See accompanying article by Khin et al p1060

Summary of Findings From the FDA Regulatory Science Forum on Measuring Sexual Dysfunction in Depression Trials

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ABSTRACT

Objective: Sexual dysfunction is a significant treatment-emergent adverse reaction to the serotonergic antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]). However, the rate of sexual dysfunction is often underestimated in registration trials, which have relied on unsolicited reports. We conducted a literature search to examine the rates of sexual dysfunction with SSRIs/SNRIs when these rates were ascertained by structured questionnaires or standardized instruments. Additionally, we conducted exploratory analyses of major depressive disorder (MDD) registration trial data.

Data Sources: For the literature search, we used the PubMed and EMBASE databases, with a cutoff date of April 1, 2011. We included all the SSRIs and SNRIs that at the time had been approved for the treatment of MDD. For each of these drugs, a search was conducted with the following terms: *sexual dysfunction, SD, sexual adverse effects, desire, arousal, excitement,* and *orgasm*. For the exploratory analyses of US Food and Drug Administration in-house trial data, we searched our database for short-term (6–8 weeks), randomized, placebo-controlled MDD monotherapy trials of approved drugs included in New Drug Application submissions that used a standardized instrument to assess sexual function.

Study Selection: For the literature search, we initially found a total of 123 nonduplicate articles, some of which included multiple studies. After screening based on our inclusion/exclusion criteria (and to remove duplicate trial-level data), we were left with 7 articles representing 11 unique studies in which sexual dysfunction was assessed with direct questioning or standardized instruments. The Changes in Sexual Functioning Questionnaire–Short-Form (CSFQ-14) and Arizona Sexual Experiences Scale (ASEX) were the only instruments represented. For the exploratory analyses of in-house MDD trial data, we found controlled studies using either the CSFQ-14 (6 trials) or ASEX (5 trials).

Data Extraction: For the literature search, we were able to pool the results for the studies that included direct questioning. For the studies that used standardized instruments to assess sexual function, we simply describe our findings. For the exploratory analyses of in-house MDD trial data, we constructed a dataset containing all subject-level CSFQ-14 or ASEX item scores for each of the trials as well as demographic and other relevant variables. For each treatment or placebo group, analyses were performed on pooled data, including multiple studies, and on individual studies.

Results: For our literature search, regardless of which method was used to assess sexual function, the data from these articles were informative and showed the expected effects on sexual function with SSRIs/SNRIs. However, for our exploratory analyses, no trend was observed in CSFQ-14 or ASEX results for individual drugs or drug classes.

Conclusions: These results raise the question as to why the CSFQ-14 and ASEX appeared to perform well in the published studies but not in our exploratory analyses of in-house MDD trial data. We discuss possible reasons and solutions.

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Sexual dysfunction, defined as a disturbance in desire (ie, libido), arousal/excitement (eg, vaginal lubrication, penile erection), and/or orgasm, is an important treatment-emergent adverse reaction to antidepressant treatment, as it can interfere with quality of life and treatment compliance. This problem appears to be more prominent for the serotonergic antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]) than for other antidepressants. However, the rate of sexual dysfunction is substantially underestimated and underreported in the registration trials, which have relied on unsolicited reports rather than structured questionnaires, so that true rates are uncertain. For example, in the current labeling, the rate of treatment-emergent ejaculatory disturbance for the SSRIs approved for the treatment of major depressive disorder (MDD) ranges from 6.1% to 26% (median, 13%), with placebo rates of no more than 1%.[1] However, most clinicians would probably agree that the rates of treatment-emergent ejaculatory disturbance associated with the SSRIs are much higher. This is supported by the literature, including a meta-analysis by Serretti and Chiesa,[2] which found rates of orgasm dysfunction with SSRIs in men of 72%–80% (with the limitation that very few articles provided complete data on both male and female patients).

In order to find better ways to assess sexual dysfunction associated with antidepressant treatment, the Division of Psychiatry Products (DPP) at the US Food and Drug Administration (FDA), together with the Division of Biometrics I, held a Regulatory Science Forum in August 2012, inviting expert clinicians from academia and some industry representatives. This article summarizes the 2 principal FDA presentations from the forum:

1. The results of our literature search to examine the rates of sexual dysfunction with SSRIs and SNRIs when these rates were ascertained by methods other than unsolicited reports, such as direct questioning or standardized instruments.

Clinical Points

- Sexual dysfunction, as adverse reaction to antidepressant treatment, can interfere with quality of life and lead to treatment noncompliance.
- The rate of sexual dysfunction is underestimated and underreported in registration trials.
- Characterization of sexual dysfunction using methods other than unsolicited reports is important in depression trials.

2. Exploratory analyses of in-house MDD trial data included in New Drug Application (NDA) submissions of approved drugs that used a standardized instrument to assess sexual function.

For both the literature search and the search of our in-house clinical trial data, the Changes in Sexual Functioning Questionnaire–Short-Form (CSFQ-14) and the Arizona Sexual Experiences Scale (ASEX) were the only instruments found that were used to assess sexual function. Details of the CSFQ-14 and ASEX, including the advantages and limitations of each, will be discussed.

It should be emphasized that the FDA does not endorse any particular instrument to assess sexual function in depression trials. The focus on the CSFQ-14 and ASEX at the forum was based on the availability of data, as determined by our search criteria for both the literature review and the in-house clinical trial data. Development of additional scales, such as the Derogatis Interview for Sexual Functioning (DISF/DISF-SR) and others, was also reported.[3–5] Among the academic experts in psychiatry who participated in the forum, there was a consensus that sexual function can be evaluated using quantitative measures and that the existing scales appear to be useful in evaluating patients' sexual function.

Finally, it should be mentioned that the academic experts who participated in the forum had industry connections. That said, although the FDA presentation on the literature search included references to particular drug products, the subsequent scientific discussion was a much more general exchange of ideas.

METHOD

Literature Search

We began with a comprehensive review of existing literature to examine the rates of sexual dysfunction associated with the SSRIs and SNRIs approved to treat MDD when rates were ascertained by methods other than unsolicited reports, such as direct questioning or standardized scales. We used the PubMed and EMBASE databases, with a cutoff date of April 1, 2011, and included all the SSRIs and SNRIs that at the time had been approved for the treatment of MDD. The SSRIs were fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro). The SNRIs were venlafaxine (Effexor), desvenlafaxine (Pristiq), and duloxetine (Cymbalta). For each of these drugs, further search was conducted using the following terms: *sexual dysfunction, SD, sexual adverse effects, desire, arousal, excitement,* and *orgasm*.

Like our search criteria, our inclusion/exclusion criteria were based, with some modifications, on those used by Serretti and Chiesa.[2] One of the major differences was that we limited our search to randomized, placebo-controlled trials.

Inclusion criteria. Studies had to:

- contain at least 10 patients on drug therapy for major depression;
- be randomized, double-blind, placebo-controlled;
- investigate sexual function in patients taking antidepressants;
- clearly specify that clinicians investigated sexual dysfunction through direct inquiry or a specific sexual questionnaire;
- allow only monotherapy, apart from benzodiazepines;
- clearly provide data for single drugs;
- provide dichotomous variables for at least 1 outcome (eg, total sexual dysfunction) versus placebo.

Exclusion criteria. Studies were excluded if:

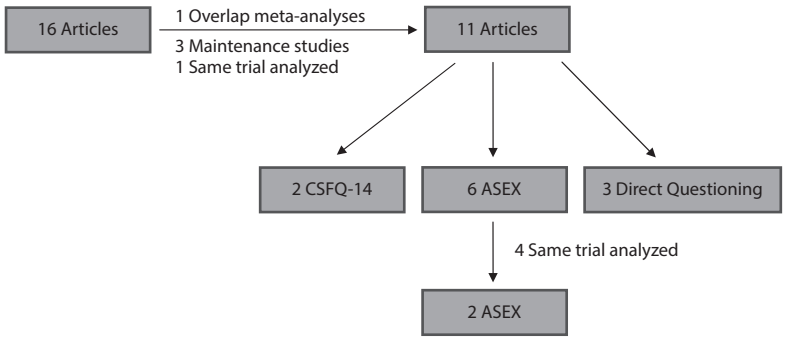
- Antidepressants were given for primary sexual dysfunction (eg, premature ejaculation);
- Antidepressants were given in substitution for a previous antidepressant (eg, studies in which a switch was allowed);
- Two or more antidepressants were given at the same time so that it would be impossible to determine if observed dysfunction was related to one drug or another;
- Patients were treated with other psychotropic drugs (benzodiazepines not included) in the days before study entry;
- Antidepressants were taken for only a few days each month (eg, fluoxetine in premenstrual dysphoric disorder);
- The study included patients with severe medical illnesses or patients taking other nonpsychiatric medications that could be related to sexual dysfunction;
- The study included only healthy or nondepressed subjects;
- No comparisons to placebo were provided.

It was not possible to conduct a pooled analysis of all the studies found, as the type of data was too varied from study to study. However, for the studies that included direct questioning, we were able to pool the results. For the studies that used standardized scales, we simply describe our findings.

FDA In-House Clinical Trial Data

We also searched our in-house database for short-term (6–8 week), randomized, placebo-controlled MDD monotherapy

Figure 1. Flowchart Depicting Literature Search Conducted to Examine Rates of Sexual Dysfunction With SSRIs/SNRIs When Rates Ascertained by Direct Questioning or Standardized Instruments



Abbreviations: ASEX = Arizona Sexual Experiences Scale, CSFQ-14 = Changes in Sexual Functioning Questionnaire–Short-Form.

trials of approved drugs included in NDA submissions that used a standardized instrument to assess sexual function. We excluded trials limited to known drug responders, such as maintenance studies using a randomized withdrawal design. All the trials we identified used either the CSFQ-14 or ASEX. For each of the trials, we constructed a dataset containing all subject-level CSFQ-14 or ASEX item scores, as well as demographic and other relevant variables. For each treatment or placebo group, analyses were performed on pooled data, including multiple studies, and on individual studies. For each group of antidepressants and placebo (for male/female combined, and by male and female separately), descriptive statistics and distributions of the following variables were obtained: CSFQ-14 total score, CSFQ-14 subscale scores, sum of all 5 ASEX questions (only when all questions were answered), and sum of first 2 ASEX questions of all available patients. The variables for primary comparisons were change from baseline scores (and also placebo-subtracted change from baseline scores) for the CSFQ-14 and the proportion of patients with treatment-emergent sexual dysfunction for the ASEX. For each scale, the endpoint was the last observed score in the double-blind phase. Unadjusted means were used to summarize the outcomes because of several concerns, such as high dropout rates, the limited number of trials available, and the nature of trial designs.

LITERATURE SEARCH RESULTS

We initially found a total of 123 nonduplicate articles, some of which included multiple studies. The references for the articles were reviewed, yielding 396 additional articles of interest. After these 519 articles were screened for trial design, based on our inclusion/exclusion criteria, and after duplicates were removed, 16 articles remained. These articles were screened for duplicate trial-level data, and a maintenance study (with a randomized withdrawal design) was removed (see Figure 1 for details), leaving a total of 11 articles in which sexual dysfunction was assessed with direct questioning or standardized instruments. The CSFQ-14 and ASEX were the only instruments represented.

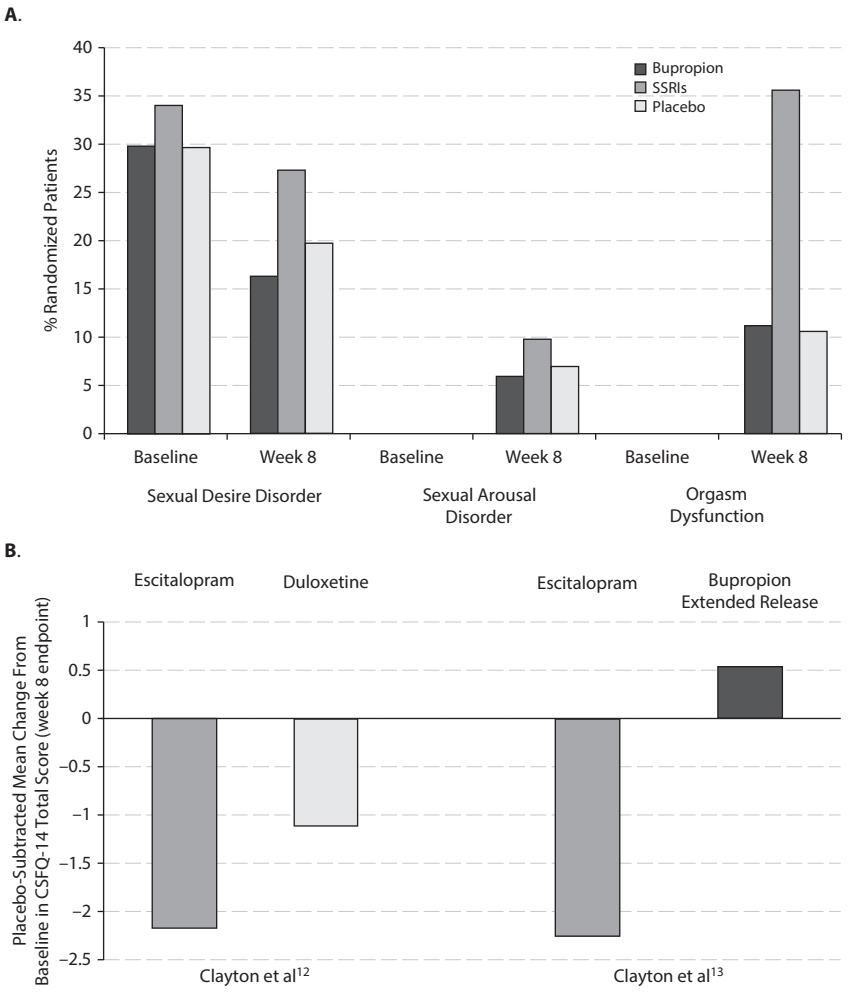
Of the 6 articles with the ASEX,[6–11] 2 of them (by Delgado et al[6] and Hudson et al[10]) included the same 4 duloxetine studies. (Although the article by Hudson et al contained a total of 8 duloxetine studies, only 4 collected ASEX data.) We chose the article by Delgado et al to represent the 4 duloxetine studies, as only that article contained data from the paroxetine arms found in 3 of the 4 studies. Of the 4 remaining ASEX articles, 3 of them[7,9,11] described single studies already included in the Delgado article. In the end, we were left with 7 articles (representing 11 unique studies), 2 of which described studies that used the CSFQ-14,[12,13] 2 of which described studies that used the ASEX,[6,8] and 3 of which described studies with direct questioning[14–16] to assess sexual function.

Direct Questioning Studies

The 3 studies (described in 3 separate articles) with direct questioning were designed in an almost identical manner, using *DSM-IV* criteria to establish the presence or absence of (1) sexual desire disorder, (2) sexual arousal disorder, and (3) orgasm dysfunction.[14–16] They also had very similar inclusion/exclusion criteria, requiring that subjects have no sexual arousal disorder and no orgasm dysfunction at baseline. However, they did allow sexual desire disorder at baseline, as that is commonly seen as part of the depressive syndrome. It should be noted that all 3 studies were industry sponsored.

Two of the studies used sertraline,[14,16] and 1 used fluoxetine.[15] All of the studies had bupropion as a comparator as well as a placebo control. Because of the similarity of the study designs and observed proportions of occurrences, we pooled the results of these studies, combining the 3 bupropion and 3 placebo arms into a single bupropion group and a single placebo group, respectively, and combining the 2 sertraline and 1 fluoxetine arms into an SSRI group. The results are shown in Figure 2A.

Figure 2. (A) Combined Results of Direct Questioning Trials[14–16] and (B) Placebo-Subtracted Mean Observed Change in CSFQ-14 Total Score From Baseline to Week 8[a]



[a]A positive value for the placebo-subtracted mean change from baseline in CSFQ-14 total score indicates that patients in the drug group had better sexual function on average than those in the placebo group (negative value indicates worse function).
Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire–Short-Form, SSRI = selective serotonin reuptake inhibitor.

Focusing first on the results for orgasm dysfunction, at week 8, approximately 35% of the subjects in the SSRI group met criteria for orgasm dysfunction. Although perhaps not surprising to many clinicians, this percentage is significantly higher than the percentages for orgasm dysfunction listed in the various SSRI drug labels.[1] The rates for the bupropion and placebo groups were similar and much lower, a little over 10%. Additionally, sexual arousal disorder was observed in the SSRI group (10%) at week 8 at a greater rate than in the bupropion and placebo groups (approximately 6%). About a third of all subjects met criteria for sexual desire disorder at baseline, and this improved in all 3 groups, but there was a greater improvement at week 8 in the bupropion and placebo groups than in the SSRI group. The fact that all 3 groups improved in terms of the percentage of subjects with sexual desire disorder presumably reflects the overall improvement in depressive symptoms. The lesser improvement in the SSRI group may indicate that the SSRIs (sertraline and fluoxetine) were also causing some degree of impairment in sexual desire.

Changes in Sexual Functioning Questionnaire Studies

We found 2 articles[12,13] (representing 3 studies) that reported the results of studies that used the CSFQ-14. A brief description of the scale[17–19] follows.

- The CSFQ-14 is a brief, gender-specific questionnaire consisting of 14 items rated on a Likert scale with a range of 1–5, with higher score indicating better sexual function.
- The total CSFQ-14 score is calculated by adding up the values of the responses for all 14 items (each has a possible score of 1 to 5, giving a maximum total score of 70).

- Subscale scores are calculated by adding up the values of items that correspond to a particular subscale: pleasure: item 1, desire/frequency: items 2 + 3, desire/interest: items 4 + 5 + 6, arousal/excitement: items 7 + 8 + 9, orgasm/completion: items 11 + 12 + 13.
- CSFQ-14 threshold scores for both the total and subscale scores have been used by the questionnaire authors and were developed by comparing mean scores from patients and normal volunteers. A total score of < 47 for men and < 41 for women indicates sexual dysfunction.
- Analysis may be continuous or dichotomous.

The authors of the scale have proposed that a placebo-subtracted score on the CSFQ-14 at endpoint that shows worsening in sexual function of no more than 1 unit would suggest noninferiority of the drug compared to placebo (personal communication with A.H. Clayton, MD, main scale author; written communication, August 2012). That is, noninferiority (an absence of a negative effect on sexual function) would be established if one can rule out > 1 unit worsening based on the 95% confidence interval of the treatment effect relative to placebo.

This proposed non-inferiority margin initially seems reasonable if the study were clearly capable of detecting such an effect, in which case the study would also need an active control to show that a drug with known effects on sexual function would have a worsening (compared to placebo) of the expected magnitude on the CSFQ-14. The following results of controlled trials, however, suggest that the 1 unit magnitude of noninferiority margin may be too small. Further comprehensive evaluations would be needed to help guide a clinically relevant noninferiority margin.

The results reported in these 2 articles show how the CSFQ-14 can be used to evaluate sexual function in antidepressant trials. The first article[12] reports the results of a trial looking at the changes in sexual function associated with duloxetine, escitalopram, and placebo in the treatment of MDD. Subjects with sexual dysfunction at baseline were not excluded from this trial. The second article[13] presents the combined results of 2 randomized, double-blind, placebo-controlled trials comparing the antidepressant efficacy and effects on sexual function of bupropion extended release compared with escitalopram and placebo. Subjects with sexual dysfunction at baseline and randomization, except sexual desire disorder related to the depression, were excluded from the 2 trials. As shown in Figure 2B, for each article, we graphed the placebo-subtracted mean observed change in CSFQ-14 total score from baseline to week 8.

Escitalopram was used in all 3 trials, and the placebo-subtracted change in CSFQ-14 total score for escitalopram in both articles was around −2.2 (despite the difference in exclusion criteria with regard to sexual dysfunction at baseline). A negative number indicates more sexual dysfunction than placebo, and the magnitude of the change is greater than the suggested noninferiority margin of 1. This is what we would expect to see based on clinical experience. Using the same criteria, it appears that duloxetine is also worse than placebo in terms of sexual dysfunction but perhaps less so than escitalopram in this single study. On the other hand, if duloxetine had had a slightly smaller magnitude of worsening effect, say 0.9 units, the result could plainly not be interpreted as evidence of no effect, because the 95% confidence interval would still not have entirely stayed above −1 (Figure 2B). For bupropion, however, which had a mean effect better than placebo, the result likely could be interpreted as evidence of no effect, although we lack information about confidence intervals. Any possible differences among the SSRIs/SNRIs will need further study.

Although further discussion of CSFQ-14 data analysis is beyond the scope of this article, the 2 CSFQ-14 articles we found show how the data from this instrument can be analyzed in a categorical fashion. For instance, one can compare the rates of treatment-emergent sexual dysfunction (and conversely rates of resolution) between study arms.[12] Subscale scores can be analyzed in a similar manner to compare, for example, the rates of treatment-emergent orgasm dysfunction between study arms.[13]

Arizona Sexual Experiences Scale Studies

We found 2 unique articles[6,8] that utilized the ASEX,[20] a brief description of which follows.

- The ASEX is a self- or clinician-administered scale that assesses 5 domains of sexual function, each with 1 question, using 6-point Likert scales scored from 1 (hyperfunction) to 6 (extreme hypofunction).
- The domains, in order of the questions, are sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and orgasmic satisfaction.
- In most articles (and clinical trials) we have reviewed, questions 3 to 5 are answered only if the patient has been sexually active in the past month.
- The following criteria are used to categorize a patient as having clinically relevant sexual dysfunction:
  An ASEX total score of 19 or greater; or
  A score of 5 or greater on any item; or
  A score of 4 or greater on any 3 items.
- The scale was validated for use only in a dichotomous fashion (presence or absence of sexual dysfunction), as we confirmed at our "Regulatory Science Forum on Measuring Sexual Dysfunction in Depression Trials" in August 2012, which included a developer of the ASEX. In addition, the mean change from baseline is not intended to provide a graded estimate of the extent of sexual dysfunction.

Of the 2 unique articles we found with the ASEX, however, 1 of them[8] analyzed the results in a continuous (rather than dichotomous) fashion. We therefore present some of the results from the meta-analysis by Delgado et al,[6] who used the intended dichotomous analysis.

A total of 1,466 subjects were randomly assigned in 4 studies to duloxetine (40–120 mg/d; n = 736), paroxetine (20 mg/d, n = 359), or placebo (n = 371). A total of 1,345 subjects provided responses to the ASEX, 833 of whom answered all 5 questions. (Questions 3 to 5 are answered only if the subject has been sexually active in the previous month.) Of the subjects who provided responses to the ASEX, 870 (64.7%) met ASEX criteria for sexual dysfunction at baseline within the acute phase database. The large percentage of subjects with sexual dysfunction at baseline can probably be attributed to the depression itself. (Also, these studies did not exclude patients with other medical conditions that might cause sexual dysfunction.) In the 475 subjects (35.3%) who did not meet ASEX criteria for sexual dysfunction at baseline, the percentages of treatment-emergent sexual dysfunction were 61.4% with paroxetine, 46.4% with duloxetine, and 28.8% with placebo. Paroxetine and duloxetine were both statistically significantly worse than placebo ($P < .01$) in terms of treatment-emergent sexual dysfunction, and the difference between paroxetine and duloxetine was also statistically significant ($P = .015$). Although beyond the scope of this article, the meta-analysis by Delgado et al[6] demonstrates how the ASEX subscales can also be analyzed in a dichotomous fashion.

FDA IN-HOUSE CLINICAL TRIAL DATA

As described in the Method, we searched our in-house database for short-term (6–8 week), randomized, placebo-controlled MDD monotherapy trials of approved drugs included in NDA submissions that used a standardized instrument to assess sexual function. We identified 6 trials that used the CSFQ-14 (total of 8 active drugs arms, with 3 SSRI/SNRIs and 2 other drugs [drugs 1 and 2 in the figures] studied) and 5 trials that used the ASEX (total of 9 active drug arms, with 3 SSRI/SNRIs and 1 other drug [drug 3 in the figures] studied). It should be noted that in all of the trials, the doses for each drug were within the range shown to be effective for the treatment of MDD. For the 6 trials that included the CSFQ-14, the number of subjects randomized ranged from 310 to 723, and the average baseline total CSFQ-14 score ranged from 36 to 43. For the 5 trials that included the ASEX, the number of subjects randomized ranged from 173 to 409, and the average baseline total ASEX score (for the subjects who were able to answer all 5 questions) ranged from 16.0 to 19.4.

Changes in Sexual Functioning Questionnaire In-House Trial Data Results

For each of the 6 trials that used the CSFQ-14, Figure 3A shows the mean change from baseline for the CSFQ-14 total score for the placebo arms only. Except for Trial 1, in which there is almost no change from baseline for the CSFQ-14 total score, all the changes are in the positive direction, indicating at least some degree of improvement in sexual function for the placebo arms. The remaining CSFQ-14 results will all be shown as the placebo-subtracted change from baseline values.

Figure 3B shows the placebo-subtracted mean change from baseline for the CSFQ-14 total score for the 8 drug arms in Trials 1–6. A positive value indicates better sexual function as compared to placebo, while a negative value indicates worse sexual function. Note that for both SSRI-a and SSRI-b (in Trials 1 and 2; confidentiality prohibits the naming of the 2 SSRIs), the placebo-subtracted mean change from baseline is quite small in magnitude (approx. 0.5) and goes in opposite directions. Although we recognize the large variation in each estimate, this is in contrast to the results from the 2 articles by Clayton et al,[12,13] described earlier in this review, in which the placebo-subtracted change from baseline for the CSFQ-14 total score for escitalopram was clearly adverse, around −2.2. Note also, in Figure 3B, that the placebo-subtracted change from baseline for the same drug (drug 1) varies in both magnitude and direction in the 4 different trials (Trials 2–5) in which it was studied, although again all of the effects are fairly small.

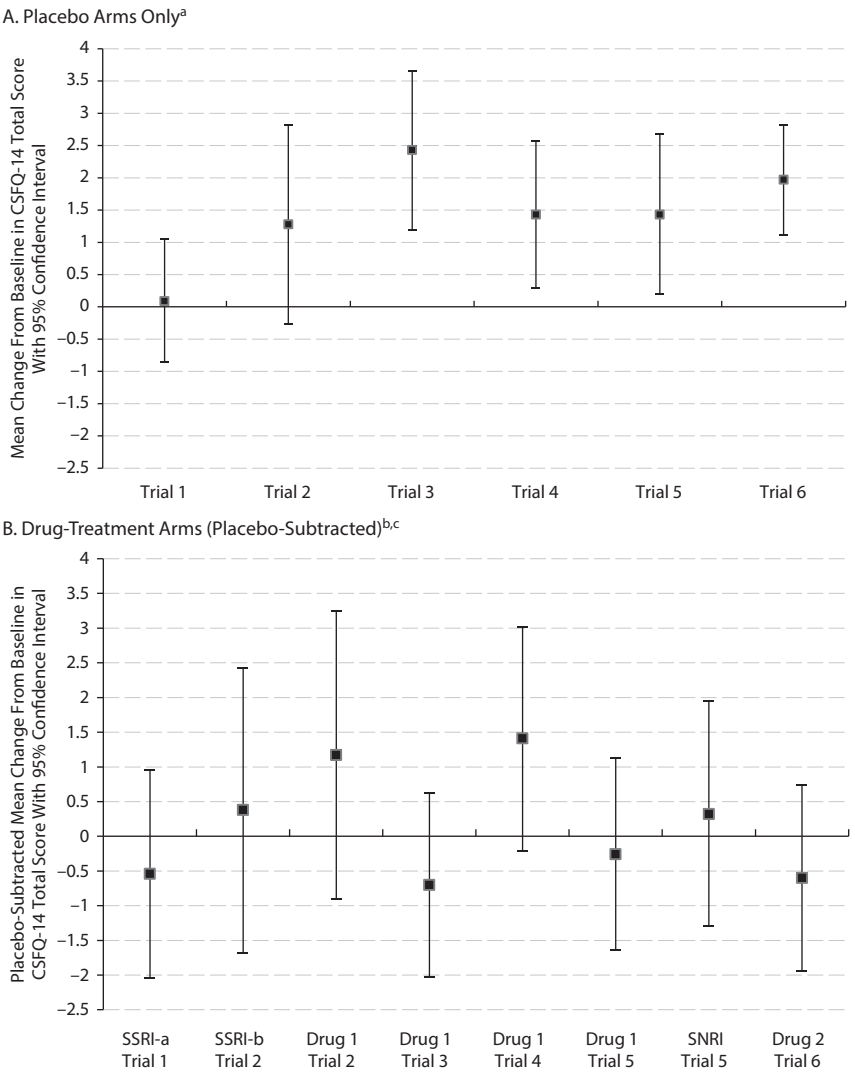
Figure 4A compares the results from 2 SSRI drug arms, SSRI-a (in Trial 1) and SSRI-b (in Trial 2). The placebo-subtracted mean change from baseline for the CSFQ-14 total score as well as for each of the 5 subscales (pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion) is shown. Again, a positive value indicates better sexual function as compared to placebo, while a negative value indicates worse sexual function. Keeping in mind that for most of the domains the effects were fairly small, it is interesting to note that in Trial 2, SSRI-b demonstrated slightly better sexual function on most of the subscales as compared to placebo. Focusing on the orgasm domain, SSRI-a was almost the same as placebo, while SSRI-b was about 0.3 units worse than placebo. (Of note, the authors of the CSFQ-14 have suggested that a difference of ≥ 0.5 on a subscale/domain score appears to be clinically meaningful [personal communication with A. H. Clayton, MD, main scale author; written communication, August 2012].) So, these subscale results are clearly not what one would expect to see, given that all the SSRIs are believed to cause some degree of sexual dysfunction, with particularly prominent effects on orgasm.

Figure 4B compares the results for the same drug (drug 1) in 4 different trials (Trials 2–5). For the drug 1 arm in each of the trials, the placebo-subtracted mean change from baseline for the CSFQ-14 total score and for each of the 5 subscales is shown. Note the variation in the results for drug 1 between the 4 trials. This is obviously not what one would expect to see. For some of the domains, such as desire/frequency, the magnitude of the changes for each of the 4 trials is so small that it could just be noise. However, for the desire/interest and orgasm/completion domains, there appear to be real differences between the trials.

Arizona Sexual Experiences Scale In-House Trial Data Results

For each of the 5 trials that used the ASEX, Figure 5A shows the percentage of patients who met ASEX criteria for clinically relevant sexual dysfunction at baseline, broken

Figure 3. Mean Change From Baseline in CSFQ-14 Total Scores With 95% Confidence Interval



[a]A positive value for the mean change from baseline in CSFQ-14 total score indicates that placebo patients had better sexual function on average than at baseline.
[b]A positive value for the placebo-subtracted mean change from baseline in CSFQ-14 total score indicates that patients in the drug group had better sexual function on average than those in the placebo group (negative value indicates worse function).
[c]Confidentiality prohibits the naming of the 2 SSRIs, Drug 1, Drug 2, or the SNRI.
Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire–Short-Form, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

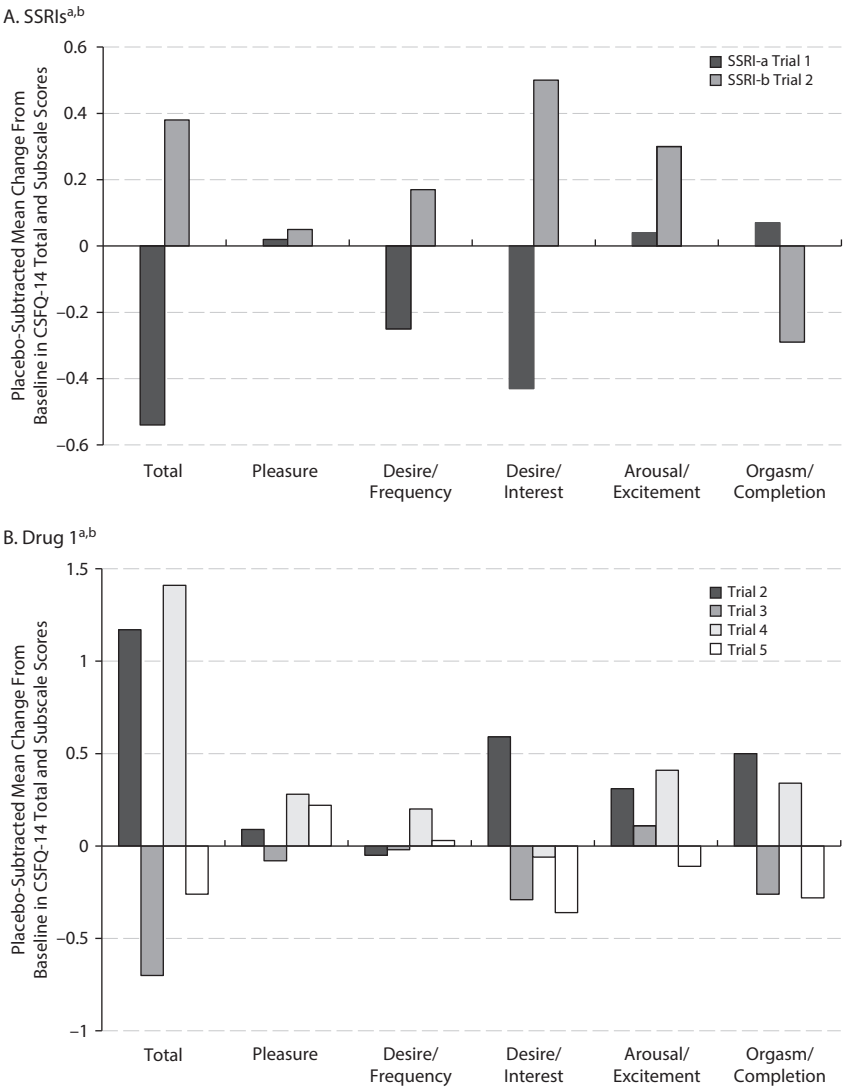
down by gender. Approximately half of all the subjects in Trials 1–4 met criteria for sexual dysfunction at baseline, with the percentage in Trial 5 being closer to 65%. Also, in all of the trials, the percentage of female subjects with sexual dysfunction at baseline is notably greater than that for male subjects; in Trial 5, the percentage for females is almost 80%.

However, for the subset of subjects without sexual dysfunction at baseline, Figure 5B shows the percentage of subjects with treatment-emergent sexual dysfunction at endpoint for each drug in the 5 ASEX trials. Note that for SSRI-a and SSRI-b in Trials 1–4, the difference between drug and placebo in the percentage of subjects with treatment-emergent sexual dysfunction varies greatly between trials. Only for SSRI-b in Trial 3 and the SNRI in Trial 1 does one see results similar to those presented in the meta-analysis of 4 ASEX trials by Delgado et al,[6] which was discussed above.

DISCUSSION

In our literature search, we were not able to find placebo-controlled data on all the SSRIs and SNRIs approved to treat MDD. However, we did find a limited number of articles demonstrating the use of direct questioning, the CSFQ-14, and the ASEX to assess changes in sexual function in MDD

Figure 4. Placebo-Subtracted Mean Change From Baseline in CSFQ-14 Total and Subscale Scores

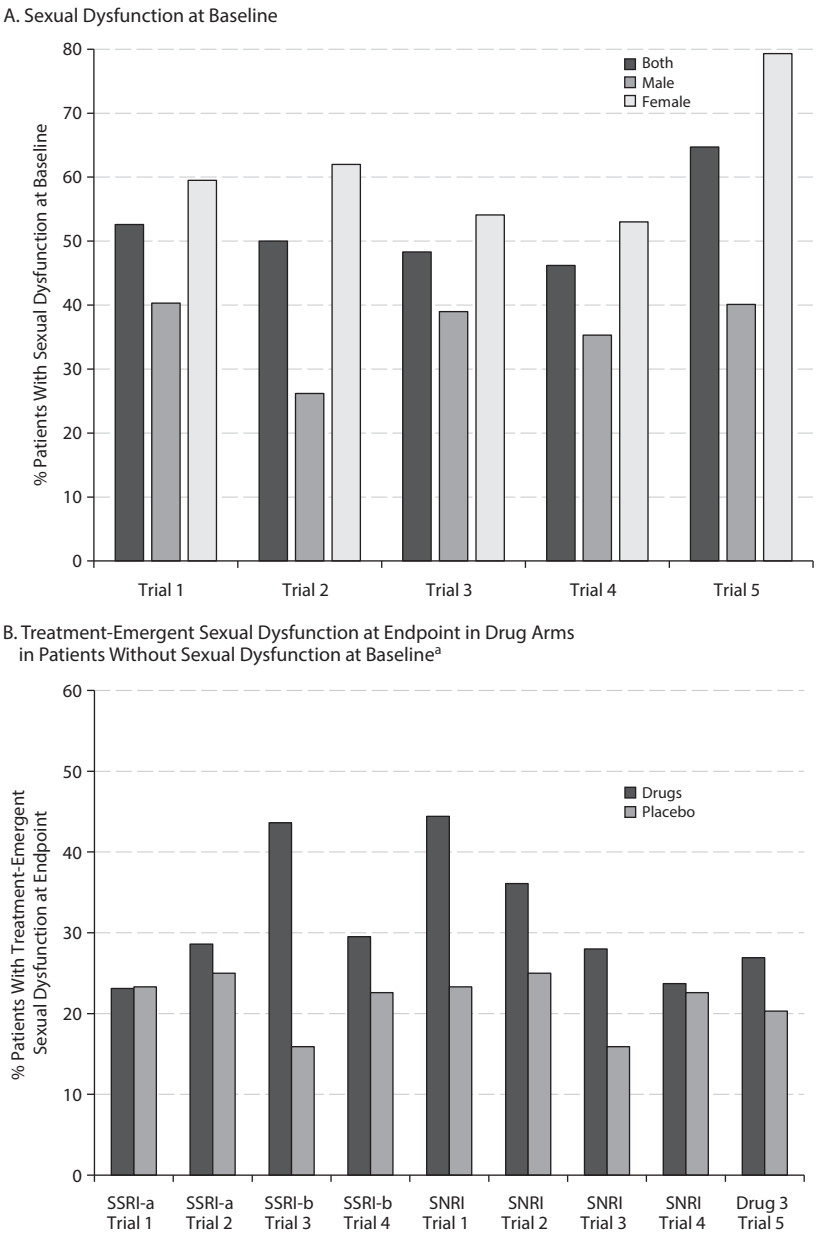


[a]A positive value for the placebo-subtracted mean change from baseline indicates that patients in the drug group had better sexual function on average than those in the placebo group (negative value indicates worse function).
[b]Confidentiality prohibits the naming of the 2 SSRIs or Drug 1.
Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire–Short-Form, SSRI = selective serotonin reuptake inhibitor.

patients with several of the drugs. Regardless of which method was used to assess sexual function, the data from these articles were informative (as long as the results were analyzed as intended, eg, the ASEX in a dichotomous fashion) and showed the expected adverse effects on sexual function associated with SSRIs/SNRIs. In fact, during our "Regulatory Science Forum on Measuring Sexual Dysfunction in Depression Trials," there seemed to be general agreement among the academic experts that the currently available quantitative measures of sexual function (if used and analyzed correctly), in particular the CSFQ-14 and ASEX, are adequate.

However, in our exploratory analyses of the very limited available in-house clinical trial data, no trend was observed in CSFQ-14 or ASEX results for individual drugs or drug classes. This raises the question as to why these measures appeared to perform well in the published studies but not in our exploratory analyses. Although publication bias could be a factor, in that negative studies are less likely to be published, such bias is unlikely the sole explanation. A possible reason for the discrepant results is that the trials included in our analyses of in-house data were generally designed to look at efficacy, with the CSFQ-14 or ASEX being one of many additional assessments. In contrast, the published trials either were designed specifically to look at the impact of the drugs on sexual function or had the assessment of such as an important secondary endpoint. It is therefore possible that in the trials found in our literature search, the CSFQ-14 and ASEX data were collected with

Figure 5. Percentage of Patients With Sexual Dysfunction According to ASEX Score



[a]Confidentiality prohibits the naming of the 2 SSRIs, the SNRI, or Drug 3.
Abbreviations: ASEX = Arizona Sexual Experiences Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

greater care. This discrepancy highlights the critical importance of having a positive control to assess assay sensitivity in all trials evaluating the impact of antidepressant drugs on sexual function. The Regulatory Science Forum provided information that led to further consideration of the regulatory and scientific issues in designing studies to evaluate sexual function in antidepressant drug trials, the discussion of which can be found in a separate article.[21]

Limitations

Certain limitations should be noted when considering the findings of our literature search and the results of our exploratory analyses of in-house depression trial data. For the literature search, the number of studies found was small due to limiting our search to placebo-controlled trials. It was not possible to conduct a pooled analysis of all the studies found, as the type of data was too varied from study to study. In addition, industry sponsorship and publication bias should be taken into account. For the exploratory analyses of available trial data, the data were very limited and the effects were quite small, so definitive conclusions cannot be drawn. Future studies are needed using standardized instruments to measure sexual function in controlled trials.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others). For reasons of confidentiality, individual drug names for part of FDA's in-house data presentation are not reported here.

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