informative data. For example, the ASEX, CSFQ, and Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) assess aspects of desire, arousal and orgasm (phases of the sexual response cycle). These scales, which have also been validated, can be used to calculate scores that indicate the level of impaired sexual functioning.
In addition, the ability to calculate abnormal and normal sexual functioning from scale scores provides a more reliable assessment of odds ratios compared to calculations using adverse event reporting.

**Data Analysis**

The data were analyzed using SPSS (version 25) and specialized meta-analysis macros written specifically for this program (Lipsey & Wilson, 2001).

**Effect Size Metrics**

Odds ratios (ORs) were used as the effect size metric for binary outcomes and standardized mean difference effect sizes were used as the effect size metric for continuous outcomes for each antidepressant. Effect sizes were coded such that the larger effect size represents positive outcomes (i.e., better sexual functioning compared to placebo).

Odds ratios were calculated for overall rates of sexual dysfunction (percent of patients with abnormal sexual dysfunction after antidepressant treatment). The logged odds-ratio was calculated as follows:

\[ ES_{\text{LOR}} = \ln(OR) \frac{ad}{bc} \]

Where \( \ln(OR) \) is the natural log of the odds ratio, a and b are the frequencies of normal and abnormal sexual functioning in the treatment group, and c and d are the respective frequencies in the comparison (placebo) group.

The sampling variance of the logarithm of the odds ratios was calculated as follows:

\[ \text{Var}_{\ln(OR)} = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d} \]
The standardized mean difference effect for each antidepressant were used as the effect size metric for sexual functioning scale scores after treatment. Mean effect sizes were calculated following the independent groups pretest-posttest design in which two groups of participants are assigned to alternate treatment conditions (e.g., experimental and control) (Becker, 1988; Morris & DeShon, 2002; Morris, 2008). The majority of the studies reported mean change or gain scores (i.e., the difference between pretest and posttest sexual functioning scores) and standard deviations of the change for each treatment group; therefore, standardized effect sizes for each comparison (antidepressant versus control) within study were calculated using mean change scores and standard deviations of the change. None of the studies reported the population correlation between pretest and posttest scores, so the correlation was assumed to be 0.8. Standardized effect sizes were calculated using an online calculator companion to Practical Meta-Analysis by Mark W. Lipsey and David B. Wilson, 2001, which can be accessed at the following web address: http://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-Home.php. Formulas for the effect size calculations can be found in Morris and DeShon (2002).

Because the standardized effect size can be upwardly biased in small samples, the standardized effect size was adjusted using the following Hedges correction (Hedges, 1981):

\[ ES_{sm} = \left[ 1 - \frac{3}{4N - 9} \right] ES \]

Where N is the total sample size and ES is the unadjusted effect size.

All effect sizes were reported using a 95% confidence interval.

In studies that included treatment groups with more than one effective dose of a particular antidepressant, effect sizes were calculated within study by dose and pooled to create the mean effect size for that antidepressant, as there were insufficient studies to calculate effect sizes by
dose. Some studies compared different antidepressants (e.g., duloxetine and paroxetine versus placebo) to the same placebo arm; therefore, some effect sizes utilized multiple comparisons to placebo. This was also true for antidepressants of different doses in the same study.

**Missing Data**

Data from the intent-to-treat analyses were used. When analysis from intent-to-treat (ITT) population was not available, the analysis from patients who completed study were used. When information needed to complete the primary measures was missing, additional information was gathered by contacting the authors, via the clinicaltrials.gov or via pharmaceutical company websites. Review of FDA summary basis of approvals did not reveal any additional data.

**Descriptive Statistics**

Descriptive statistics were used to summarize the current state of the literature and highlight gaps in research on sexual dysfunction associated with antidepressant treatment. Descriptives were synthesized across primary studies on the characteristics of methodology, participants, type of intervention, assessment scale(s) used and outcome.

**Sensitivity Analysis**

The data were evaluated for outliers. The effect size distributions were evaluated for outliers using Tukey’s (1977) inner fence criterion. The distribution of sample sizes as well as weights (for odds-ratios) were examined for any extreme values. Publication bias was evaluated using funnel plots. Underrepresentation of unpublished studies, which are more likely to have unfavorable results, can substantially bias effect size estimates (Borenstein et al., 2009). All reasonable attempts were made to include unpublished research such as accessing clinicaltrials.gov, and pharmaceutical websites and FDA summary basis of approval documents.
Synthesis of Effect Sizes and Assessment of Heterogeneity

The distribution of effect sizes across all antidepressants was examined descriptively using forest plots. Random effects models were planned to account for heterogeneity between studies given the likely variation in study characteristics and for the importance of supporting generalization of findings beyond the included studies (Borenstein et al., 2009). Random effects weighed mean effect sizes and 95% confidence intervals for each study were calculated if sufficient comparisons existed. The random effects variance component was calculated using the DerSimonian/Laird estimate (DerSimonian & Laird, 1986). Using random effects models allows for the accounting for within study sampling variance and between study variability; however, if the number of studies is small it is not possible to obtain a good estimate of the random effects variance. Because mean effect sizes were calculated for each antidepressant, there were too few comparisons to estimate the random effects variance for each antidepressant; therefore, the data calculated using the fixed effects model is presented.

Assessment of heterogeneity of the effect size differences between studies was evaluated using both the $\chi^2$ and $I^2$ statistics. Tests of heterogeneity are a measure of the variability in the distribution of effect sizes, and in a homogeneous distribution, the amount of variability is no greater than that which is expected due to sampling error alone. The null hypothesis of homogeneity was rejected in the case of a $\chi^2$ value with $p<0.05$. For interpretation of the $I^2$ statistic, the guidance suggested in The Cochrane Handbook was used for substantial to considerable heterogeneity (i.e., $I^2$ more than 50%). Discussion is included for heterogeneity in results found.
**Moderator Analyses**

A number of moderator analyses were planned if there were sufficient studies eligible. Significant variability in effects (i.e., the $Q$ statistic indicates significant heterogeneity in effect sizes) was expected. It is known that many antidepressants have negative effects on sexual functioning, and antidepressants may differ in these effects. Thus, separate meta-analyses were conducted for each antidepressant. In addition, the effects of antidepressants often differ by gender and potentially by type of sexual functioning scale.

Moderator analyses were planned for gender and sexual functioning scale; however, only gender differences were examined since there was insufficient number of studies and data to examine differences by sexual functioning scale, or any other study characteristic. Gender differences are discussed in the Results section.
CHAPTER FOUR

RESULTS

Literature Search, Identification and Selection

Figure 1 shows a flow diagram summary of the search and selection of all data sources evaluated for this meta-analysis. In the initial search, 320 reports were identified, with 240 being identified through searching within the electronic database, Ovid. Ovid allows for removal of duplicates during the search; therefore, the 240 sources reflect removal of duplicates. An additional 80 reports were identified through other means, such as, Clinicaltrials.gov, citation searches, pharmaceutical websites with study results posted, and the FDA summary basis of approval documents. Abstracts (or titles when abstracts were not available) were screened for initial relevance. Of the 320 screened, 222 were excluded that were clearly not eligible for inclusion. Full text copies were obtained or retrieved for the remaining 98 reports and further reviewed for inclusion. Of these, 79 were deemed not eligible with the primary reasons being irrelevant or simply wrong study design, and no sexual functioning questionnaire used. Details of the reasons for exclusion are provided in Figure 1. The remaining 19 reports were used for coding of the 17 eligible studies. During the coding process, an additional 3 sources of data were obtained in order to complete the required data for calculation of effects sizes and odds ratios. Two of the reports included pooled data on two or more studies. Data sources for the original study reports were obtained if possible.
Figure 1. Flow diagram, summary of search and selection

Records identified through database searching: duplicates removed (n=240)

Additional records identified through other sources (n=80)

Records after duplicates removed (n=320)

Records screened (n=320)

Records excluded (n=222)

Full-text data sources assessed for eligibility (n=98)

79 full-text data sources excluded, with reasons
- Wrong study design (n=27)
- No sexual dysfunction scale (n=20)
- Incomplete sexual functioning data (n=14)
- Sexual functioning scaled not validated (n=10)
- Wrong drug/dose/population (n=6)
- No placebo arm (n=2)

Reports included in qualitative synthesis (n=19)

Reports included in quantitative synthesis (meta-analysis) (n=19)
Characteristics of Included Studies

The details of the eligible studies are provided in Table 2. The 17 eligible studies included 9,475 men and women who were diagnosed with acute major depressive disorder (MDD). The total patients included in the sample excluded Study 5, which was pooled data from studies 6 and 7, but included pooled Study 10 and not studies 16-18. Study 10 included data from 4 of the Lilly studies, but only 3 of the 4 Lilly studies referenced in study 10 were available as individual reports. All but two studies had 8-week treatment periods, with the remaining two having a 10-week and 12-week treatment period. All 17 studies were placebo-controlled as per inclusion criteria to allow for consistent comparison of mean effect sizes; however, 13 of the studies also included more than one antidepressant in addition to placebo allowing for multiple calculation of effect sizes versus placebo within the same trial, potentially reducing inter-study variability. However, multiple comparisons to placebo also introduces dependencies in effect sizes. As mentioned, study duration was also consistent, with 15 of the 17 studies having an 8-week treatment period. All of the eligible studies were randomized controlled trials funded by pharmaceutical companies likely because the inclusion criteria required that the sexual functioning scale utilized be validated, and pharmaceutical companies tend to prioritize the use of validated scales, primarily for regulatory reasons. The randomization schemes for these studies were centrally generated and treatment assignment was allocated in a double-blind fashion with investigative sites utilizing either interactive voice response system or a web-based system.

Only studies that utilized the ASEX and CSFQ-14 were included in the analysis as they contained the necessary data to calculate mean effect sizes from total score and odd ratios from determination of normal and abnormal sexual functioning. The Psychotropic-Related Sexual
Dysfunction Questionnaire (PRSexDQ) has been predominantly used in schizophrenia populations and results in depressed populations were published in Spanish; therefore, no studies that utilized this scale met eligibility criteria. Six studies utilized the CSFQ-14 scale and 11 used the ASEX scale.

Publication year ranged from 2004 through 2015 and reflected the fact that inclusion of validated sexual functioning questionnaires in studies is fairly recent. Most (81%) of the studies were conducted in the United States. The majority (64%) of participants were women and ranged from 56% to 74%, which is consistent with the prevalence of women versus men with MDD in the overall population. Participants were predominantly Caucasian (80%) and African American (17%). The slightly higher percentage of Caucasians in the overall population reflects the inclusion of studies with sites in Europe, which enrolled over 95% Caucasians. The mean age in the overall population of studies combined was 42 years.
Table 2. Summary of study design and references.

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Antidepressant</th>
<th>Dose per arm (mg/QD)</th>
<th>Number of Subjects (ITT)</th>
<th>Study Design</th>
<th>Time of endpoint</th>
<th>Sexual Function tool</th>
<th>Endpoints</th>
<th>Reported by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Clayton et al., 2006 (a)</td>
<td>Buproprion Escitalopram Placebo</td>
<td>300-450 mg flexible 10-20 mg flexible NA</td>
<td>133</td>
<td>130</td>
<td>127</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>CSFQ-14</td>
</tr>
<tr>
<td>2.Clayton et al., 2006 (a)</td>
<td>Buproprion Escitalopram Placebo</td>
<td>300-450 mg flexible 10-20 mg flexible NA</td>
<td>129</td>
<td>130</td>
<td>125</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>CSFQ-14</td>
</tr>
<tr>
<td>3.Clayton et al., 2007</td>
<td>Duloxetine Escitalopram Placebo</td>
<td>60 mg fixed 10 mg fixed NA</td>
<td>67M, 118F 62M, 145F 37M, 59F</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>CSFQ-14</td>
<td>Mean change from BL; percent SD</td>
<td>Male/female reported separately; combined calculated</td>
</tr>
<tr>
<td>4.Clayton, Reddy, et al., 2013; Dunlop, et al., 2011</td>
<td>Desvenlafaxine Placebo</td>
<td>50 mg fixed NA</td>
<td>82M, 157F 37M, 74F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 12</td>
<td>ASEX</td>
<td>Mean at endpoint; percent SD</td>
<td>Male/female reported separately; combined calculated</td>
</tr>
<tr>
<td>5.Clayton, Kennedy, et al., 2013 (b)</td>
<td>Vilazodone Placebo</td>
<td>40 mg fixed NA</td>
<td>159M, 241F 174M, 227F</td>
<td>Pooled SD data from studies 6 and 7</td>
<td>Week 8</td>
<td>ASEX, CSFQ-14</td>
<td>Percent SD</td>
<td>Male/female reported separately; combined calculated</td>
</tr>
<tr>
<td>Study identifier</td>
<td>Antidepressant</td>
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<td>Number of Subjects (ITT)</td>
<td>Study Design</td>
<td>Time of endpoint</td>
<td>Sexual Function tool</td>
<td>Endpoints</td>
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<tr>
<td>6.Clayton, Kennedy, et al., 2013 (b); Rickels et al., 2009</td>
<td>Vilazodone Placebo</td>
<td>40 mg fixed NA</td>
<td>72M, 124F 72M, 124 F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL</td>
<td>Male/female reported separately; combined calculated</td>
</tr>
<tr>
<td>7.Clayton, Kennedy et al., 2013 (b); Khan et al., 2011</td>
<td>Vilazodone Placebo</td>
<td>40 mg fixed NA</td>
<td>87M, 119F 102M, 108F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 8</td>
<td>CSFQ-14</td>
<td>Mean change from BL</td>
<td>Male/female reported separately; combined calculated</td>
</tr>
<tr>
<td>8.Clayton, Tourian, et al, 2015 (c)</td>
<td>Desvenlafaxine Desvenlafaxine Placebo</td>
<td>50 mg fixed 100 mg fixed NA</td>
<td>138M, 300F 149M, 307F 135M, 300F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD</td>
<td>Male/female reported separately and combined</td>
</tr>
<tr>
<td>9.Clayton, Gommoll, et al., 2015; Mathews et al., 2015</td>
<td>Vilazodone Vilazodone Citalopram Placebo</td>
<td>20 mg fixed 40 mg fixed 40 mg fixed NA</td>
<td>201M, 267F 192M, 259F 205M, 257F 212M, 264F</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 10</td>
<td>CSFQ-14</td>
<td>Mean change from BL, percent SD</td>
<td>Male/female reported separately and combined</td>
</tr>
<tr>
<td>10.Nelson et al., 2006 (d)</td>
<td>Duloxetine Paroxetine Placebo</td>
<td>40-120 mg fixed 20 mg fixed NA</td>
<td>736 736 736 736</td>
<td>Pooled data from 4 Rand, DB, PBO, and active controlled, efficacy; including studies 16-18</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Percent SD</td>
<td>Male/female combined</td>
</tr>
<tr>
<td>Study identifier</td>
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<tr>
<td>11. Hewett et al., 2010</td>
<td>Bupropion, Venlafaxine, Placebo</td>
<td>150-300 mg flexible</td>
<td>193, 202, 186</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>CSFQ-14</td>
<td>Mean change from BL</td>
<td>Male and female combined</td>
</tr>
<tr>
<td>12. Boullenger et al., 2014; Clinicaltrials.gov NCT01140906</td>
<td>Vortioxetine, Vortioxetine, Duloxetine, Placebo</td>
<td>15 mg fixed, 20 mg fixed, 60 mg fixed NA</td>
<td>147, 148, 144, 156</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL</td>
<td>Male/female combined</td>
</tr>
<tr>
<td>13. Mahalshwarkar, Jacobsen, Chen et al., 2015 (e)</td>
<td>Vortioxetine, Vortioxetine, Duloxetine, Placebo</td>
<td>15 mg fixed, 20 mg fixed, 60 mg fixed NA</td>
<td>31M, 81F, 25M, 86F, 28M, 85F, 35M, 93F</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD</td>
<td>Male/female reported separately and combined</td>
</tr>
<tr>
<td>14. Jacobsen et al., 2015 (e)</td>
<td>Vortioxetine, Vortioxetine, Placebo</td>
<td>10 mg fixed, 20 mg fixed NA</td>
<td>30M, 93F, 31M, 89F, 41M, 96F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD</td>
<td>Male/female reported separately and combined</td>
</tr>
<tr>
<td>15. Mahalshwarkar, Jacobsen, Serenko et al., 2015 (e)</td>
<td>Vortioxetine, Vortioxetine, Placebo</td>
<td>10 mg fixed, 15 mg fixed NA</td>
<td>38M, 91F, 33M, 88F, 44M, 89F</td>
<td>Rand, DB, PBO controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD</td>
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<tr>
<td>16. [<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMATa](<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMATa)</td>
<td>Duloxetine Duloxetine Paroxetine Placebo</td>
<td>40 mg fixed 80 mg fixed 20 mg fixed NA</td>
<td>58 52 44 47</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD in pooled Study 10</td>
<td>Male/female combined</td>
</tr>
<tr>
<td>17. [<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMATb](<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMATb)</td>
<td>Duloxetine Duloxetine Paroxetine Placebo</td>
<td>40 mg fixed 80 mg fixed 20 mg fixed NA</td>
<td>50 45 48 49</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD in pooled Study 10</td>
<td>Male/female combined</td>
</tr>
<tr>
<td>18. [<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMAYa](<a href="https://www.lilly.com/clinical-study-report-csr-synopses">https://www.lilly.com/clinical-study-report-csr-synopses</a> FIJ-MC-HMAYa)</td>
<td>Duloxetine Duloxetine Paroxetine Placebo</td>
<td>80 mg fixed 120 mg fixed 20 mg fixed NA</td>
<td>19M, 40F 21M, 32F 17M, 39F 17M, 31F</td>
<td>Rand, DB, PBO and active controlled, efficacy</td>
<td>Week 8</td>
<td>ASEX</td>
<td>Mean change from BL, percent SD in pooled Study 10</td>
<td>Male/female reported separately and combined</td>
</tr>
</tbody>
</table>

ITT = Intent-to-treat; QD = once daily; Rand = randomized; DB = double-blind; PBO = placebo; CSFQ-14 = Changes in Sexual Functioning Questionnaire; BL = Baseline; SD = sexual dysfunction; ASEX = Arizona Sexual Experiences Scale; M = male; F = female

(a) Two studies of identical design were reported in the same publication.
(b) Clayton, Kennedy et al. (2013) report sexual functioning change scores for 2 separate studies and pooled data for percent patients with and without sexual dysfunction at endpoint (identified as studies 5, 6, and 7 for clarity).

(c) Number of patients per group is different for ASEX total score change from baseline and for percent patients with and without sexual dysfunction. The larger number is reported here.

(d) Nelson et al. (2006) reports percent patients with and without sexual dysfunction for 4 studies pooled, however, the sexual functioning change scores were obtained from 3 of those studies from clinical trial synopses provided on the pharmaceutical companies website (studies 16, 17 and 18).

(e) Additional data was provided by one of the publication authors in order to calculate mean effect scores.
**Study Level Demographic Characteristics**

Baseline demographic characteristics by study are listed in Table 3. Pooled studies 5 and 10 are not included as they are represented by individual studies as described in Table 2. Mean Montgomery–Åsberg Depression Rating Scale (MADRS) total scores, where included, indicated that the population enrolled was moderate to severely depressed (MADRS total score >30). Three studies (16, 17 and 18) enrolled mildly depressed patients with mean MADRS total scores of 22 and 23. Hamilton Depression Rating Scale (HAM-D) 17-item total scores were generally consistent with MADRS total scores with regard to severity of depression in studies where both were assessed. Mean baseline CSFQ-14 and ASEX total scores, where reported, indicated a range of patients with various levels of sexual functioning upon study entry.
Table 3. Baseline demographics by study.

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Antidepressant arms</th>
<th>Mean age</th>
<th>% Women</th>
<th>Mean MADRS</th>
<th>Mean HAM-D (b)</th>
<th>Mean CSFQ-14</th>
<th>Mean ASEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Clayton et al., 2006 (a)</td>
<td>Buproprion Escitalopram Placebo</td>
<td>35.7</td>
<td>62.0</td>
<td>-</td>
<td>24</td>
<td>51.5</td>
<td>-</td>
</tr>
<tr>
<td>2.Clayton et al., 2006 (a)</td>
<td>Buproprion Escitalopram Placebo</td>
<td>36.6</td>
<td>58.0</td>
<td>-</td>
<td>23</td>
<td>53.4</td>
<td>-</td>
</tr>
<tr>
<td>3.Clayton et al., 2007</td>
<td>Duloxetine Escitalopram Placebo</td>
<td>42.2</td>
<td>63.5</td>
<td>-</td>
<td>18</td>
<td>36.0</td>
<td>-</td>
</tr>
<tr>
<td>4.Clayton, Reddy, et al., 2013; Dunlop, et al., 2011</td>
<td>Desvenlafaxine Placebo</td>
<td>42.5</td>
<td>65.2</td>
<td>31</td>
<td>22</td>
<td>-</td>
<td>18.9</td>
</tr>
<tr>
<td>6.Clayton, Kennedy, et al., 2013; Rickels et al., 2009</td>
<td>Vilazodone Placebo</td>
<td>39.9</td>
<td>63.7</td>
<td>31</td>
<td>25</td>
<td>-</td>
<td>19.4</td>
</tr>
<tr>
<td>7.Clayton, Kennedy et al., 2013; Khan et al., 2011</td>
<td>Vilazodone Placebo</td>
<td>41.7</td>
<td>53.2</td>
<td>32</td>
<td>25</td>
<td>42.8</td>
<td>-</td>
</tr>
<tr>
<td>9.Clayton, Gommoll, et al., 2015; Mathews et al., 2015</td>
<td>Vilazodone Citalopram Placebo</td>
<td>41.8</td>
<td>55.7</td>
<td>31</td>
<td>-</td>
<td>41.6</td>
<td>-</td>
</tr>
<tr>
<td>11.Hewett et al., 2010</td>
<td>Buproprion Venlafaxine Placebo</td>
<td>44.7</td>
<td>67.0</td>
<td>30</td>
<td>-</td>
<td>36.1</td>
<td>-</td>
</tr>
<tr>
<td>12.Boulenger et al., 2014;</td>
<td>Vortioxetine Duloxetine Placebo</td>
<td>46.7</td>
<td>69.6</td>
<td>31</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study Identifier</td>
<td>Antidepressant arms</td>
<td>Mean age</td>
<td>% Women</td>
<td>Mean MADRS</td>
<td>Mean HAM-D (b)</td>
<td>Mean CSFQ-14</td>
<td>Mean ASEX</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------</td>
<td>----------</td>
<td>---------</td>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Clinicaltrials.gov NCT01140906</td>
<td>Vortioxetine</td>
<td>42.9</td>
<td>72.0</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13. Mahableshwarkar, Jacobsen, Chen et al., 2015</td>
<td>Vortioxetine Duloxetine Placebo</td>
<td>42.8</td>
<td>70.1</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14. Jacobsen et al., 2015</td>
<td>Vortioxetine Placebo</td>
<td>45.0</td>
<td>67.5</td>
<td>34</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15. Mahableshwarkar, Jacobsen, Serenko et al., 2015</td>
<td>Vortioxetine Placebo</td>
<td>43.7</td>
<td>65.6</td>
<td>22</td>
<td>18</td>
<td>-</td>
<td>17.9</td>
</tr>
<tr>
<td>16. F1J-MC-HMATA, 2004</td>
<td>Duloxetine Paroxetine Placebo</td>
<td>40.5</td>
<td>64.0</td>
<td>23</td>
<td>18</td>
<td>-</td>
<td>16.1</td>
</tr>
<tr>
<td>17. F1J-MC-HMATb, 2004</td>
<td>Duloxetine Paroxetine Placebo</td>
<td>42.9</td>
<td>74.2</td>
<td>22</td>
<td>20</td>
<td>-</td>
<td>19.7</td>
</tr>
</tbody>
</table>

MADRS = Montgomery–Asberg Depression Rating Scale; HAM-D = Hamilton Depression Rating Scale; CSFQ-14 = Changes in Sexual Functioning Questionnaire; ASEX=Arizona Sexual Experiences Scale.

(a) Two studies of identical design were reported in the same publication.

(b) The 17-item HAM-D was used for assessment of depressive symptoms in these studies.
Assessment of Risk of Bias

Each study was assessed for risk of bias utilizing the Cochrane Collaboration’s tool as outlined in Table 1. All studies evaluated had low risk for bias on all domains with the exception of one study evaluating desvenlafaxine (Clayton, Tourian et al., 2015), for reporting bias. The publication indicated that the ASEX total scores were only reported for patients who had been sexually active in the past week. Most depressed patients have some level of sexual dysfunction, so this reduced the sample size to 422 from 907 patients. The full 907 patients were evaluated in assessment of odds ratios. The article stated that the results of the subgroup for change scores was consistent with the analysis done for all patients; however, those data were not reported. Although reporting bias cannot be ruled out, the odds ratio data, which contained the entire sample, was consistent in direction and by sex with the standardized mean effect scores. Thus, the determination was made to include these data.

Assessment of Publication Bias

Publication bias was evaluated through the use of funnel plots. Publication bias stems from failing to detect unpublished studies, which are more likely to have unfavorable results, and/or may have small samples with greater variance, and can substantially bias effect size estimates. The majority of the studies included were published; however, data from 7 of the 17 studies came from unpublished sources, ether partially or entirely (Table 2). Of the 17 included studies, 9 were authored by Anita Clayton, MD. Since this meta-analysis included only studies which utilized ASEX or CSFQ, it is not unusual for Clayton to be the author on many publications as she developed the CSFQ. The ASEX is an older tool and has been adopted in more studies in the
past, but not necessarily with inclusion of the scale developer. The ASEX and CSFQ-14 were both included in large studies.

The smallest unpublished studies included in this analysis were obtained from the Lilly website and included paroxetine and duloxetine. The sample sizes per arm ranged from 44 to 59, so were not unusually small. The funnel plots for effect sizes (Figure 2) and odds ratios (Figure 3) are presented below. In fact in Figure 2, two observations (observation 20 corresponding to duloxetine 80 mg in unpublished study 16, and observation 40 corresponding to paroxetine 20 in unpublished study 18, Lilly studies) are shown to have higher variances. However the sample sizes are not particularly small, so the data were included. In Figure 3, the funnel plot for logged odds ratios, observation 4 corresponding to desvenlafaxine 50 mg in study 4 has a higher variance compared to other observations, but the sample size was relatively large (N=239), so the data were included. It should be noted that all of the publications that met criteria were funded by pharmaceutical companies. Individual sponsored studies tend not to be double-blinded, placebo-controlled studies that utilize validated sexual functioning questionnaires. Because no non-pharmaceutical funded studies met eligibility criteria, it is not known whether studies conducted similarly by individuals outside the pharma industry would have yielded different results in this analysis.
Figure 2. Funnel Plot for Sexual Functioning Standardized Mean Effect Sizes, Both Sexes

Figure 3. Funnel Plot for Sexual Functioning Logged Odds Ratios, Both Sexes
Assessment of Outliers

The distributions of mean effect sizes (75 cases) and logged odds ratio effect sizes (28 cases) were examined for outliers. Outliers were defined as values that fell more than three interquartile ranges (IQR) above the 75th percentile or below the 25th percentile of the distribution (Tukey, 1977). No outliers were identified in the logged odds ratio effect size distributions. One outlier was identified in the mean effect size distribution, paroxetine 20 mg in men from the Lilly study 18. Based on the literature, men taking paroxetine report more negative sexual side effects compared to women in general. Because of the possibility of gender effects, the data for this observation was included without adjustment.

Effects on Sexual Functioning of Antidepressants versus Placebo

Standardized mean effect sizes for each antidepressant were calculated for 13 of the 17 studies. Four of the studies did not provide sufficient data to calculate mean effects, e.g., study did not report standard deviations or standard errors, and attempts to obtain data were not successful. Odds ratios for developing sexual dysfunction versus placebo were calculated for 9 of the 17 included studies based on available data. Odds ratios were only calculated for studies that provided normal or abnormal sexual dysfunction data that were calculated based on the accepted definition for the ASEX or CSFQ-14 scales.

Standardized Effect Sizes for Mean Change Scores

Standardized effect sizes were calculated based on change scores (mean gains) for placebo and antidepressant in the 13 studies where data were reported. Table 4 lists the standardized mean effect sizes, standard errors, CIs, the $Q$ statistic and its significance for each antidepressant versus placebo. There were insufficient eligible studies to calculate reliable mean effect sizes by
dose and antidepressant. Therefore, effect sizes were calculated within study by dose and pooled to create the mean effect size for that antidepressant, as long as the dose was in the approved therapeutic range. Standardized effect sizes by subscales or single items were also not calculated due to insufficient sample size. The $Q$ statistic was calculated to determine if there was significant heterogeneity of variance. The $Q$ statistic could not be calculated for comparisons between citalopram versus placebo, or for venlafaxine versus placebo because only one study each was eligible for inclusion in the analysis. Some subgroups by gender included only one study as well, so the $Q$ statistic was not calculated (see Table 4).
<table>
<thead>
<tr>
<th>Antidepressant Comparison</th>
<th>Doses (mg)</th>
<th>Sex</th>
<th>Scale</th>
<th>Number studies</th>
<th>Effect Size (a)</th>
<th>SE</th>
<th>Q</th>
<th>Significance of Q</th>
<th>CI Low</th>
<th>CI High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buproprion XL</td>
<td>150 – 450</td>
<td>Both</td>
<td>CSFQ</td>
<td>3</td>
<td>0.034</td>
<td>0.042</td>
<td>0.200</td>
<td>0.905</td>
<td>-0.049</td>
<td>0.117</td>
</tr>
<tr>
<td>Citalopram</td>
<td>40</td>
<td>Both</td>
<td>CSFQ</td>
<td>1</td>
<td>-0.087</td>
<td>0.062</td>
<td>-</td>
<td>-</td>
<td>-0.208</td>
<td>0.034</td>
</tr>
<tr>
<td>Citalopram</td>
<td>40</td>
<td>Men</td>
<td>CSFQ</td>
<td>1</td>
<td>-0.117</td>
<td>0.095</td>
<td>-</td>
<td>-</td>
<td>-0.304</td>
<td>0.070</td>
</tr>
<tr>
<td>Citalopram</td>
<td>40</td>
<td>Women</td>
<td>CSFQ</td>
<td>1</td>
<td>-0.062</td>
<td>0.082</td>
<td>-</td>
<td>-</td>
<td>-0.222</td>
<td>0.099</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50 and 100</td>
<td>Both</td>
<td>ASEX</td>
<td>3</td>
<td>0.025</td>
<td>0.043</td>
<td>3.305</td>
<td>0.192</td>
<td>-0.060</td>
<td>0.110</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50 and 100</td>
<td>Men</td>
<td>ASEX</td>
<td>3</td>
<td>-0.095</td>
<td>0.066</td>
<td>0.136</td>
<td>0.934</td>
<td>-0.224</td>
<td>0.034</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50 and 100</td>
<td>Women</td>
<td>ASEX</td>
<td>3</td>
<td>0.086</td>
<td>0.066</td>
<td>0.937</td>
<td>0.626</td>
<td>-0.044</td>
<td>0.215</td>
</tr>
<tr>
<td>Duloxetine (b)</td>
<td>40-120</td>
<td>Both</td>
<td>ASEX, CSFQ</td>
<td>9</td>
<td>-0.018</td>
<td>0.034</td>
<td>22.16</td>
<td>*0.005</td>
<td>-0.085</td>
<td>0.048</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>40-120</td>
<td>Men</td>
<td>ASEX, CSFQ</td>
<td>4</td>
<td>-0.028</td>
<td>0.083</td>
<td>1.717</td>
<td>0.633</td>
<td>-0.191</td>
<td>0.135</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>40-120</td>
<td>Women</td>
<td>ASEX, CSFQ</td>
<td>4</td>
<td>-0.080</td>
<td>0.059</td>
<td>3.312</td>
<td>0.346</td>
<td>-0.194</td>
<td>0.035</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>20</td>
<td>Both</td>
<td>CSFQ</td>
<td>3</td>
<td>-0.190</td>
<td>0.046</td>
<td>0.061</td>
<td>0.970</td>
<td>-0.280</td>
<td>-0.101</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>20</td>
<td>Men</td>
<td>CSFQ</td>
<td>1</td>
<td>-0.080</td>
<td>0.132</td>
<td>-</td>
<td>-0.338</td>
<td>0.177</td>
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<tr>
<td>Escitalopram</td>
<td>20</td>
<td>Women</td>
<td>CSFQ</td>
<td>1</td>
<td>-0.290</td>
<td>0.099</td>
<td>-</td>
<td>-0.483</td>
<td>-0.097</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>Both</td>
<td>ASEX</td>
<td>3</td>
<td>-0.169</td>
<td>0.073</td>
<td>1.152</td>
<td>0.562</td>
<td>-0.312</td>
<td>-0.027</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>Men</td>
<td>ASEX</td>
<td>1</td>
<td>-0.529</td>
<td>0.226</td>
<td>-</td>
<td>-0.972</td>
<td>-0.085</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>Women</td>
<td>ASEX</td>
<td>1</td>
<td>-0.148</td>
<td>0.153</td>
<td>-</td>
<td>-0.448</td>
<td>0.151</td>
<td></td>
</tr>
<tr>
<td>Antidepressant Comparison</td>
<td>Doses (mg)</td>
<td>Sex</td>
<td>Scale</td>
<td>Number of studies</td>
<td>Effect Size (a)</td>
<td>SE</td>
<td>Q</td>
<td>Significance of Q CI Low</td>
<td>CI High</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>-------</td>
<td>----------------</td>
<td>-------------------</td>
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<td>-----</td>
<td>------</td>
<td>-------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-150</td>
<td>Both</td>
<td>CSFQ</td>
<td>1</td>
<td>0.041</td>
<td>0.064</td>
<td>-</td>
<td>-</td>
<td>-0.084</td>
<td>0.167</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>20-40</td>
<td>Both</td>
<td>ASEX, CSFQ</td>
<td>4</td>
<td>-0.015</td>
<td>0.032</td>
<td>1.133</td>
<td>0.769</td>
<td>-0.077</td>
<td>0.046</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>20-40</td>
<td>Men</td>
<td>ASEX, CSFQ</td>
<td>4</td>
<td>-0.144</td>
<td>0.048</td>
<td>1.120</td>
<td>0.772</td>
<td>-0.238</td>
<td>-0.049</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>20-40</td>
<td>Women</td>
<td>ASEX, CSFQ</td>
<td>4</td>
<td>0.048</td>
<td>0.042</td>
<td>2.754</td>
<td>0.431</td>
<td>-0.033</td>
<td>0.129</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10-20</td>
<td>Both</td>
<td>ASEX</td>
<td>8</td>
<td>0.046</td>
<td>0.028</td>
<td>4.838</td>
<td>0.680</td>
<td>-0.008</td>
<td>0.100</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10-20</td>
<td>Men</td>
<td>ASEX</td>
<td>6</td>
<td>0.113</td>
<td>0.066</td>
<td>1.715</td>
<td>0.887</td>
<td>-0.016</td>
<td>0.241</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10-20</td>
<td>Women</td>
<td>ASEX</td>
<td>6</td>
<td>0.018</td>
<td>0.039</td>
<td>3.165</td>
<td>0.675</td>
<td>-0.057</td>
<td>0.094</td>
</tr>
</tbody>
</table>

CSFQ = Changes in Sexual Functioning Questionnaire; ASEX = Arizona Sexual Experiences Scale; ES = effect size; SE = standard error; Q = the Q statistic; CI = confidence interval

(a) Decreases indicate worsening of sexual functioning.

(b) The Q statistic for heterogeneity of variance was significant for the standardized mean effect size for both sexes combined. $I^2$ statistic for this effect size and was 59%.
Random effects models were planned to account for heterogeneity between studies; however, in many cases the number of studies for each antidepressant was too small to calculate a reliable random variance component (see Table 4). In cases where there were 3 or more comparisons, random effects weighted mean effect sizes and 95% confidence intervals for each study were calculated. A total of 15 comparisons included 3 or more studies and of these, only 3 comparisons had population variance components that were different than 0. These comparisons were for desvenlafaxine versus placebo, and for duloxetine versus placebo for both sexes combined, and for duloxetine versus placebo for women. Overall there were no directional changes in the point estimates for random effects weighted means for these 3 comparisons. Arguably, comparisons that include even 3 studies are likely to be too small to calculate random effects variance, and in fact most of the random variance components in these cases were negative, thus 0.

The studies included in this meta-analysis were very similar in conduct due to the strict inclusion criteria, e.g., randomized, placebo-controlled, acute MDD population, similar age range and use of validated sexual functioning scale; therefore, it is appropriate to present the data using a fixed-effect model.

The standardized mean effect size, standard error, $Q$ statistic and its significance, and 95% confidence intervals were also calculated for each study (see Appendix C). The mean effect sizes were calculated by combining all active arms within the study, if more than one was included, compared with placebo. Effect sizes were generally small with approximately half were negative and half positive. Because antidepressants are known to have varying effects on sexual functioning, from minimal (e.g., buproprion) to significant (e.g., paroxetine), the overall effect sizes by studies was not particularly informative as many included more than one antidepressant.
Figures 4-6 plot the mean standardized effect sizes for each antidepressant versus placebo for both sexes combined and by sex.

**Figure 4. Sexual Functioning Mean Standardized Effect Sizes with Antidepressants versus Placebo, Both Sexes Combined**

Only one comparison has significant heterogeneity ($Q=22.16; p=0.005$): duloxetine, both sexes combined (see Table 3). The $I^2$ statistic was calculated (59%) for this effect size. Given that the $I^2$ assessment for heterogeneity was greater than 50%, the individual effect sizes for this comparison were evaluated. The comparison between duloxetine and placebo included the highest number of studies in this analysis, which may contribute to the larger range of effect sizes. In addition, this comparison included several dose groups for duloxetine (40 mg, 60 mg, 80 mg and 120 mg daily), and the level of sexual dysfunction may be dose-dependent. Review of the individual effect sizes showed that typically lower dose studies with duloxetine had less negative effects; however, it also appeared to be related to gender. Citalopram, duloxetine,
escitalopram, paroxetine and vilazodone have point estimates that are worse than placebo; however, escitalopram and paroxetine are the only antidepressants that are significantly worse than placebo for both sexes combined. The point estimate for citalopram is somewhat higher, but the difference is not significant. The remaining antidepressants do not differ significantly versus placebo when both sexes are combined.

Mean effect sizes were calculated by sex as it was suspected to be a moderator of sexual dysfunction and antidepressant. Figures 5 and 6 show forest plots for each antidepressant for which data by sex were available. The $Q$ statistic was not significant for any antidepressant comparison for the subgroup gender. In men (Figure 5), significant differences are found between paroxetine and placebo, similar to both sexes combined, but while the point estimate for escitalopram is worse than placebo, it is not significantly different. However, in men, vilazodone is significantly worse than placebo, but the confidence intervals are very narrow and the point estimate is similar to desvenlafaxine and citalopram, which are not significantly worse than placebo. The relatively narrow confidence intervals should be taken into consideration when assessing the clinical relevance of the significance of this effect.
In women (Figure 6) escitalopram is the only antidepressant significantly worse than placebo; however, point estimates for paroxetine, citalopram and duloxetine are worse than placebo, but not significantly. The confidence intervals for the point estimate for paroxetine are wide for both men and women; however, it is clear that sexual functioning for both men and women on paroxetine is worse than placebo (even in women where the CI does not cross 0). While duloxetine was not significantly worse than placebo in men or women, the point estimate for women was worse than for men, which likely contributed to the heterogeneity in the combined sex group where the $Q$ statistic was significant.
Figure 6. Sexual Functioning Mean Standardized Effect Sizes with Antidepressants versus Placebo, Women

Finally, Figure 7 shows the standardized effects sizes for each antidepressant versus placebo by men and women, and by combined sexes together in one figure. Gender differences are most striking for paroxetine and escitalopram. Men are more negatively impacted with treatment of paroxetine than women, but women are more negatively impacted by treatment with escitalopram than men.
Odds Ratios for Developing Sexual Dysfunction

Odds ratios were calculated from the proportion of patients with and without sexual dysfunction, per ASEX or CSFQ-14 scale definition, at study endpoint. Table 5 lists the mean standardized odds ratios, standard errors, CIs, the $Q$ statistic and its significance for each antidepressant versus placebo. There were insufficient eligible studies to calculate reliable mean effect sizes by dose and antidepressant. Therefore, effect sizes were calculated within study by dose and pooled to create the mean effect size for that antidepressant, as long as the dose was in
the approved therapeutic range. The $Q$ statistic was not significant for any comparison for sexes combined or for the gender subgroups.

Similar to the mean effect size calculation, calculation of random effects weighted odds ratios and 95% confidence intervals for each study were planned if sufficient comparisons existed. About half of the comparisons had less than 3 studies, indicating accurate calculation of the population variance would be difficult or not possible. A total of 6 comparisons included 3 or more studies and of these, only one (desvenlafaxine versus placebo for both sexes) had a calculated population variance different from 0; therefore, random effects weighted odds ratios were not calculated. As discussed previously, study characteristics were similar enough to support effect size calculations using fixed-effect model.
Table 5. Mean Standardized Odds Ratios for Antidepressant by Sex

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Sex</th>
<th>Scale</th>
<th>N</th>
<th>Mean OR (a)</th>
<th>SE</th>
<th>Q</th>
<th>Significance of Q</th>
<th>CI Low</th>
<th>CI High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Both</td>
<td>CSFQ</td>
<td>1</td>
<td>0.275</td>
<td>0.197</td>
<td>-</td>
<td>-</td>
<td>-0.111</td>
<td>0.661</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Men</td>
<td>CSFQ</td>
<td>1</td>
<td>0.393</td>
<td>0.312</td>
<td>-</td>
<td>-</td>
<td>-0.219</td>
<td>1.005</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Women</td>
<td>CSFQ</td>
<td>1</td>
<td>0.164</td>
<td>0.259</td>
<td>-</td>
<td>-</td>
<td>-0.343</td>
<td>0.671</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Both</td>
<td>ASEX</td>
<td>3</td>
<td>0.024</td>
<td>0.103</td>
<td>4.205</td>
<td>0.122</td>
<td>-0.179</td>
<td>0.226</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Men</td>
<td>ASEX</td>
<td>1</td>
<td>0.149</td>
<td>0.430</td>
<td>-</td>
<td>-</td>
<td>-0.693</td>
<td>0.991</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Women</td>
<td>ASEX</td>
<td>1</td>
<td>0.682</td>
<td>0.298</td>
<td>-</td>
<td>-</td>
<td>0.098</td>
<td>1.265</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Both</td>
<td>ASEX</td>
<td>3</td>
<td>0.346</td>
<td>0.105</td>
<td>1.788</td>
<td>0.409</td>
<td>0.140</td>
<td>0.553</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Both</td>
<td>CSFQ</td>
<td>1</td>
<td>0.687</td>
<td>0.265</td>
<td>-</td>
<td>-</td>
<td>0.168</td>
<td>1.206</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Both</td>
<td>ASEX</td>
<td>1</td>
<td>0.545</td>
<td>0.151</td>
<td>-</td>
<td>-</td>
<td>0.250</td>
<td>0.841</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Both</td>
<td>ASEX</td>
<td>3</td>
<td>0.105</td>
<td>0.100</td>
<td>0.167</td>
<td>0.920</td>
<td>-0.091</td>
<td>0.301</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Men</td>
<td>ASEX</td>
<td>3</td>
<td>0.349</td>
<td>0.156</td>
<td>0.095</td>
<td>0.953</td>
<td>0.043</td>
<td>0.655</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Women</td>
<td>ASEX</td>
<td>3</td>
<td>-0.088</td>
<td>0.132</td>
<td>0.189</td>
<td>0.910</td>
<td>-0.347</td>
<td>0.171</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>Both</td>
<td>ASEX</td>
<td>6</td>
<td>0.076</td>
<td>0.104</td>
<td>2.513</td>
<td>0.775</td>
<td>-0.128</td>
<td>0.279</td>
</tr>
</tbody>
</table>

CSFQ = Changes in Sexual Functioning Questionnaire; ASEX = Arizona Sexual Experiences Scale; OR = odds ratio; SE = standard error; Q = the Q statistic; CI = confidence interval

(a) Positive values indicate greater odds of developing sexual functioning compared to placebo.

Figures 8 and 9 show the odds ratio for developing sexual dysfunction by antidepressant compared to placebo. With both sexes combined, the odds of developing sexual dysfunction with paroxetine, escitalopram and duloxetine are significantly worse than placebo; however, the confidence intervals for duloxetine are narrow; therefore, more emphasis should be placed on the relative risk.
Odds ratios by sex could not be calculated for all antidepressants included in the overall due to insufficient data presented in publications. Where data were available, the odds of developing sexual dysfunction versus placebo by sex were calculated and are presented in Figure 9. Gender differences are apparent with desvenlafaxine (worse in women) and vilazodone (worse in men). In most cases the results are consistent as expected from the standardized mean effect sizes with the exception of desvenlafaxine, which is worse in men based on total score effect sizes and contrasts with the odds ratios. As only one study contributed to the desvenlafaxine data, the conflicting results could be due to the smaller sample.
Figure 9. Odds Ratios of Developing Sexual Dysfunction, Antidepressant versus Placebo, by Sex
CHAPTER FIVE
DISCUSSION

The aim of this meta-analysis was to evaluate treatment-associated sexual dysfunction with second generation antidepressants utilizing studies that collected sexual functioning data via validated prospective questionnaires. It also included more recently approved antidepressants not found in previous meta-analyses, i.e., vilazodone and vortioxetine (‘atypical’ antidepressants).

The results of this meta-analysis confirm that there are differences in the effects of antidepressants on sexual functioning, and that generally the SSRIs (e.g., citalopram, escitalopram, and paroxetine) have worse impact on sexual functioning than antidepressants of other classes, and that ‘atypical’ antidepressants (e.g., buproprion, vilazodone, and vortioxetine) have less impact on sexual functioning than either SSRIs or SNRIs (e.g., duloxetine, desvenlafaxine, and venlafaxine).

These results are not surprising given that SSRIs function by increasing serotonin in the brain, which is diminished in depressed individuals; however, the serotonergic system has an inhibitory effect on sexual desire, orgasm and ejaculation (Clayton et al., 2016). Antidepressants that target the norepinephrine, as well as serotonergic systems (SNRIs), or dopaminergic (e.g., buproprion) systems have a positive impact on sexual functioning, which may account for the fewer sexual side-effects. Furthermore, the specific serotonin receptors that are activated have differential effects on sexual functioning. Some 5-hydroxytryptamine (HT) receptors inhibit sexual activity, such as 5-HT3, the primary target of SSRIs, while others (5-HT1A) stimulate sexual functioning. Two of the recently approved antidepressants (vilazodone and vortioxetine)
have activity at the 5-HT1A receptor as well, which may mitigate some of the negative activity at the 5-HT3 receptor.

This analysis also highlighted some important gender effects on sexual functioning, which vary by antidepressant. Standardized mean change effect sizes indicated that overall paroxetine and escitalopram were associated with significantly greater sexual dysfunction compared to placebo, with the mean effect size for escitalopram being slightly worse than paroxetine. Gender differences were apparent with these two antidepressants; women had greater sexual dysfunction with escitalopram, and men had greater sexual dysfunction with paroxetine.

In general, the results of the mean odds ratio analysis confirmed the results of the standardized mean effect sizes. The odds of developing sexual dysfunction with escitalopram and paroxetine were significantly worse than placebo; however, each comparison was based on only one study, while the mean effect sizes were based on three comparisons for each. There was insufficient data to calculate odds ratios by gender for paroxetine and escitalopram. Interestingly, the odds of developing sexual dysfunction with duloxetine for both sexes combined was also significantly worse than placebo based on three comparisons; however, the mean effect size for duloxetine on any comparison did not differ significantly from placebo. In addition, the point estimate of the mean effect size for women on duloxetine was numerically worse compared to men.

As mentioned above, gender differences in the impact on sexual functioning were apparent for some of the antidepressants evaluated. In addition to paroxetine and escitalopram, significant differences were found in mean effect size and in the odds ratio between men taking vilazodone and placebo. However, in these comparisons, which included 4 comparisons for the mean effect size and 3 comparisons for the odds ratio, the effects for both sexes combined and for women did
not differ significantly from placebo. In addition, the odds of developing sexual dysfunction in women with desvenlafaxine were significantly worse than placebo, but that was not the case for men. The mean effect sizes for sexual functioning for desvenlafaxine versus placebo were not consistent with the odds ratios, that is, the trend was opposite although no effect size was significantly worse than placebo. In this case the odds ratios for sex were based on one comparison while the mean effect sizes were based on three comparisons; therefore, conclusions should be made with caution. However, clear gender differences were seen with paroxetine, escitalopram and vilazodone, which highlights an important consideration that antidepressants can have differential effects on sexual functioning in men and women.

The results of this meta-analysis add to the body of information in the literature by in some cases confirming what has been reported, and it others adding with information on newer antidepressants. The level of sexual dysfunction with paroxetine is generally well known; however, some analyses have shown escitalopram to have less sexual dysfunction by comparison to other antidepressants than this analysis (Serretti & Chiesa, 2009), while other analyses confirm these two SSRIs are associated with worse sexual functioning compared to other antidepressants (Reichenpfader et al, 2014). This difference could be due to the small sample for the escitalopram comparison included in this analysis, or may reflect the varying methods of assessing sexual functioning in the studies included in other meta-analyses.

Few studies have evaluated the effects of antidepressants on sexual functioning utilizing validated questionnaires. Sexual dysfunction by adverse event reporting was not addressed in this analysis as it is well documented that spontaneous reporting of sexual dysfunction adverse events is very low and does not represent true levels of sexual dysfunction. Meta-analyses conducted to date (Serretti & Chiesa, 2009; and Reichenpfader et al, 2014) have generally cast a
wider net in order to include as much sexual functioning data as possible. While being inclusive has merit, it also suffers from increased heterogeneity across studies and brings into question the robustness of the results. For example, combining studies that do not utilize a validated questionnaire capable of assessing normal and abnormal sexual functioning with those that do, relies on greater manipulation of data based on assumptions. Analysis of studies that have utilized similar measures and procedures can allow for a more straightforward interpretation of results. Similarly comparisons to placebo are easier to interpret versus multiple comparisons between one antidepressant and another as in the Reichenpfader analysis. While this analysis had narrow selection criteria and was therefore less inclusive, the results have fewer confounding variables, e.g., not based on multiple measures that may not assess the same construct or based on adverse event reporting only which is known to be inaccurate.

The strict selection criteria resulted in a sample that had little heterogeneity across studies. Therefore, the use of a fixed effect model for reporting of mean effect sizes and odds ratios was justified, because the studies were consistent in design characteristics and the results of this analysis apply to MDD patients treated with antidepressants and are not intended to be generalized beyond this population. The limited number of studies that utilized validated questionnaires to assess sexual functioning in a randomized, placebo-controlled fashion, resulted in a smaller sample size which did not allow for analysis of effects by antidepressant dose or by sexual functioning subgroups. As research expands and more data is collected in this fashion, further analyses should be conducted that evaluates dose dependency of antidepressants on sexual functioning and on various dimensions of the sexual response cycle. Finally, conducting an analysis of this rigor (meeting the eligibility criteria) in a real-world setting would yield results that would more closely represent depressed patients receiving antidepressant treatment
versus clinical trial patients. To conduct a analysis of this kind would be challenging given that
treatment providers do not typically administer validated sexual functioning questionnaires, and
in cases where this is done, the data may not be accessible for analysis. Education of the
importance of addressing sexual functioning issues in depressed patients, methods to accurately
evaluate sexual functioning, and various treatment options will improve the assessment and
treatment of sexual dysfunction, and hopefully lead to more systematic and accurate evaluation
of antidepressant-associated sexual dysfunction.

Limitations
This meta-analysis has some limitations. There were relatively small number of comparisons for
some antidepressants, as strict study eligibily criteria eliminated a number of studies that did not
include placebo and/or did not include a validated questionnaire. All the eligible studies were
funded by pharmaceutical companies and it is not known if individuals conducting studies
meeting the same criteria would have resulted in different findings. Some commonly used
antidepressants were not represented, such as sertraline, due to studies not meeting criteria. Older
studies tended not to include the CSFQ-14 or ASEX as the use of validated questionnaires is
more recent, and subsequently many of the older SSRIs are not represented. In additon, eligible
studies included patients experiencing actute depression (experiencing a current major depressive
episode). Fewer studies have evaluated the effects of antidepressants on sexual functioning in
patients whose depression symptoms are well-treated. Since sexual dysfunction is associated
with depression even in the absense of antidepressant treatment, depression symptoms are a
confounding effect. Therefore, selecting studies that are similar in inclusion criteria for the
severity of depression helps to reduce the effects of this confounder. Because many of the studies
included more than one active treatment (antidepressant) compared to placebo, multiple
comparisons to placebo were made in calculating effect sizes within study which introduces dependency of effect sizes.
Step 1: Study Identifiers, Study Design, Patient Selection, Sexual functioning assessment.

STUDY IDENTIFIERS

Each study will have its own unique Study identifier (e.g., StudyID 12). If there is more than one study within the same source (e.g., journal article references multiple studies), then the source will have multiple study ID numbers, and each study will be coded on separate coding sheets. If there is more than one reference for a particular research study, then the coding should be done from the most complete source of data (e.g., publication). If data fields are incomplete using only one source of data, another data source can be utilized if the criteria are met. Each data source will have its own unique identifier (e.g., 12.1; 12.2, etc.), but may be coded on the same set of coding sheets. The relevant fields should be coded from the most appropriate source with the study ID noted in the margin if one set of coding sheets is used.

If data is missing and there is no coded option for a required field enter NA for not applicable or UNK for unknown. If entire section is not applicable, leave blank or line through.

[StudyID]_________ If multiple sources, list all here if using one coding sheet. Also, indicate in margins StudyID for source of data.

[Coder] Coder’s initials:_______

[CodDT]_________ (Date coding began)

[QCDT]__________ (only use for recoding or QC review of coding is done)

[CMNTS]: This field used to comment on relevant information that is not captured in other fields.

[PubYR] Publication: ________ (Year of publication, FDA review or posting of results online)
[Region] Region study was conducted:

A. United States
B. Europe
C. Asia
D. South Africa
E. Global
F. Other________________ [Region1]
G. UNK

[PubTyp] Type of publication:

A. Journal article
B. Clinicaltrials.gov
C. Summary Basis of Approval (SBA)

STUDY DESIGN

[Source] Source of data:

A. Single study
B. Pooled studies.

[Rand] Method of study randomization

A. Centralized/IVR/IRT
B. Site
C. UNK

[Bias] Risk of bias in randomization assignments:

A. Low (potential for bias)
B. Unclear
C. High (bias based on methodology)

[Blind] Blinding method:
A. Double-blind
B. Single-blind
C. None (note this is exclusionary)

[PBO] Was study placebo-controlled?
A. Yes
B. No

[Dur] Treatment duration in weeks _______ (If several, select the acute phase, e.g., 6-12 weeks)

[Visit] Number of study visits during treatment? ___________ (including Baseline)

[Design] Study design:
A. Parallel
B. Active-reference
C. Comparator/head-to-head

[Arms] Number of study arms including placebo_____

[STDrug] Name of study drug: ______________________________

[STReg] Regimen (eg QD): ____________________________

[STflex] Fixed or flexible dosing? (do not include titration)
A. Fixed
B. Flexible
C. Dose increase allowed

[STDose1] Dose of study drug: _____________________________mg (if flexible put low dose)

[STDose2] Second dose of study drug: _________________________mg (if flexible put high dose)
[Titrate1] Was study drug 1 titrated?

A. Yes
B. No
C. NA

[ActDrug] Name of reference or comparator drug, if applicable: _____________________

[ActReg] Regimen (eg QD): ____________________________

[Actflex] Fixed or flexible dosing? (do not include titration)

A. Fixed
B. Flexible
C. Dose increase allowed

[ActDose1] Dose of reference/comparator drug:______________mg (if flexible put low dose)

[ActDose2] Second dose of reference/comparator drug:_________mg (if flexible put high dose)

[Titrate2] Was the reference or comparator drug titrated, if applicable?

A. Yes
B. No
C. NA

[Primary] What was the primary objective of the study?

A. Sexual dysfunction
B. MDD
C. UNK
D. Both

[Outcome] Overall result on the efficacy endpoint:

A. Significant differences found
B. No significant differences found

C. Mixed

**SUBJECT SELECTION CRITERIA**

[DX] Patient diagnosis for entry to study:

A. MDD
B. Recurrent MDD
C. Depression not specified per diagnostic criteria

[Status] Depressive episode status:

A. Acute
B. Stable
C. Remitted

[Episode] Criteria for duration of current depressive episode in weeks._______

[AgeGrp] Age group enrolled ______________ E.g., 18+, 18-65, 18-45

[MDREnt] Entry criteria for MADRS, if applicable: ______

[HMDEnt] Entry criteria for HAM-D17, if applicable: ______

[CGIEnt] Entry criteria for CGI-S, if applicable: ______

[AxisIEx] Excluded any other axis I other than MDD?

A. Yes
B. No

[NonRes] Excluded non-responders to treatment?

A. Yes
B. No
[MedCon] Excluded significant medical conditions?
   A. Yes
   B. No

[SexDys] Excluded Sexual dysfunction disorders?
   A. Yes
   B. No

[Sexfxn] Sexual functioning enrollment status
   A. All
   B. Normal
   C. Abnormal

MDD EFFICACY ASSESSMENT

[Effic] Type of efficacy endpoint, if measured:
   A. MADRS
   B. HAM-D17
   C. Other _____________________ [EffScale]

[Effect] Type of treatment effect of therapy reported, if assessed.
   A. Mean change from baseline total score
   B. Mean change from baseline total score, difference to placebo/active

SEXUAL FUNCTIONING ASSESSMENT

[Scale] Scale used to assess sexual functioning:
   A. ASEX
   B. CSFQ

[Specify] Other: _____________________
[Version] Version of scale used to assess sexual functioning (e.g., short form, full scale, or version number)___________

[Subs] Subscales reported?
   A. Yes
   B. No

[Single] Single items reported?
   A. Yes
   B. No

[Shift] Shift assessment reported (e.g., shift from normal to abnormal functioning)?
   A. Yes
   B. No

[SDScore] Primary score data reported?
   A. Mean change from Baseline total score
   B. Mean change from Baseline total score difference to placebo
   C. Mean change from Baseline total score difference to active control/reference
   D. Shift from normal to abnormal sexual functioning

PATIENT DEMOGRAPHICS TOTAL POPULATION

[TotalN] Total patients randomized _______________ Includes all treatment groups

[FAS] Full analysis set (total patients included in primary analysis) ____________ N for the primary results often listed in table, note this is not the N for safety set which is usually used for Baseline characteristics. Demographic data below is usually derived from safety set.

[CmpltN] Number of patients completing study _____________
[LTFU] Number of patients lost to follow-up ______________

[WDAE] Number of patients who withdrew due to adverse event __________

[Female] Percent Female whole study _____________

[Race...] Percent each

  A. Percent Caucasian_____[RaceA]
  B. Percent Black_____[RaceB]
  C. Percent Asian_____[RaceC]
  D. Percent Hispanic_____[RaceD]
  E. Other_____[RaceE]

[AgeMn] Mean age. _____________

[MDEMn] Mean duration of MDE in weeks. __________

[EpisMn] Mean number of prior episodes. __________

[MDRMn] Mean baseline MADRS total score. _________

[HMDMn] Mean baseline HAM-D17 total score. __________

[CGIMn] Mean CGI-S score. __________
STUDY OUTCOMES: BASELINE CHARACTERISTICS

Use multiple pages to complete this section. Data coded in database as A, B, C, or D then
remaining field name. Pages should be labeled 6A-9A, 6B-9B on coding sheets, etc, based
on response to [Group] below.

[StudyID]: __________ [Coder] Coder’s initials:________

[Group] Study group being coded:

A. Placebo

B. Study drug dose 1 (use if only 1 dose or lower dose)

C. Study drug dose 2 (higher dose if more than 1 dose)

D. Active reference/comparator

[…GrpN] Number of patients included in group. __________ (# included for BL sexual
functioning scores, N usually provided for results)

[…GrpFem] Percent Female in group. ______________

Percent each

A. Percent Caucasian_______ […GrpRacA]

B. Percent Black_________ […GrpRacB]

C. Percent Asian_______ […GrpRacC]

D. Percent Hispanic _______ […GrpRacD]

E. Other_______ […GrpRacE]

[…GrpAge] Mean group age. ______________

[…GrpMDE] Mean duration of MDE in weeks. ______________

[…GrpEpis] Mean number of prior episodes. _____________

[…MDRBL] Mean baseline MADRS total score. ___________
[…HMDBL] Mean baseline HAM-D17 total score. __________

[…CGIBL] Mean baseline CGI-S score. __________

**Baseline sexual functioning status**

[…BLNorm] Baseline percent normal sexual functioning (both sexes)__________

[…BLNormM] Baseline percent normal sexual functioning male. __________

[…BLNormF] Baseline percent normal sexual functioning female. __________

[…BLAbn] Baseline percent abnormal sexual functioning (both sexes)__________

[…BLAbnM] Baseline percent abnormal sexual functioning male. __________

[…BLAbnF] Baseline percent abnormal sexual functioning female. __________

[…BLSDAE] Baseline sexual dysfunction adverse events (percent) __________

**Baseline sexual function scale scores (Score/Standard Deviation/Error)**

Enter either SD or SE if provided. Indicate UNK if neither is provided. If SD is provided, leave SE blank.

[..SFBL] BL Sexual fxn total/mean score (both sexes)_____[..SDBL]____[..SEBL]____

[…SFBLM] BL Sexual fxn total/mean score male ____[..SDBLM]____[..SEBLM]____

[…SFBLF] BL Sexual fxn total/mean score female ____[..SDBLF]____[..SEBLF]____

**Baseline Subscales or sub-items (Score/Standard Deviation/Error) Cross out if NA**

Enter either SD or SE if provided. Indicate UNK if neither is provided. If SD is provided, leave SE blank. Eg for subscale names enter, “Pleasure” or “Desire/Freq,” or “Desire/Int” etc. Order used should be same order as per the instrument. Enter the N for each subgroup, note that the Ns may all be the same across each subscale group.

[…SFsub1] Subscale/item name #1_____________________ Grp N: ______[..SFsub1N]

[…Sub1] Subscale/item BL score (both sexes)_____[..SDBL1]____[..SEBL1]____
STUDY OUTCOMES: ENDPOINT

Enter endpoint as mean total score if provided. If endpoint score is listed as mean change from Baseline, or difference to Placebo or active ONLY, the total score should be calculated and entered here. Indicate if calculated. If unable to calculate, enter as provided with note in margin.

[...MDREP] Mean endpoint MADRS total score. _________

[...HMDEP] Mean endpoint HAM-D17 total score. __________

[...CGIEP] Mean endpoint CGI-S score. __________

[...Rem] Percent remission __________

[...Resp] Percent responders __________

Endpoint sexual functioning status including TESD/shift assessment (line through if not reported, leave blank). Note that shift analysis includes only subjects who initiate treatment with Normal sexual functioning and shift to Abnormal.

[...EPNorm] Endpoint percent normal sexual functioning (both sexes).________

[...EPNormM] Endpoint percent normal sexual functioning male. ______

[...EPNormF] Endpoint percent normal sexual functioning female. ______

[...EPAbn] Endpoint percent abnormal sexual functioning (both sexes).________

[...EPAbnM] Endpoint percent abnormal sexual functioning male. ______

[...EPAbnF] Endpoint percent abnormal sexual functioning female. ______

[...Shift] Percent shift to abnormal sexual functioning (both sexes).________

[...ShiftM] Percent shift to abnormal sexual functioning Male. ______

[...ShiftF] Percent shift to abnormal sexual functioning Female. ______

[...EPSDAE] Endpoint sexual dysfunction adverse events (percent). _______
### Endpoint sexual function scale scores

<table>
<thead>
<tr>
<th>Subscale/item</th>
<th>Score</th>
<th>Std Deviation</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>...SFEP</td>
<td>End sexual function total score (both sexes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...SDEPM</td>
<td>End sexual function total score male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...SDEPF</td>
<td>End sexual function total score female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...SFChg</td>
<td>Sexual fxn change from BL (both sexes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...SFChgM</td>
<td>Sexual fxn change from BL male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...SFChgF</td>
<td>Sexual fxn change from BL female</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Endpoint Subscales or sub-items (Score/Std Deviation/Error) Cross out if NA

Enter either SD or SE if provided. Indicate UNK if neither is provided. If SD is provided, leave SE blank. Transfer subscale/item name from Baseline section. Use same order.

<table>
<thead>
<tr>
<th>Subscale/item</th>
<th>Score</th>
<th>Std Deviation</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>...SFsub1</td>
<td>Subscale/item name #1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...Sub1EP</td>
<td>Subscale/item end score (both sexes)</td>
<td></td>
<td></td>
</tr>
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<td></td>
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<tr>
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<td>Subscale/item end score female</td>
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(Complete the table with the appropriate scores and standard deviations/errors)
[…Sub2ChgF] Subscale change score female____[..SDChg2F]____[..SEChg2F]____

 […SFsub3] Subscale/item name #3 ____________________________ (same as BL)

 […]SubEP3] Subscale/item end score (both sexes) ______[..SD3]____[..SE3]____

 […]Sub3EPM] Subscale/item end score male ______[..SD3M]____[..SE3M]____

 […]Sub3EPF] Subscale/item end score female ______[..SD3F]____[..SE3F]____

 […]Sub3Chg] Subscale change score (both sexes) ______[..SDChg3]____[..SEChg3]____

 […]Sub3ChgM] Subscale change score male ______[SDChg3M]____[SEChg3M]____

 […]Sub3ChgF] Subscale change score female ______[SDChg3F]____[SEChg3F]____

 […]SFsub4] Subscale/item name #4 ____________________________ (same as BL)

 […]SubEP4] Subscale/item end score (both sexes) ______[..SD4]____[..SE4]____

 […]Sub4EPM] Subscale/item end score male ______[..SD4M]____[..SE4M]____

 […]Sub4EPF] Subscale/item end score female ______[..SD4F]____[..SE4F]____

 […]Sub4Chg] Subscale change score (both sexes) ______[..SDChg4]____[..SEChg4]____

 […]Sub4ChgM] Subscale change score male ______[..SDChg4M]____[..SEChg4M]____

 […]Sub4ChgF] Subscale change score female ______[..SDChg4F]____[..SEChg4F]____

 […]SFsub5] Sub-item/ sub scale name ____________________________ (same as BL)

 […]SubEP5] Sub-item/ subscale endpoint score__________SD5____

 […]Sub5EPM] Sub-item/ subscale endpoint score male __________SD5M____

 […]Sub5EPF] Sub-item/ subscale endpoint score female__________SD5F____

 […]Sub5Chg] Sub-item/subscale endpoint change from BL__________SE5____

 […]Sub5ChgM] Sub-item/ subscale endpoint change from BL male ___SE5M___

 […]Sub5ChgF] Sub-item/ subscale endpoint change from BL female___SE5F___
Any data that are not provided, but can be calculated from other data present should be done and entered. Show calculation on coding sheet, use back or margin. Indicate next to field that data was calculated, e.g., “Calc”
APPENDIX B

SEXUAL DYSFUNCTION ASSESSMENT TOOLS
ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-MALE

For each item, please indicate your **overall** level during the **past week**, including **today**.

1. How strong is your sex drive?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>extremely strong</td>
<td>very strong</td>
<td>somewhat strong</td>
<td>somewhat weak</td>
<td>very weak</td>
<td>no sex drive</td>
</tr>
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</table>

2. How easily are you sexually aroused (turned on)?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>extremely easily</td>
<td>very easily</td>
<td>somewhat easily</td>
<td>somewhat difficult</td>
<td>very difficult</td>
<td>never aroused</td>
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3. Can you easily get and keep an erection?

<table>
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<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>extremely easily</td>
<td>very easily</td>
<td>somewhat easily</td>
<td>somewhat difficult</td>
<td>very difficult</td>
<td>never</td>
</tr>
</tbody>
</table>

4. How easily can you reach an orgasm?

<table>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>extremely easily</td>
<td>very easily</td>
<td>somewhat easily</td>
<td>somewhat difficult</td>
<td>very difficult</td>
<td>never reach orgasm</td>
</tr>
</tbody>
</table>

5. Are your orgasms satisfying?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>extremely satisfying</td>
<td>very satisfying</td>
<td>somewhat satisfying</td>
<td>somewhat unsatisfying</td>
<td>very unsatisfying</td>
<td>can’t reach orgasm</td>
</tr>
</tbody>
</table>

COMMENTS:

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ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-FEMALE

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

<table>
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<tr>
<th></th>
<th>1 extremely strong</th>
<th>2 very strong</th>
<th>3 somewhat strong</th>
<th>4 somewhat weak</th>
<th>5 very weak</th>
<th>6 no sex drive</th>
</tr>
</thead>
</table>

2. How easily are you sexually aroused (turned on)?

<table>
<thead>
<tr>
<th></th>
<th>1 extremely easily</th>
<th>2 very easily</th>
<th>3 somewhat easily</th>
<th>4 somewhat difficult</th>
<th>5 very difficult</th>
<th>6 never aroused</th>
</tr>
</thead>
</table>

3. How easily does your vagina become moist or wet during sex?

<table>
<thead>
<tr>
<th></th>
<th>1 extremely easily</th>
<th>2 very easily</th>
<th>3 somewhat easily</th>
<th>4 somewhat difficult</th>
<th>5 very difficult</th>
<th>6 never</th>
</tr>
</thead>
</table>

4. How easily can you reach an orgasm?

<table>
<thead>
<tr>
<th></th>
<th>1 extremely easily</th>
<th>2 very easily</th>
<th>3 somewhat easily</th>
<th>4 somewhat difficult</th>
<th>5 very difficult</th>
<th>6 never reach orgasm</th>
</tr>
</thead>
</table>

5. Are your orgasms satisfying?

<table>
<thead>
<tr>
<th></th>
<th>1 extremely satisfying</th>
<th>2 very satisfying</th>
<th>3 somewhat satisfying</th>
<th>4 somewhat unsatisfying</th>
<th>5 very unsatisfying</th>
<th>6 can’t reach orgasm</th>
</tr>
</thead>
</table>

**COMMENTS:**

---

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# Changes in Sexual Functioning Questionnaire (CSFQ-M-C)

**Patient Name**

**Today's Date**

**NOTE:** This is a questionnaire about sexual activity and sexual function. By sexual activity, we mean sexual intercourse, masturbation, sexual fantasies, and other activity.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
   - [ ] 1-No enjoyment or pleasure
   - [ ] 2-Little enjoyment or pleasure
   - [ ] 3-Some enjoyment or pleasure
   - [ ] 4-Much enjoyment or pleasure
   - [ ] 5-Great enjoyment or pleasure

2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

3. How often do you desire to engage in sexual activity?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

5. Do you enjoy books, movies, music, or artwork with sexual content?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
   - [ ] 1-No enjoyment or pleasure
   - [ ] 2-Little enjoyment or pleasure
   - [ ] 3-Some enjoyment or pleasure
   - [ ] 4-Much enjoyment or pleasure
   - [ ] 5-Great enjoyment or pleasure

7. How often do you have an erection related or unrelated to sexual activity?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

---

8. Do you get an erection easily?
   - [ ] 1-Never
   - [ ] 2-Rarely (much less than half the time)
   - [ ] 3-Sometimes (about half the time)
   - [ ] 4-Often (much more than half the time)
   - [ ] 5-Always

9. Are you able to maintain an erection?
   - [ ] 1-Never
   - [ ] 2-Rarely (much less than half the time)
   - [ ] 3-Sometimes (about half the time)
   - [ ] 4-Often (much more than half the time)
   - [ ] 5-Always

10. How often do you experience painful, prolonged erections?
    - [ ] 5-Never
    - [ ] 4-Rarely (once a month or less)
    - [ ] 3-Sometimes (more than once a month, up to twice a week)
    - [ ] 2-Often (more than twice a week)
    - [ ] 1-Every day

11. How often do you have an ejaculation?
    - [ ] 1-Never
    - [ ] 2-Rarely (once a month or less)
    - [ ] 3-Sometimes (more than once a month, up to twice a week)
    - [ ] 4-Often (more than twice a week)
    - [ ] 5-Every day

12. Are you able to ejaculate when you want to?
    - [ ] 1-Never
    - [ ] 2-Rarely (much less than half the time)
    - [ ] 3-Sometimes (about half the time)
    - [ ] 4-Often (much more than half the time)
    - [ ] 5-Always

13. How much pleasure or enjoyment do you get from your orgasms?
    - [ ] 1-No enjoyment or pleasure
    - [ ] 2-Little enjoyment or pleasure
    - [ ] 3-Some enjoyment or pleasure
    - [ ] 4-Much enjoyment or pleasure
    - [ ] 5-Great enjoyment or pleasure

14. How often do you have painful orgasms?
    - [ ] 5-Never
    - [ ] 4-Rarely (once a month or less)
    - [ ] 3-Sometimes (more than once a month, up to twice a week)
    - [ ] 2-Often (more than twice a week)
    - [ ] 1-Every day

---

= Pleasure (Item 1)
= Desire/Frequency (Item 2 + Item 3)
= Desire/Interest (Item 4 + Item 5 + Item 6)
= Arousal/Erection (Item 7 + Item 8 + Item 9)
= Orgasm/Ejaculation (Item 11 + Item 12 + Item 13)
= Total CSFQ Score (Items 1 to 14)

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# CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFQ-F-C)

Patient Name ____________________________

**NOTE:** This is a questionnaire about sexual activity and sexual function. By sexual activity, we mean sexual intercourse, masturbation, sexual fantasies and other activity.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
   - [ ] 1-No enjoyment or pleasure
   - [ ] 2-Little enjoyment or pleasure
   - [ ] 3-Some enjoyment or pleasure
   - [ ] 4-Much enjoyment or pleasure
   - [ ] 5-Great enjoyment or pleasure

2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

3. How often do you desire to engage in sexual activity?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

5. Do you enjoy books, movies, music or artwork with sexual content?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
   - [ ] 1-No enjoyment or pleasure
   - [ ] 2-Little enjoyment or pleasure
   - [ ] 3-Some enjoyment or pleasure
   - [ ] 4-Much enjoyment or pleasure
   - [ ] 5-Great enjoyment or pleasure

7. How often do you become sexually aroused?
   - [ ] 1-Never
   - [ ] 2-Rarely (once a month or less)
   - [ ] 3-Sometimes (more than once a month, up to twice a week)
   - [ ] 4-Often (more than twice a week)
   - [ ] 5-Every day

8. Are you easily aroused?
   - [ ] 1-Never
   - [ ] 2-Rarely (much less than half the time)
   - [ ] 3-Sometimes (about half the time)
   - [ ] 4-Often (much more than half the time)
   - [ ] 5-Always

9. Do you have adequate vaginal lubrication during sexual activity?
   - [ ] 1-Never
   - [ ] 2-Rarely (much less than half the time)
   - [ ] 3-Sometimes (about half the time)
   - [ ] 4-Often (much more than half the time)
   - [ ] 5-Always

10. How often do you become aroused and then lose interest?
    - [ ] 1-Never
    - [ ] 2-Rarely (more than half the time)
    - [ ] 3-Sometimes (about half the time)
    - [ ] 4-Often (less than half the time)
    - [ ] 5-Always

11. How often do you experience an orgasm?
    - [ ] 1-Never
    - [ ] 2-Rarely (much less than half the time)
    - [ ] 3-Sometimes (about half the time)
    - [ ] 4-Often (much more than half the time)
    - [ ] 5-Always

12. Are you able to have an orgasm when you want to?
    - [ ] 1-Never
    - [ ] 2-Rarely (much less than half the time)
    - [ ] 3-Sometimes (about half the time)
    - [ ] 4-Often (much more than half the time)
    - [ ] 5-Always

13. How much pleasure or enjoyment do you get from your orgasms?
    - [ ] 1-No enjoyment or pleasure
    - [ ] 2-Little enjoyment or pleasure
    - [ ] 3-Some enjoyment or pleasure
    - [ ] 4-Much enjoyment or pleasure
    - [ ] 5-Great enjoyment or pleasure

14. How often do you have painful orgasms?
    - [ ] 1-Never
    - [ ] 2-Rarely (once a month or less)
    - [ ] 3-Sometimes (more than once a month, up to twice a week)
    - [ ] 4-Often (more than twice a week)
    - [ ] 5-Every day

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<td>Desire/Frequency (Item 2 + Item 3)</td>
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<td>Desire/Interest (Item 4 + Item 5 + Item 6)</td>
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<td>____</td>
<td>Arousal/Excitement (Item 7 + Item 8 + Item 9)</td>
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<tr>
<td>____</td>
<td>Orgasm/Completion (Item 11 + Item 12 + Item 13)</td>
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<td>____</td>
<td>Total CSFQ Score (Items 1 to 14)</td>
</tr>
</tbody>
</table>

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APPENDIX C

EFFECT SIZES BY STUDY
Effect sizes by study.

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<tr>
<th>Study Identifier (a)</th>
<th>Antidepressant arms</th>
<th>Mean ES</th>
<th>SE</th>
<th>Q</th>
<th>Significance of Q</th>
<th>CI Low</th>
<th>CI High</th>
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<td>1. Clayton et al., 2006</td>
<td>Bupropion Escitalopram Placebo</td>
<td>-0.075</td>
<td>0.056</td>
<td>3.171</td>
<td>0.075</td>
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<td>2. Clayton et al., 2006</td>
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<td>0.056</td>
<td>5.212</td>
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<td>3. Clayton et al., 2007</td>
<td>Duloxetine Escitalopram Placebo</td>
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<td>0.056</td>
<td>0.710</td>
<td>0.701</td>
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<td>4. Clayton, Reddy, et al., 2013; Dunlop, et al., 2011</td>
<td>Desvenlafaxine Placebo</td>
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<td>0.073</td>
<td>-</td>
<td>-</td>
<td>-0.014</td>
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<td>6. Clayton, Kennedy, et al., 2013; Rickels et al., 2009</td>
<td>Vilazodone Placebo</td>
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<td>-</td>
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<td>7. Clayton, Kennedy et al., 2013; Khan et al., 2011</td>
<td>Vilazodone Placebo</td>
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<td>0.063</td>
<td>-</td>
<td>-</td>
<td>-0.177</td>
<td>0.068</td>
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<td>8. Clayton, Tourian, et al, 2015</td>
<td>Desvenlafaxine Desvenlafaxine Placebo</td>
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<td>-0.138</td>
<td>0.073</td>
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<td>9. Clayton, Gommoll, et al., 2015; Mathews et al., 2015</td>
<td>Vilazodone Vilazodone Citalopram Placebo</td>
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<td>0.036</td>
<td>1.194</td>
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<td>Buproprion Venlafaxine Placebo</td>
<td>0.031</td>
<td>0.045</td>
<td>0.046</td>
<td>0.830</td>
<td>-0.058</td>
<td>0.120</td>
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<tr>
<td>12. Boulenger et al., 2014 Clinicaltrials.gov</td>
<td>Vortioxetine Vortioxetine Duloxetine Placebo</td>
<td>0.130</td>
<td>0.042</td>
<td>4.262</td>
<td>0.119</td>
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<td>0.213</td>
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<td>Mean ES</td>
<td>SE</td>
<td>Q</td>
<td>Significance of Q</td>
<td>CI Low</td>
<td>CI High</td>
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<td>Vortioxetine Vortioxetine Placebo</td>
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<td>2.108</td>
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<td>-0.324</td>
<td>-0.042</td>
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<td>Duloxetine Duloxetine Paroxetine Placebo</td>
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<td>0.003</td>
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</tbody>
</table>

ES = effect size; SE = standard error; Q = the Q statistic; CI = confidence interval

(a) Pooled studies 5 and 10 are not included since mean effect sizes were calculated from the individual studies.
References marked with an asterisk (*) indicate studies included in the meta-analysis.


VITA

Paula Jacobsen was born and raised in Warrenville, Illinois. Before attending Loyola University in Chicago, she attended North Central College, where she earned her Bachelor of Arts in Biology in 1990. From 1990 to 1992 she also attended the University of Texas, Arlington where she received her Master of Science in Biology.

After graduating from the University of Texas, Paula taught biology courses at community colleges in Texas and Illinois. Paula began her career as a researcher at Tarrant County Mental Health and Mental Retardation Services in Fort Worth Texas where she evaluated the effectiveness of mental health and addiction services programs. Since 1999 Paula has been working in the pharmaceutical industry and is currently a clinical scientist who oversees the development of medications to treat psychiatric conditions.