Treatment-Emergent Sexual Dysfunction Related to Antidepressants

A Meta-Analysis

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Background: Sexual dysfunction (SD) is an important underestimated adverse effect of antidepressant drugs. Patients, in fact, if not directly questioned, tend to scarcely report them. The aim of the present meta-analysis was to quantify SD caused by antidepressants on the basis of studies where sexual functioning was purposely investigated through direct inquiry and specific questionnaires.

Methods: A literature search was conducted using MEDLINE, ISI Web of Knowledge, and references of selected articles. Selected studies performed on patients without previous SD were entered in the Cochrane Collaboration Review Manager (RevMan version 4.2). Our primary outcome measure was the rate of total treatment-emergent SD. Our secondary outcome measures were the rates of treatment-emergent desire, arousal, and orgasm dysfunction.

Results: Our analyses indicated a significantly higher rate of total and specific treatment-emergent SD and specific phases of dysfunction compared with placebo for the following drugs in decreasing order of impact: sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine, with SD ranging from 25.8% to 80.3% of patients. No significant difference with placebo was found for the following antidepressants: agomelatine, amineptine, bupropion, moclobemide, mirtazapine, and nefazodone.

Discussion: Treatment-emergent SD caused by antidepressants is a considerable issue with a large variation across compounds. Some assumptions, such as the inclusion of open-label studies or differences in scales used to assess SD, could reduce the significance of our findings. However, treatment-emergent SD is a frequent adverse effect that should be considered in clinical activity for the choice of the prescribed drug.

Key Words: antidepressants, SSRI, serotonin and noradrenaline reuptake inhibitor, sexual dysfunction

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First-generation antidepressants, tricyclics and monoamine oxidase, are associated with sedation, weight gain, and anticholinergic, cardiac, and potentially lethal adverse effects: when these were the predominantly prescribed antidepressants, greater attention is given to these adverse effects.[1] Nonetheless, when new drugs with a safer profile, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors, were developed and became largely available, greater attention was paid to previously unconsidered adverse effects, in particular, to sexual dysfunction (SD).[2,3] Sexual dysfunction can be divided into 3 phases reflecting the disruption in the sequential aspects of the normal sexual response cycle of sexual desire, arousal (including clitoral engorgement and lubrication in women and erectile function in men), and orgasm,[4] and many drugs, especially those acting on the serotoninergic system, were shown to negatively affect all the 3 phases, although with possible differences between men and women.[5,6]

Unfortunately, despite the increasing interest toward sexual adverse effects, early studies largely underestimated the real prevalence of SD among newer antidepressants.[6–9] Two main reasons can explain this factor: the first one is that patients, if not directly questioned, tend to underreport sexual adverse effects[7,9]; the second one is that SD is often associated with mood and anxiety disorders, even when untreated.[10]

In recent times, new studies using specific questionnaires or direct inquiry on sexual function confirmed the importance of the specific investigation of the sexual life of the patients.[6,9,11–13] Recent studies directly comparing spontaneous reports by patients to direct inquiry by clinicians confirmed these data,[6–9] underlying that only works in which sexual function is specifically investigated through direct inquiry and sexual scales can provide precise estimates of their real incidence.

The aim of the present meta-analysis was to quantify treatment-emergent SD associated with presently used antidepressant therapies on the basis only of selected papers that specifically investigated this type of adverse effect.

METHODS

Literature Research

A literature search was conducted using MEDLINE, ISI Web of Knowledge, and references of selected articles. The search included articles published until July 2008. The search strategy sought only studies published in English. The main search terms were SD, sexual adverse effects, tricyclics, all SSRIs, all serotonin and noradrenaline reuptake inhibitors, desire, arousal, and orgasm.

Selection of Trials

Inclusion Criteria

A summary of the included studies is provided in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/A1027). Drugs investigated in at least one study on a minimum of 10 patients were considered for the analysis. The included studies had to (1) investigate sexual functioning in patients taking antidepressants; (2) clearly specify

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that the clinicians investigated SD through direct inquiry or a specific sexual questionnaire; (3) allow only monotherapy, apart from benzodiazepines, allowed only in one study[6] that we included given the scarce influence they are supposed to have on sexual function[45]; (4) include only patients, or perform specific analysis on a subsample of patients, without previous SD; (5) clearly provide data on single drugs; and (6) provide dichotomous variables for at least one outcome (eg, total SD). Double-blind, open-label, cross-sectional, and retrospective studies were all included. No time limits were considered; nonetheless, the greatest quantity of studies' duration varied from 4 to 12 weeks, the period in which SD is maximally prevalent, and when long-term studies provided data between the 4th and 12th weeks, we considered the investigated parameters in a specific week (at the 8th week if possible) to make comparisons more homogeneous.

Exclusion Criteria

The exclusion criteria were the following: (1) antidepressants were given for a primary SD (eg, premature ejaculation), (2) antidepressants were given in substitution of a previous antidepressant (ie, we excluded studies where switches were allowed to avoid samples of patients with SD related to the previous treatment), (3) 2 or more drugs were contemporary given so that it would have been impossible to distinguish the dysfunction related to a drug or another, (4) patients were treated with other psychotropic drugs in the days before the entry in the study, (5) the authors referred to a class of drugs (eg, SSRI) and not to single drugs, (6) the authors included only patients with previous SD, (7) antidepressants were taken only a few days a month (eg, as it usually happens in the premenstrual dysphoric disorder[46]), (8) the study included patients with other severe medical illnesses or further nonpsychiatric medications that could be related to SD, (9) the study included only healthy subjects, and (10) no dichotomous outcomes were given.

Outcome Measures

Primary Outcome Measure

The primary outcome measure was the rate of total treatment-emergent SD.

Secondary Outcome Measures

The secondary outcome measures were the rates of the 3 main phases of sexual response, namely, desire, arousal, and orgasm dysfunction. Furthermore, when possible, separate analyses were conducted for men and women separately. We also performed a sensitivity analyses focusing on the impact of different scales and on the influence of diagnosis on SD. Other clinical features possibly influencing SD were not available.

Data Extraction

Data were extracted by the authors from the original reports. Further variables that did not fit with our definition of primary and secondary outcome measures were calculated in agreement with the criteria explained in the next section.

Data Analysis

Data were entered into the Cochrane Collaboration Review Manager Software (RevMan version 4.2; Cochrane Collaboration, Oxford, UK) and analyzed by RevMan analysis 1.01. For dichotomous outcomes, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using a fixed-effect model, as the population was supposed to be homogeneous. The analysis was performed on the intent-to-treat population, apart from those cases where authors specified a particular subsample of patients to which their analysis were referred.

For the variables desire dysfunction, arousal dysfunction, and orgasm dysfunction, when the authors provided only particular subclasses of a specific outcome measure (eg, delayed orgasm and/or anorgasmia instead of total orgasm problems), we conservatively considered the higher percentage value as the representative value of that outcome variable (and not the arithmetic sum to avoid double inclusions of the same patients).

Moreover, for studies that did not include the placebo control group, we calculated the weighted mean of the placebo samples for the considered variable from placebo-controlled studies that investigated the same variable and applied it to studies not including a placebo group in the following manner: we considered the number of the virtual placebo group equal to the number of patients treated with SD in the specific studies, and the hypothetical number of subjects with global or specific SD was rescaled to the percentage of the same class we obtained from the weighted mean analysis.

Finally, when 2 studies focused on partially or totally overlapping groups of subjects, we considered (1) whether only 1 of the 2 studies provided a dichotomous outcome, that particular study; (2) whether only 1 of the 2 studies was performed on patients without previous SD, we considered that particular study as well; and (3) whether no difference existed between the 2 studies in outcome measures, we considered the study with the greatest sample. The previous methods were used both alone and in various combinations as needed.

To better establish the influence on our results of a possible publication bias, for the variable total SD and for drugs investigated in at least 5 independent studies, we considered the funnel plot and calculated quantitatively the influence of the publication bias through Egger's analysis.[47]

Assessment of Heterogeneity

Heterogeneity between studies was assessed by the χ^2 and I^2 statistics and by visually inspecting the results. The χ^2 statistic $P < 0.05$ was taken to be suggestive of heterogeneity; I^2 statistic of more than 50% was taken to be indicative of moderate heterogeneity.[48] Heterogeneity, as expressed from the χ^2 and I^2 statistics, measures the extent of inconsistency among the studies' results, and it is interpreted as approximately the proportion of total variation in study estimates independent from sampling errors. Possible reasons for the heterogeneity of the results will be considered in the discussion.

RESULTS

Primary Outcome Measure

Our primary outcome measure was the rate of total treatment-emergent SD caused by antidepressants. Mean total SD associated with placebo was 14.2%. The absolute percentage values and the OR between drugs and placebo are reported in Figure 1. The absence or presence of significant differences with placebo and the heterogeneity between the studies are shown in Supplementary Table 2 (Supplemental Digital Content 2, http://links.lww.com/A1028). Most of the drugs (as shown on the said supplementary table) were associated to a significantly higher rate of SD compared with placebo. Citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine showed the highest rates of total SD. Sensitivity analysis about these drugs focusing separately on patients with major depression did not show any significant difference.

Fluvoxamine, escitalopram, duloxetine, phenelzine, and imipramine showed significantly higher percentages of related

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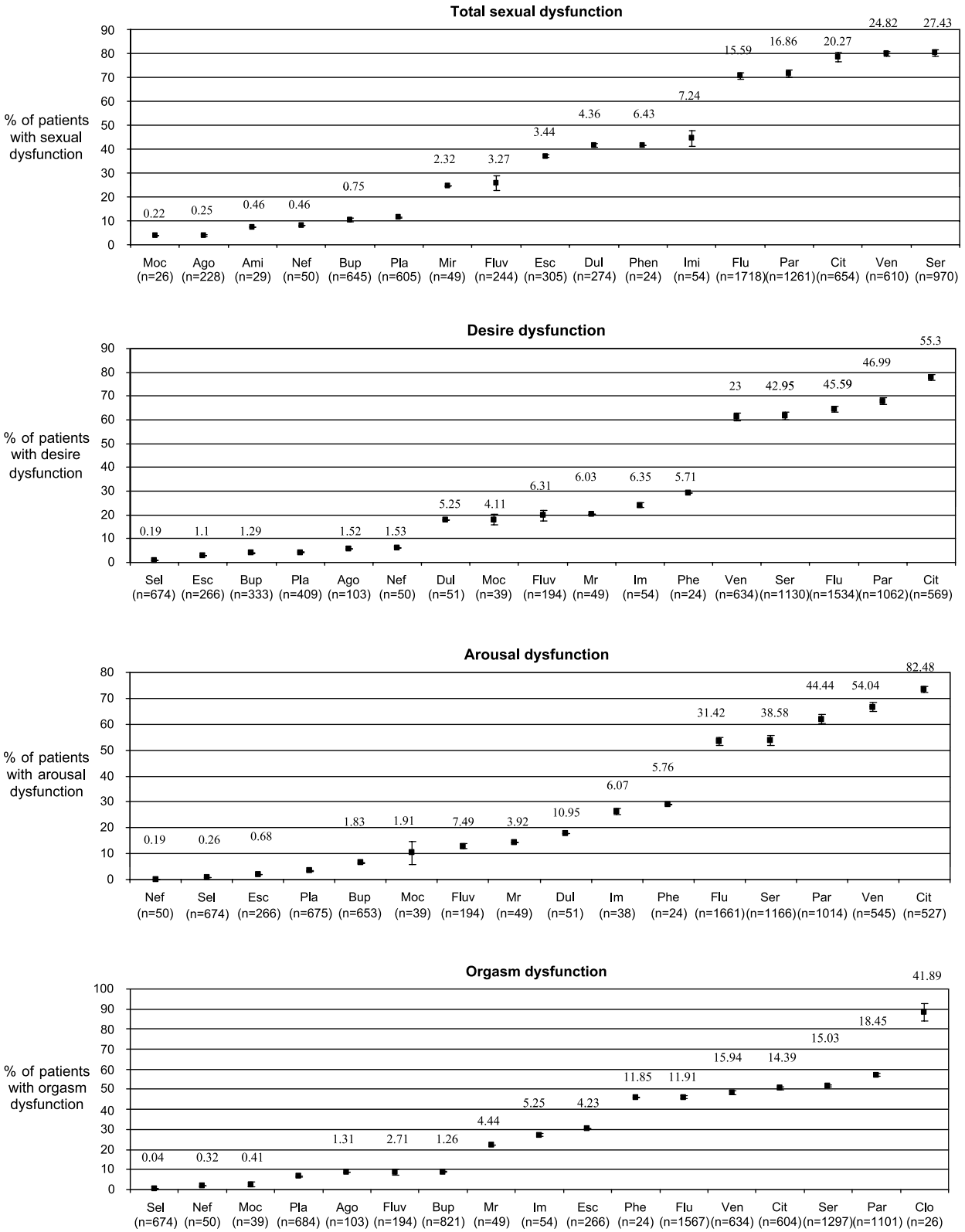

FIGURE 1. Total and specific SDs. Percent of patients with total, desire, arousal, and orgasm SD. Absolute values, 95% CI and OR compared with placebo (above each symbol) are reported. The number of subjects treated with a specific drug is shown between brackets. Ago indicates agomelatine; Ami, amineptine; Bup, bupropion; Cit, citalopram; Clo, clomipramine; Dul, duloxetine; Esc, escitalopram; Flu, fluoxetine; Fluv, fluvoxamine; Im, imipramine; Mr, mirtazapine; Moc, moclobemide; Nef, nefazodone; Par, paroxetine; Phe, phenelzine; Pla, placebo; Sel, selegiline; Ser, sertraline; Ven, venlafaxine.

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TABLE 1. Percent of Male and Female Patients With Total, Desire, Arousal, and Orgasm Dysfunction Separately

Drug	Patients With SD, M/F	Percentage, M/F	OR	95% CI	*P*	Heterogeneity χ^2 *P*	Heterogeneity I^2
Desire dysfunction							
Citalopram	158/380	84.11/70.78	2.39	1.43–3.99	0.0009	0.92	0
Fluoxetine	268/801	86.18/74.39	2.95	1.88–4.63	0.00001	0.14	54.9%
Paroxetine	263/515	73.65/72.89	1.61	1.05–2.47	0.03	0.94	0
Sertraline	231/545	84.15/71.92	2.72	1.62–4.57	0.0002	0.25	27.5%
Venlafaxine	112/300	80.62/72	4.20	2.04–8.62	0.0001	0.92	0
Arousal dysfunction							
Paroxetine	233/433	64.51/83.96	0.45	0.31–0.67	0.0001	0.30	6.5%
Sertraline	186/500	67.05/82	0.50	0.34–0.74	0.0005	0.10	63.2%
Venlafaxine	112/301	75/77.71	0.99	0.59–1.65	0.96	0.0008	85.7%
Orgasm dysfunction							
Citalopram	158/380	74.05/39.47	4.60	3.01–7.02	0.00001	0.005	87.1%
Fluoxetine	268/801	77.23/40.56	6.00	4.25–8.48	<0.00001	0.0002	92.9%
Paroxetine	263/515	80.23/44.84	5.60	3.79–8.29	<0.00001	0.32	13.5%
Sertraline	261/572	71.64/44.22	4.29	3.01–6.12	<0.00001	0.01	72.3%
Venlafaxine	112/301	82.14/44.85	7.60	4.16–13.89	<0.00001	0.14	55.1%

SD compared with placebo but significantly less than the previous 5 antidepressants. On the other hand, amineptine, agomelatine, bupropion, mirtazapine, moclobemide, and nefazodone showed a low percentage of SD comparable or inferior to placebo.

Sensitivity analysis showed, however, that the use of different scales had a significant impact on the absolute value of total SD: the Changes in Sexual Functioning Questionnaire and the Psychotropic-Related Sexual Dysfunction Questionnaire were more likely to provide higher percentages, whereas sexual effects scale and direct inquiry without any specific questionnaire were associated to lower percentages (Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/A1029). Finally, data on only a few drugs (citalopram, duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine, and bupropion) were available on a minimum of 2 studies and on a minimum of 100 subjects.

Secondary Outcome Measures

Our secondary outcome measures were the rates of treatment-emergent desire, arousal, and orgasm dysfunction. Mean placebo rates were 3.8%, 3.5%, and 6.7% for phases 1, 2, and 3 of sexual function, respectively. The absolute percentage values and the OR between drug and placebo are displayed in Figure 1. The absence or presence of significant differences with placebo and the heterogeneity between the studies are shown in Supplementary Table 2 (Supplemental Digital Content 2, http://links.lww.com/A1028).

As for the total SD, the large part of drugs seems to be associated with a higher rate of sexual adverse effects compared with placebo (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/A1028). Almost all the same drugs that were not related to global sexual dysfunction showed no significant difference with placebo in the specific subanalyses. Rare exceptions included mirtazapine that showed a significant, though small, higher rate of desire dysfunction, whereas escitalopram did not seem to be associated with desire dysfunction. Moreover, data showed that bupropion could be associated with a modestly higher rate of arousal dysfunction than placebo and that selegiline transdermal could have significantly lower rates of desire and arousal dysfunction compared with placebo. Particular attention has to be given to arousal dysfunction because a few studies did not investigate arousal dysfunction in women. However, even excluding these studies, results did not significantly change. The only exception includes the impossibility to evaluate the effects of selegiline transdermal on female sexual function given that the only study investigating sexual arousal disorder in patients taking selegiline reported only male arousal dysfunction.

As for total SD, data available on a minimum of 2 studies and on a minimum of 100 subjects included only citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, and bupropion.

Differences in SD Between Men and Women

We then investigated if there was any difference between male and female patients with respect to the different phases of SD. The absolute percentage values and the OR between men and women for drugs investigated in at least 2 independent studies and the absence or presence of significant differences between sexes as well as the heterogeneity between the studies are shown in Table 1. Unfortunately, very few studies provided complete data on both male and female patients, and it is not possible to provide data on all antidepressants. Moreover, the studies performed by Hsu and Shen[29] and Shen and Hsu[40] performed only on male and female patients, respectively, and using the same criteria of evaluation were considered as a single study.

For the 5 investigated drugs, data showed that men had significantly higher rates of desire and orgasm dysfunction compared with women, whereas women, surprisingly, seemed to have higher arousal dysfunction than men, apart from a nonsignificant difference found for venlafaxine.

Publication Bias

The funnel plots of total SD for drugs studied in at least 5 independent articles were visually inspected (figures not shown). We provided quantitative data as well through Egger's analysis. A significant publication bias was detected for fluoxetine analysis ($\beta = 0.728$, $P = 0.04$; intercept, −214.37; 95% CI, −445.37 to 17.37) and paroxetine ($\beta = 0.772$; $P = 0.02$;

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intercept, −241.6; 95% CI, −488.6 to 4.6), whereas no publication bias was observed for sertraline (β = 0.824; $P = 0.08$; intercept, −188.71; 95% CI, −474.89 to 96.89).

DISCUSSION

The aim of the present meta-analysis was to quantify treatment-emergent SD associated with antidepressant therapy on the basis of selected articles that specifically investigated these types of adverse effects. Our analysis showed many important findings.

First of all, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, imipramine, and phenelzine were associated with significantly higher SD rates compared with placebo and with absolute values of SD ranging from 25% to 80% of patients. In particular, the highest rates were found for citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.

Second, there were no major differences between drugs when considering total related SD and specific dysfunction of the 3 phases of sexual response; in other words, all drugs associated with total SD were related to significant dysfunction in every single phase of sexual response, desire, arousal, and orgasm though in different proportions. Rare exceptions were mirtazapine, which showed a significant, though small, higher rate of desire dysfunction than placebo; escitalopram, compared with placebo for the variable desire dysfunction; bupropion, which was associated with a modestly higher rate of arousal dysfunction than placebo; and selegiline transdermal, which showed lower rates of desire and arousal dysfunction compared with placebo.

The results are not surprising, considering the modification induced by different antidepressant drugs on the neurotransmitter systems of the brain. The effects of several antidepressants on sexual desire could be linked to multiple factors that impact those areas of the central nervous system associated with sexual interest. The mesolimbic system was found to have a substantial role in sexual interest, and dopamine has been suggested as an important neurotransmitter required for maintaining sexual interest in this area.[49–51] Potent and selective serotonin reuptake blockade (as the one related to SSRI, clomipramine, and venlafaxine) was found to reduce dopamine activity in the mesolimbic system through the serotonin 2 (5-HT_2) receptors,[51,52] suggesting a possible mechanism of actions for induced desire dysfunction.

Arousal dysfunction can be explained as being related to the reduction in the dopamine levels in the mesolimbic system related to potent and selective 5-HT reuptake inhibition and to the inhibition of peripheral spinal reflexes of the sympathetic and parasympathetic systems, which mediate erection and clitoral engorgement and are influenced by several neurotransmitters including serotonin.[49,50,53] Moreover, a possible role in arousal dysfunction could be imputed to the reduction of nitric oxide, a mediator of vascular changes required for erection. There is some evidence, in fact, that nitric oxide can be reduced by paroxetine, an SSRI, but not by nortriptyline, a drug especially acting on the noradrenergic system,[54] although the generalizability of this finding to other SSRIs needs further investigations.

Finally, orgasm dysfunction seems to be linked to the decreased dopamine and noradrenaline levels induced by 5-HT_2 activation as well.[53,55,56] These changes result in an alteration of the sympathetic and parasympathetic systems, which tone has an important role in mediating orgasm and ejaculation.[50,53] These possible explanations are also consistent with data showing that drugs such as mirtazapine and nefazodone, which have the benefit of the 5-HT_2 antagonism, do not show significant differences with placebo in causing SD.[57]

As we can see, the specific mechanisms of action of antidepressants play a substantial role in their sexual adverse effects profile. This is particularly true for drugs that could appear similar because of their action on more neurotransmitters, such as duloxetine, venlafaxine, and phenelzine on one side and moclobemide, bupropion, and selegiline transdermal on the other, but that are significantly different in their adverse effects profile. The last 3 antidepressants, in fact, are not associated with SD. This could be because selegiline transdermal[58] and bupropion[59] have a prodopaminergic effect positively related to sexual behavior[60] as well as moclobemide that, moreover, lacks the anticholinergic effects associated with other antidepressants.[36]

The third important finding of our meta-analysis, on the basis of studies that provided separate data on both sexes, is that men had significantly higher rates of desire and orgasm dysfunction compared with women, whereas women seemed to have a higher arousal dysfunction than men, apart from a nonsignificant difference found for venlafaxine. A possible explanation for the last finding could be linked to the greater weight of cognitive compared with physiologic aspects of arousal in women.[5]

Finally, our results strongly suggest that the rate of SD can vary according to the type of assessing scale. More in detail, the Changes in Sexual Functioning Questionnaire and the Psychotropic-Related Sexual Dysfunction Questionnaire are more likely to provide higher rates of SD, whereas sexual effects scale and direct inquiry without any specific questionnaire are associated with lower percentages, suggesting the need for further investigations on the different sensitivity of commonly used methods of investigation. In any case, spontaneous reports are largely underestimating the real incidence: a review[61] specifically investigating fluoxetine-induced SD evidenced a range of 34% to 75% when it was directly investigated, whereas spontaneously reported one ranged only from 2.7% to 7.8%. This issue is of particular importance considering that included studies purposely investigating sexual function represent less than 10% of available data about antidepressant SD.

Another important aspect of antidepressant-induced SD seems to be the time at which it is considered,[6,26,62] with some evidence that only 15% of patients with treatment-emergent SD seem to obtain a moderate to total improvement between the third and sixth months, a percentage that reaches the 30% after 6 months.

Furthermore, our findings outline the need for future research to investigate those factors that could be considered as related to SD to address patients with a higher risk of SD toward antidepressants that do not significantly interfere with sexual functioning. Examples include medical comorbidities, substance abuse, hormonal changes, medications, interpersonal conflicts, and further psychological issues[57] and the possible influence of some genetic variants.[63,64]

Unfortunately, the present analysis is affected by several limitations that reduce the significance of our findings and can explain the heterogeneity detected in many analyses. First, no time limits were included, whereas as previously reported, SD seems to improve in a significant percentage of patients.[6] Nonetheless, we compensated this limitation by considering end point values from the 4th to 12th weeks when available.

Second, we considered together studies where SD was investigated through different methods such as different scales or direct inquiry. However, we performed a sensitivity analysis of

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the results for the variable total SD, showing how SD values varied depending on different measurement methods.

Third, we included both double-blind, single-blind and open-label trials to include the greatest quantity of available studies, although double-blind placebo-controlled studies showed superiority to other study designs and are usually preferred for meta-analytic purposes.[65,66] Nonetheless, our strategy has the advantage of being more representative of the general patients populations.[67]

Fourth, we included only studies providing dichotomous outcomes, given the great number of used scales, and we excluded studies considering class of drugs instead of single drugs; this could be a possible explanation of the publication bias noted in the funnel plot and by Egger's analysis, although another possible explanation is linked to the small sample size of many studies that limits their power to detect differences among different treatment options.

Fifth, we excluded studies performed on patients with previous SD, a fact that could be related to a greater severity of illness and to comorbid medical illnesses that affect sexual functioning, and we excluded patients treated with 2 or more drugs, obtaining results that could be less representative of the general population. However, the inclusion of patients with previous SD would have led to inconclusive results.

Sixth, many of the studies mentioned in the present meta-analysis would fall far short of an adequately powered study and are therefore subject to type II errors (false-negative). Anyway, this problem is partially compensated by the weights of the sample size, reducing the weight of small trials.

Then, an artificial inflation of the effect could be due to the use of the same normative control sample scores. This could explain why selegiline transdermal seems to be associated with significantly lower sexual adverse effects than placebo.

Furthermore, we did not perform separate analyses for the same drugs administered at different dosages, given the similarities of the dosages across the studies. Nonetheless, it should be more deeply considered in future studies given the scarcity of high-quality studies investigating this feature.[9]

Finally, studies including depressed patients with previous SD often showed a global improvement of sexual functioning, suggesting the usefulness of antidepressants in enhancing sexual function in depressed patients affected by illness-related SD.[36,68–72]

In conclusion, our meta-analysis shows that there is a high prevalence of SD related to antidepressant drugs, especially among those acting on the serotoninergic system, providing strong evidence that citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine are related to consistent SD, whereas bupropion-related SD is similar to placebo, and showing the necessity of further research to better investigate treatment-emergent SD related to other antidepressants.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflict of interest.

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