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SYSTEMATIC REVIEW

Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder: Results from a Systematic Review with Network Meta-Analysis

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Abstract

Background Sexual dysfunction (SD) is prevalent in patients with major depressive disorder (MDD) and is also associated with second-generation antidepressants (SGADs) that are commonly used to treat the condition. Evidence indicates under-reporting of SD in efficacy studies. SD associated with antidepressant treatment is a serious side effect that may lead to early termination of treatment and worsening of quality of life.

Objectives Our objective was to systematically assess the harms of SD associated with SGADs in adult patients with MDD by drug type.

Methods We retrieved English-language abstracts from PubMed, EMBASE, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts from 1980 to October 2012 as well as from reference lists of pertinent review articles and grey literature searches. Two independent reviewers identified randomized controlled trials (RCTs) of at least 6 weeks' duration and observational studies with at least 1,000 participants.

Study Selection Reviewers abstracted data on study design, conduct, participants, interventions, outcomes and method of SD ascertainment, and rated risk of bias. A senior reviewer checked and confirmed extracted data and risk-of-bias ratings.

Analyses Random effects network meta-analysis using Bayesian methods for data from head-to-head trials and placebo-controlled comparisons; descriptive analyses calculating weighted mean rates from individual trials and observational studies.

Results/Synthesis Data from 63 studies of low and moderate risk of bias (58 RCTs, five observational studies) with more than 26,000 patients treated with SGADs were included. Based on network meta-analyses of 66 pairwise comparisons from 37 RCTs, most comparisons showed a similar risk of SD among included SGADs. However, credible intervals were wide and included differences that would be considered clinically relevant. We observed three main patterns: bupropion had a statistically significantly lower risk of SD than some other SGADs, and both escitalopram and paroxetine showed a statistically significantly higher risk of SD than some other SGADs. We found reporting of harms related to SD inconsistent and insufficient in some trials.

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Limitations Most trials were conducted in highly selected populations. Search was restricted to English-language only.

Conclusion and Implications Because of the indirect nature of the comparisons, the often wide credible intervals, and the high variation in magnitude of outcome, we rated the overall strength of evidence with respect to our findings as low. The current degree of evidence does not allow a precise estimate of comparative risk of SD associated with a specific antidepressant. In the absence of such evidence, clinicians need to be aware of SD as a common adverse event and should discuss patients' preferences before initiating antidepressant therapy.

1 Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, affecting 15 % of the population in high-income countries once in their lifetime [1]. Antidepressants were the most frequently dispensed prescription drugs in the USA in 2011, accounting for $US11 billion in sales and 264 million prescriptions filled [2]. Sexual dysfunction (SD), which can involve any or all phases of the sexual response cycle (i.e., libido, arousal, orgasm, and ejaculation), is associated with both the condition and the treatments used, and can affect up to 50 % of untreated depressed patients [3, 4]. Particularly when treated with second-generation antidepressants (SGADs), depressed patients may experience antidepressant-induced SD [5].

Treatment-emergent SD is a frequent but often under-reported serious adverse event associated with the use of SGADs. According to the US FDA, all adverse events resulting in a substantial disruption of a person's ability to conduct normal life functions can be considered serious adverse events [6]. Onset or worsening of SD as an adverse event associated with antidepressant use can result in premature discontinuation of antidepressant treatment, relapse of depression, and worsened health outcomes and quality of life [7–9].

Rates of treatment-emergent SD in depressed patients from randomized clinical trials range from 15 to 80 % [10, 11]. Using data from a cross-sectional study in Europe, study authors estimated the prevalence of treatment-emergent SD in depressed patients prescribed either a selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitors to be between 37.1 and 61.5 % [12]. Evidence indicates under-reporting of SD in efficacy studies, particularly when no targeted or structured method is used to obtain information on sexual functioning, both at baseline and throughout drug treatment [13]. In a prospective observational study, investigators observed a considerably lower incidence of antidepressant-associated SD when SD was determined by spontaneous reports of study participants alone compared with using a validated sexual function-specific instrument: nearly 80 % of those with treatment-emergent SD would have gone undiagnosed if only reported spontaneously [14].

A few systematic reviews addressed the issue of SD associated with SGADs in patients with MDD [10, 15–19]. With the exception of an updated meta-analysis by Gartlehner et al. [11], which also included data from observational studies, previous systematic reviews have focused on efficacy trials. This study aims to systematically review and assess the comparative harms of SD in MDD patients treated with SGADs using data from both clinical trials and observational studies.

2 Methods

This systematic review updates part of a larger comparative effectiveness review on SGADs funded by and conducted for the US Agency for Healthcare Research and Quality (AHRQ) [19].

2.1 Data Sources and Study Selection

We searched PubMed, EMBASE, PsycINFO, the Cochrane Library, and International Pharmaceutical Abstracts from 1980 to October 2012. We used Medical Subject Headings as search terms when available or keywords when appropriate. We combined terms for MDD with a list of 13 specific SGADs (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine) and their specific trade names. We limited the electronic search to 'adult 19+ years,' 'human,' and 'English language.' We used semi-automated manual searches of reference lists of pertinent review articles and letters to the editor employing the Scopus™ citation database (http://www.scopus.com) [20]. The Scientific Resource Center (SRC) searched the following sources for potentially relevant unpublished literature: the US FDA website, Health Canada, Authorized Medicines for the European Union, ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials, Conference Papers Index, National Institutes of Health RePORTER, HSRProj, Hayes, Inc. Health Technology Assessment, and the New York Academy of Medicine's Grey Literature Index. The SRC also asked pharmaceutical manufacturers to submit dossiers on completed research for each drug included in this review. We received dossiers from two firms (Astra Zeneca, London, UK and Warner Chilcott, Dublin, Ireland).

Two investigators independently reviewed abstracts and full text articles (each done by two out of the authors: UR, GG, LCM, AG, BN, RAH, MVN, LL, BNG). We excluded studies available only in abstract form. We developed eligibility criteria with respect to study design, duration, patient population, interventions, and outcomes to assess SD as harms associated with SGADs or as treatment-emergent SD in adult inpatients and outpatients with MDD. We included head-to-head randomized controlled trials (RCTs) of at least 6 weeks' duration comparing SGADs. Since head-to-head evidence was lacking for many comparisons, we also included placebo-controlled trials. We also examined data from observational studies with $\geq$1,000 study participants and follow-up of at least 12 weeks. To be eligible for inclusion, a study had to report any health outcome related to SD, either as an adverse event (spontaneously reported by patients, systematically elicited, openly inquired, or observed by study clinicians), or as patient-rated or expert-rated outcomes of SD prospectively measured by a specific, validated instrument. We excluded studies that both reviewers agreed did not meet eligibility criteria. Discrepancies were resolved by discussion between both reviewers or, when necessary, by involving a third reviewer (see Electronic Supplementary Material 1 for information on characteristics of included studies, and Electronic Supplementary Material 2 for information on the Update search strategy).

2.2 Quality Assessment and Data Extraction

Two trained reviewers (two at a time out of UR, AG, BN, MVN) independently abstracted data from each study and assigned an initial risk of bias (quality) assessment using pre-defined criteria based on those developed by the Cochrane Collaboration (low, moderate, and high risk of bias) [21]. To assess the risk of bias in observational studies, we used criteria outlined by Deeks and colleagues [22]. Any disagreement was resolved by consensus between the respective two reviewers. A senior reviewer (one at a time out of GG, LCM, RAH, LL, BNG) evaluated completeness of data abstraction and confirmed the quality assessment. If disagreements occurred, they were resolved by consensus. We abstracted information on study characteristics (study design, eligibility criteria), intervention (drugs, dose, duration), study participants, sample size, loss to follow-up, withdrawals because of adverse events, method of determining and reporting harms-related data and outcomes associated with SD. We used the Evidence-based Practice Center approach, conceptually similar to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, to assign an overall grade for strength of evidence (low, moderate, or high strength of evidence) of the outcome [23].

2.3 Data Synthesis and Analyses

To be included in the quantitative analysis, studies had to provide sufficient data to calculate measures of incidence of SD. We recalculated rates of SD for each study using the number of all randomized patients as the denominator to reflect a true intention-to-treat (ITT) analysis. For statistical reasons, we combined all reported subtypes of SD (e.g., anorgasmia, ejaculation failure, ejaculation disorder, erectile dysfunction, delayed ejaculation, abnormal orgasm, decreased libido, and loss of libido) into one outcome category of SD. When available, sex-specific rates were abstracted.

We conducted a network meta-analysis using Bayesian methods to compare rates of SD between SGADs, including both head-to-head trials comparing active interventions and placebo-controlled comparisons. To be included in the network meta-analysis, RCTs had to fulfill (i) the general study eligibility criteria, and (ii) the statistical conditions required for network meta-analysis (consistency, heterogeneity, geometry of treatment network). We used the methods developed and illustrated in the UK National Institute for Health and Care Excellence (NICE) Technical Support Document 2, which details the generalized linear modeling framework for network meta-analyses of RCTs [24]. We used a random effects logistic regression model adjusting for correlations between multiple arms within each study. Study effect and outcome effect parameters were modeled by non-informative (flat) prior distributions that were normal (0, 10,000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence and then a further 100,000 simulations were used in estimating the posterior probabilities. Convergence was verified by trace plots and inspection of the Gelman–Rubin statistic for monitored parameters. Our outcome measure was adverse events of SD. To assess the consistency between the different reporting methods, we conducted a sensitivity analysis, including studies where SD was determined only by open question or spontaneous patient reports. The network meta-analysis was performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) methods. We calculated odds ratios and 95 % credible intervals (CrIs) for all possible pairwise comparisons among our drugs of interest. We analyzed RCTs reporting only male-specific rates separately from RCTs reporting total rates of SD. Only a small number of trials included in the network meta-analysis reported sex-specific rates. We used all data from these trials combining male and female rates into total rates along with data from trials reporting total rates of SD only.

We conducted descriptive analyses, when conditions to perform comparative analyses could not be met. For studies providing only sex-specific rates of SD, we calculated weighted mean rates (WMRs) and 95 % confidence intervals (CIs) on sex-specific rates of SD, pooling data from arms of both the active drug comparator and the placebo-controlled trials. We calculated all descriptive analyses using StatsDirect Statistical Software, version 2.7.9 (StatsDirect, Cheshire, UK). Due to differences in study design, we could not pool rates from all observational studies and also present rates from individual studies. For both the descriptive analyses and the network meta-analysis, we also included RCTs that did not report any baseline assessment of SD.

3 Results

Our searches identified 4,476 citations (see PRISMA flow-diagram, Fig. 1) [25] for the larger comparative effectiveness review on SGADs. We screened 1,532 full-text articles for eligibility; of these, 63 studies of low and moderate risk of bias (58 RCTs, five observational studies) reporting data on any SD outcome or adverse event met our inclusion criteria for analysis. The majority of experimental trials were 6–8 weeks in duration.

Adverse event reporting and determination of SD varied widely among studies. Specific methods included prospective, systematically monitored, and validated instruments to measure sexual function, rating scales, or structured clinical interviews to diagnose SD. Additionally, study authors relied on adverse events gathered by spontaneous patient reports, or using open questions or generic checklists by clinicians. In 22 of 58 (37.9 %) RCTs, study authors did not provide any information on the method to collect adverse event data or determine SD. Only 14 of 58 (24.1 %) RCTs reporting SD outcomes or adverse events reported a specific method to determine adverse events or outcomes of SD. In 7 of 16 RCTs, study authors used a standardized validated instrument to establish SD at baseline and during the study period; however, they did not provide sufficient data in the published article to calculate SD outcomes.

All of the observational studies with data on sexual function outcomes reported the method to ascertain SD

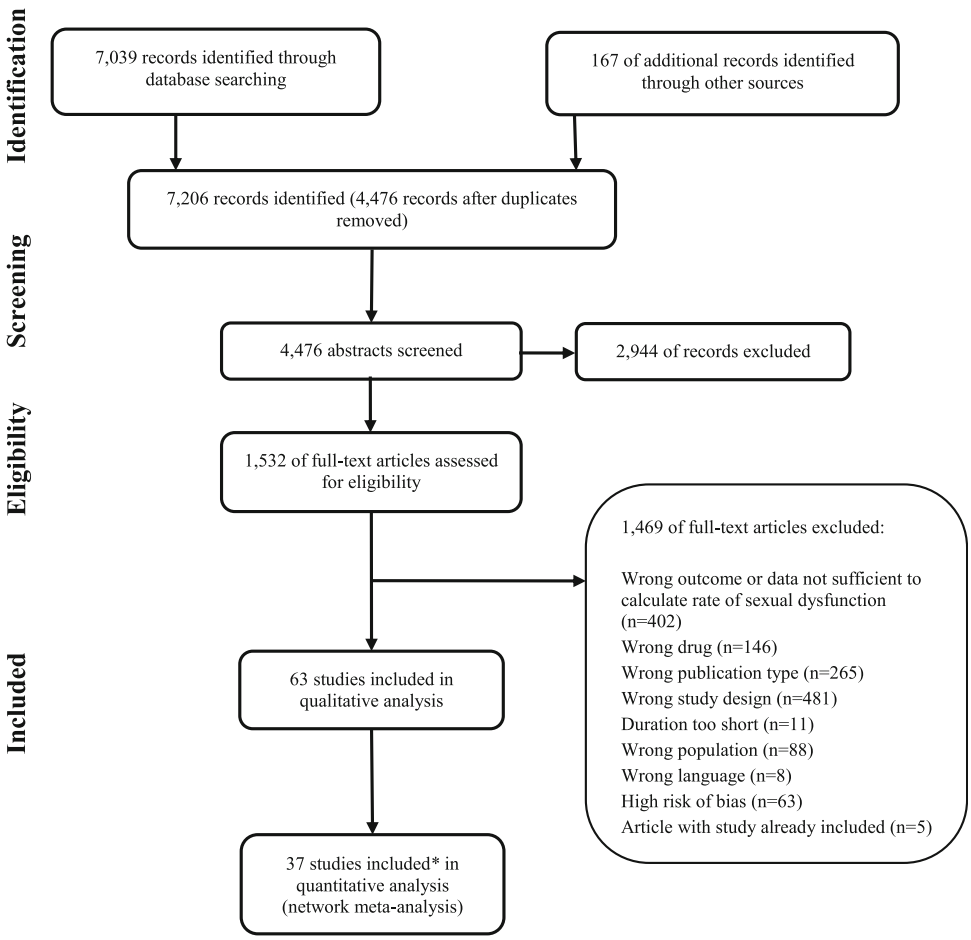

Fig. 1 Flow diagram: summary of evidence search and selection. *RCTs were included in the network meta-analysis if they fulfilled (i) general study eligibility criteria, and (ii) statistical requirements for network meta-analysis. *RCTs* randomized controlled trials

or adverse event; three of the five used a validated sexual function instrument (the Changes in Sexual Functioning Questionnaire; the Arizona Sexual Experience Scale; the Psychotropic-Related Sexual Dysfunction Questionnaire).

3.1 Evidence of Risk of Sexual Dysfunction (SD) in Patients with Major Depressive Disorder (MDD) from Randomized Controlled Trials

Our analyses (quantitative or descriptive) included 58 RCTs of low or moderate risk of bias with information on SD, representing approximately 19,000 patients treated with SGAD.

3.1.1 Network Meta-Analysis

We conducted network meta-analyses of adverse events of SD using data from placebo-controlled or head-to-head trials. Of the 58 RCTs fulfilling the study eligibility criteria, we could finally include 37 RCTs [26–62] meeting the statistical requirements for network meta-analysis. Overall, 14,576 patients were randomly assigned to placebo or one of the 11 included SGAD drugs. A total of 22 studies were two-arm trials, 11 were three-arm trials involving two different active comparisons and placebo, and four were multi-arm trials involving two or more active compounds at various dosages and placebo. The network of all included pairwise comparisons is shown in Fig. 2.

The full model random effects network meta-analysis included 66 pairwise comparisons (55 active SGAD pairwise comparisons and 11 placebo-controlled comparisons). We found statistically significant differences in adverse events of SD in 14 of the pairwise active comparisons (Table 1). Most comparisons showed a similar risk of SD among included SGADs; however, CrIs were wide and included differences that would be considered clinically relevant. Eight individual comparisons present a statistically significantly higher risk of SD of one drug over another.

Nevertheless, three main patterns emerged (see Fig. 3): (i) bupropion had a statistically significantly lower risk of SD than some other SGADs (escitalopram, paroxetine, and sertraline); (ii) escitalopram showed a statistically significantly higher risk of SD than some other SGADs (fluoxetine, mirtazapine, and nefazodone); and (iii) paroxetine had a statistically significantly higher risk of SD than some

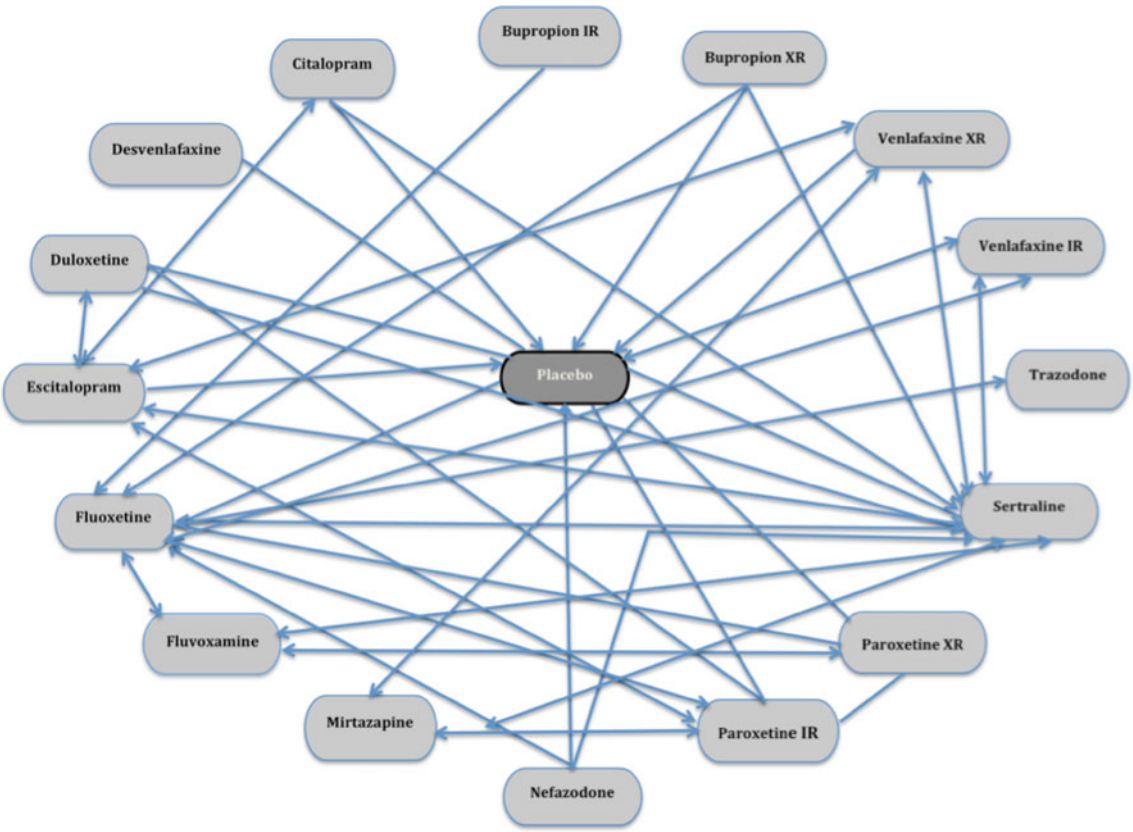

Fig. 2 Network of all included comparisons for the network meta-analysis of sexual dysfunction associated with second-generation antidepressants. *IR* immediate release, *XR* extended release

Table 1 Odds ratio of sexual dysfunction (95 % credible intervals for pairwise comparisons, mixed-treatment comparison)[a]

Pairwise comparisons	OR of sexual dysfunction[a]	95 % CrI
Bupropion vs. citalopram	2.94	0.81–7.90
Bupropion vs. duloxetine	2.21	0.88–4.67
Bupropion vs. escitalopram	3.08	1.27–6.45
Bupropion vs. fluoxetine	1.02	0.42–2.11
Bupropion vs. fluvoxamine	1.35	0.24–4.44
Bupropion vs. mirtazapine	0.82	0.20–2.29
Bupropion vs. nefazodone	0.45	0.10–1.29
Bupropion vs. paroxetine	3.56	1.45–7.38
Bupropion vs. sertraline	2.21	1.07–4.12
Bupropion vs. venlafaxine	1.30	0.47–2.93
Citalopram vs. duloxetine	0.96	0.26–2.51
Citalopram vs. escitalopram	1.31	0.41–3.15
Citalopram vs. fluoxetine	0.46	0.11–1.30
Citalopram vs. fluvoxamine	0.59	0.08–2.16
Citalopram vs. mirtazapine	0.36	0.06–1.17
Citalopram vs. nefazodone	0.20	0.03–0.66
Citalopram vs. paroxetine	1.57	0.41–4.13
Citalopram vs. sertraline	0.96	0.30–2.32
Citalopram vs. venlafaxine	0.57	0.14–1.60
Duloxetine vs. escitalopram	1.50	0.68–2.93
Duloxetine vs. fluoxetine	0.52	0.18–1.18
Duloxetine vs. fluvoxamine	0.67	0.12–2.17
Duloxetine vs. mirtazapine	0.41	0.10–1.13
Duloxetine vs. nefazodone	0.22	0.05–0.64
Duloxetine vs. paroxetine	1.72	0.81–3.20
Duloxetine vs. sertraline	1.11	0.48–2.25
Duloxetine vs. venlafaxine	0.65	0.22–1.51
Escitalopram vs. fluoxetine	0.37	0.13–0.85
Escitalopram vs. fluvoxamine	0.48	0.08–1.58
Escitalopram vs. mirtazapine	0.29	0.07–0.82
Escitalopram vs. nefazodone	0.16	0.03–0.46
Escitalopram vs. paroxetine	1.26	0.50–2.58
Escitalopram vs. sertraline	0.79	0.39–1.54
Escitalopram vs. venlafaxine	0.47	0.16–1.08
Fluoxetine vs. fluvoxamine	1.49	0.24–5.07
Fluoxetine vs. mirtazapine	0.89	0.20–2.60
Fluoxetine vs. nefazodone	0.49	0.10–1.50
Fluoxetine vs. paroxetine	3.86	1.44–8.40
Fluoxetine vs. sertraline	2.44	0.94–5.26
Fluoxetine vs. venlafaxine	1.41	0.47–3.30
Fluvoxamine vs. mirtazapine	0.96	0.12–3.60
Fluvoxamine vs. nefazodone	0.52	0.06–2.01
Fluvoxamine vs. paroxetine	4.08	0.81–12.73
Fluvoxamine vs. sertraline	2.59	0.53–7.98
Fluvoxamine vs. venlafaxine	1.54	0.25–5.29
Mirtazapine vs. nefazodone	0.73	0.11–2.56
Mirtazapine vs. paroxetine	5.73	1.55–15.29
Mirtazapine vs. sertraline	3.62	1.01–9.59
Mirtazapine vs. venlafaxine	2.03	0.57–5.31
Nefazodone vs. paroxetine	10.98	2.69–30.96
Nefazodone vs. sertraline	6.89	1.81–18.89
Nefazodone vs. venlafaxine	4.11	0.84–12.70
Paroxetine vs. sertraline	0.68	0.30–1.35
Paroxetine vs. venlafaxine	0.40	0.14–0.89
Sertraline vs. venlafaxine	0.61	0.25–1.24

[a] Relative treatment effect of each treatment relative to reference comparator expressed as OR (with 95 % CrI). An OR <1 indicates a higher rate of SD of the drug listed on the left-hand side ('first drug'); an OR >1 indicates a higher rate of SD of the drug listed on the right-hand side ('second drug'). Method and extent of adverse event assessment differed across studies; comparisons across drugs must be made cautiously. Based on random-effects network meta-analysis using Bayesian methods. *CrI* credible interval, *OR* odds ratio, *SD* sexual dysfunction

other SGADs (fluoxetine, mirtazapine, nefazodone, and venlafaxine).

Convergence was satisfied in the full model, but not fully satisfactory for citalopram comparisons in the model including only trials where SD was spontaneously reported by patients or elicited by open questions. Findings of the sensitivity analyses assessing the impact of the method used to determine SD in the network meta-analysis model were somewhat conflicting in that consistency between the different reporting methods could not always be confirmed.

Because of the indirect nature of the comparisons, the often wide CrIs, and the high variation in magnitude of outcome, we rated the overall strength of evidence with respect to our findings low.

3.1.2 *Descriptive Analysis Using Data of Trials Reporting Only Sex-Specific Rates of SD*

Due to reasons of heterogeneity, we did not combine direct and indirect evidence for pairwise comparisons from the trials reporting only sex-specific incidence of SD. Instead, we performed descriptive analysis calculating WMRs pooling data from both active comparator and placebo-controlled trials. Overall, we used data from 21 RCTs [63–83] providing sex-specific rates of SD from 4,159 patients including six different SGADs (44 study arms: 34 active arms, ten placebo-controlled arms).

We analyzed sex-specific rates separately and required a minimum of two trials to calculate WMRs. Only trials reporting male-specific rates of SD provided sufficient data

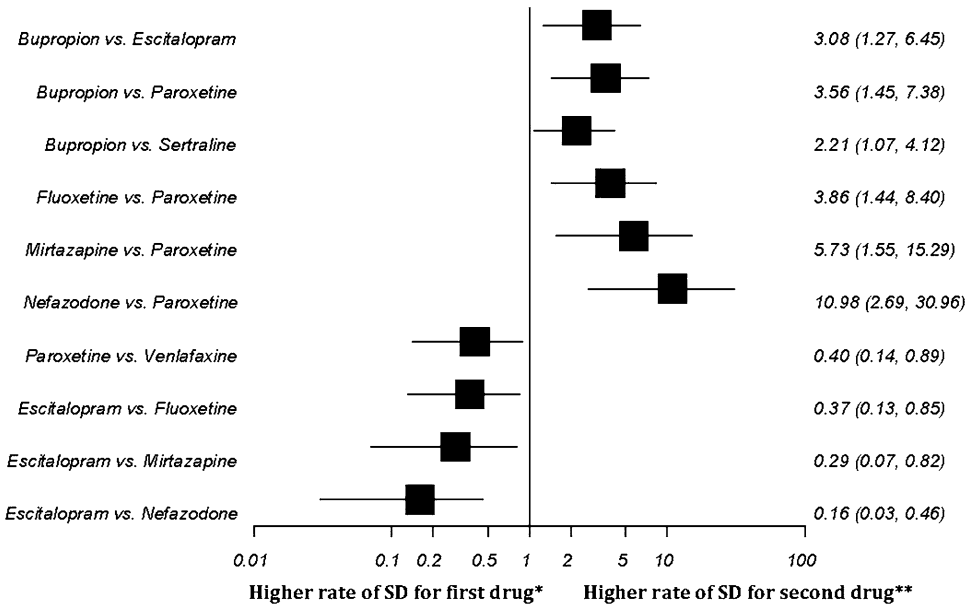

Fig. 3 Results of network meta-analysis of sexual dysfunction for selected pairwise second-generation antidepressant comparisons, odds ratios. * Odds ratios <1 indicate a higher rate of SD of the drug listed on the *left-hand side* ('first drug'). ** Odds ratios >1 indicate a higher rate of SD of the drug listed on the *right-hand side* ('second drug'); selected results from full model of random effects network meta-analysis. *SD* sexual dysfunction

to allow calculation of WMRs. Figure 4 summarizes by specific drug, the WMR of SD based on male-specific rates and 95 % CIs in patients with MDD reported in RCTs of SGADs. Across all trials reporting male-specific rates, the WMR of SD was 12.3 % (95 % CI 8.8–15.8), with a range of 8.8 % of SD for fluoxetine (95 % CI 0.5–17.0) and 15.8 % for sertraline (95 % CI 1.2–30.4). Overall, rates of SD did not differ among duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.

3.2 Evidence of SD in Patients with MDD from Observational Studies

Descriptive analysis of tolerability used data from almost 7,200 study participants using SGADs (with a total of $n = 10$ different drugs). We were able to include five observational studies providing data on SD: three prospective cohort studies [14, 84, 85], one prescription-event monitoring database study [86], and one cross-sectional survey [87]. Except for the study by Mackay et al. [86] and the one by Meijer et al. [84], standardized validated instruments to ascertain SD at baseline and throughout follow-up were used. All of the five studies were conducted in various international outpatient settings. We present crude rates and incidence density rates of individual studies separately.

Table 2 summarizes, by specific drug, the incidence and prevalence of SD reported in three prospective cohort studies of SGADs in patients with MDD. Due to differences in study design and patient follow-up we did not calculate pooled WMR. Instead, rates from the individual studies are shown. In two of these prospective studies [14, 85], incidence rates at 6 months of follow-up were used. The rates reported by Clayton et al. [87] refer to prevalence data from a cross-sectional study using data of a subsample of patients free of other possible causes of SD, yet with a wide range of treatment duration.

Rates of SD tended to be higher than those reported in RCTs. Overall, the weighted mean incidence of SD across all observational studies was 40.4 % (95 % CI 28.3–52.6). Reported rates by specific drug ranged from 7.0 % prevalence for bupropion in a cross-sectional study [87] to a 72.7 % 6-month incidence for citalopram in a prospective cohort study [14]. Both studies relied on validated instruments to ascertain sexual function, although only the study by Montejo et al. [14] established a cohort free of SD at the outset. Six-month incidence rates tended to be higher than the prevalence rates gathered from the cross-sectional survey (citalopram 72.7 vs. 30.0 %, fluoxetine 57.7 vs. 23.0 %, paroxetine 70.7 vs. 25.0 %, sertraline 62.9 vs. 25.0 %, and venlafaxine 67.3 vs. 30.0 %, respectively). Duenas et al. [85] reported a 6-month incidence rate of 23.4 % for duloxetine in outpatients from a prospective cohort study including only sexually active patients without SD at study enrolment.

Due to differences in study design, rates of SD from two additional observational studies could not be pooled with those from the above-mentioned three prospective cohort studies. Incidence density rates, which adjust for time of exposure, reported in the individual studies were converted and are shown in Table 3. From a prescription-event monitoring database study [86], adverse events of only male SD (impotence or ejaculation failure) were recorded, showing a rate of 9.6 per 1,000 person-years for nefazodone, and 30 per 1,000 person-years for paroxetine. SD adverse events for sertraline in a prospective observational

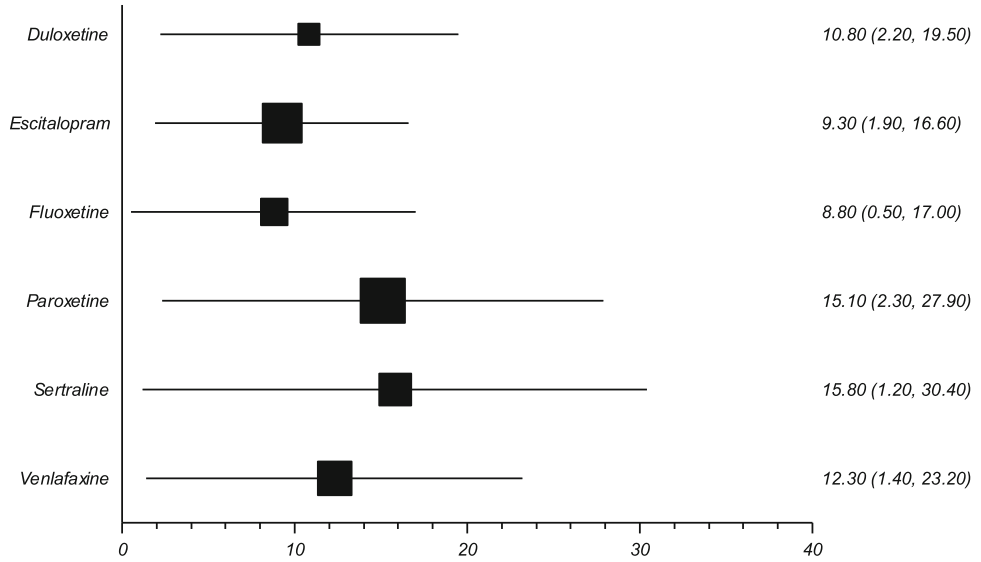

Fig. 4 Male-specific weighted mean rates of sexual dysfunction from individual randomized controlled trials. Data are presented as % (95 % confidence intervals). Weighted mean rates (%) calculated using drug-specific rates of sexual dysfunction from individual randomized controlled trials pooling data from active-comparator trials and placebo-controlled trials. Rates were calculated only if data from at least two trials were available (only male-specific rates could be calculated; we did not use data from a small randomized controlled trial for desvenlafaxine and trazodone). Comparisons across drugs must be made cautiously; method and extent of adverse event assessment differed across studies

Table 2 Prevalence/incidence of sexual dysfunction from three observational studies (crude rates as percentages from individual studies)

Drug	Sexual dysfunction (mean %)	Study design	*N* included in analysis
Bupropion	7.0	Cross-sectional survey[a]	45
Citalopram	30.0	Cross-sectional survey[a]	83
	72.7	Prospective study[b]	66
Duloxetine	23.4	Prospective study[c]	406
Fluoxetine	23.0	Cross-sectional survey[a]	245
	57.7	Prospective study[b]	279
Fluvoxamine	62.3	Prospective study[b]	77
Mirtazapine	24.4	Prospective study[b]	49
Nefazodone	8.0	Prospective study[b]	50
Paroxetine	25.0	Cross-sectional survey[a]	159
	70.7	Prospective study[b]	208
Sertraline	25.0	Cross-sectional survey[a]	161
	62.9	Prospective study[b]	159
Venlafaxine	30.0	Cross-sectional survey[a]	70
	67.3	Prospective study[b]	55

MDD major depressive disorder, *SD* sexual dysfunction,

[a] Prevalence rates; patients with MDD; subsample with patients free of other possible causes of SD; length of treatment varied (1 % less than a week; 24 % more than a week but less than 3 months; 17 % more than 6 months but less than 12 months; 28 % 1–3 years; 12 % more than 3 years) [87]

[b] Incidence rates calculated at 6 months of follow-up in participants free of SD prior to antidepressant medication [14]

[c] Incidence rates calculated at 6 months of follow-up in sexually active patients without SD at study enrolment [85]

study [84] were reported as number of first adverse events per 1,000 person-years, yet study authors did not ascertain participants' baseline status of sexual function prior to antidepressant medication. Patients were followed for an average duration of 5.7 months (range 1–365 days). Reported rates were higher for men than for women (loss of

Table 3 Incidence density rate of sexual dysfunction from two observational studies

Drug	Sexual dysfunction (incidence density rates)	Study design	*N* included in analysis
Nefazodone	9.6/1,000 PY	Prescription-event monitoring, database study[a]; only male SD (impotence or ejaculation failure), 1 study	4,418
Paroxetine	30/1,000 PY	Prescription-event monitoring, database study[a]; only male SD (impotence or ejaculation failure), 1 study	4,373
Sertraline	Loss of libido 31/1,000 PY; ejaculation failure 14/1,000 PY; impotence 9/1,000 PY; other sexual function disorder (male) 4/1,000 PY; anorgasmia (female) 6/1,000 PY; other sexual function disorder (female) 3/1,000 PY	Prospective observational study[b], 1 study	659

PY person years, *SD* sexual dysfunction

[a] Unclear whether study participants were free of SD prior to antidepressant medication; SD recorded in patient's record after the date of first prescription [86]

[b] Unclear whether study participants were free of SD prior to antidepressant medication; SD adverse events were ascertained by open question by clinician; start and stop dates of the events and assessment of severity ('mild,' 'moderate,' or 'severe') were recorded; patients were followed for an average duration of 5.7 months (range 1–365 days) [84]

libido 31 per 1,000 person-years; ejaculation failure 14 per 1,000 person-years; impotence 9 per 1,000 person-years; other male sexual function disorder 4 per 1,000 person-years; female anorgasmia 6 per 1,000 person-years; other female sexual function disorder 3 per 1,000 person-years).

4 Discussion

In this systematic review with data from 63 studies with low and moderate risk of bias (58 RCTs, five observational studies) with more than 26,000 patients treated with SGADs, we found some variation in SD associated with SGAD across drugs, yet no consistent differences between drugs. The methods used to assess adverse events varied considerably in efficacy trials, with about one-third of the trials included in our analysis providing no information on how harms-related data were collected or how sexual function was assessed, and only one-fifth of the trials using a specific method or instrument to determine SD. We rated the overall strength of evidence as low, indicating a low confidence that the evidence reflects the true effect.

In our network meta-analyses, most comparisons showed a similar risk of SD among included SGADs. However, CrIs were wide and included differences that would be considered clinically relevant. Since we conducted multiple comparisons and found differences in the method by which SD was defined and reported in individual trials, these results should be interpreted cautiously. Nevertheless, we observed three main patterns: bupropion had a statistically significantly lower risk of SD than some other SGADs, and both escitalopram and paroxetine showed a statistically significantly higher risk of SD than some other SGADs.

Our findings of varying rates of adverse events are consistent with previous studies. Authors of a systematic review and meta-analysis using data from 234 studies with direct and indirect comparisons of SGADs found no substantial differences in efficacy for the treatment of MDD; however, differences were found with respect to onset of action, frequency of adverse events, and rates of discontinuation [11]. With respect to the observed lower risk of SD for bupropion, our findings are consistent with a previous systematic review and meta-analysis comparing sexual adverse events of bupropion and three SSRIs (fluoxetine, paroxetine, sertraline), which found bupropion to cause significantly less SD than the comparator drugs while having similar effectiveness [15], a finding that was later replicated in a US cross-sectional study [87] and by authors of a comparative-effectiveness review and meta-analysis [11]. That patients treated with bupropion experience less frequent treatment-emergent SD has been explained with the lack of serotonergic activity of this drug (a selective norepinephrine and dopamine reuptake inhibitor). We found mirtazapine to be associated with a lower risk of SD in some pairwise comparisons. Mirtazapine, classified a noradrenergic and specific serotonergic antidepressant, has been described as having minimum effects on monoamine reuptake and was shown as less likely to be associated with sexual adverse events than SSRIs (fluoxetine, paroxetine, sertraline) [17].

As to the results of the descriptive analyses, we cannot draw firm conclusions about the comparative harms of SGADs. Using data from all trials reporting male-specific rates, rates of SD did not differ among included SGADs. We observed lower rates of SD across trials reporting only sex-specific rates as compared with those reported in observational studies. Underscoring the validity of the

estimate of SD associated with antidepressants reported in observational studies is the use of prospectively defined populations free from SD at baseline and the prospective assessment of sexual function with standardized and validated instruments. Conversely, the majority of the efficacy trials included in our analysis did not include such study procedures, thus making it difficult to establish treatment-emergent SD.

We found that reporting of adverse events related to SD in some of the RCTs included in our analysis was inconsistent and insufficient. In the majority of trials, investigators did not specify how harms-related information was gathered: definitions of adverse events of SD were often not explicit and clear. Also, investigators sometimes relied on scales to assess sexual function that lacked appropriate instrument development and validation. Additionally, authors often did not state the time frame of surveillance for adverse events, thus not specifying whether recording of adverse events occurred retrospectively or prospectively; also, only collecting data on adverse events for some time after the study intervention can capture longer latency. Only rarely did authors provide information on reasons for discontinuations and withdrawals due to adverse events. In none of the included RCTs did authors report on whether attribution of a specific cause was blinded to the assigned treatment. Also, it was difficult to establish from the data of the individual studies whether or how study investigators combined data for different subsets of SD adverse events into one outcome measure. Further, SD as a harm of SGAD treatment was chosen as a major primary outcome in only a minority of included studies and authors did not describe an a priori plan of statistical analysis. Problems of low power for uncommon events or adjustment for multiple outcomes were not addressed. Due to these shortcomings by investigators of individual trials included in our analysis, comparison of rates of SD, particularly from efficacy trials, must be made with great caution.

Our study has several limitations. Selection of studies was limited to English-language publications only. We did not account for observed differences in medication dosages, study duration, or any confounding from use of concomitant medications or comorbid conditions potentially affecting sexual function. The majority of included RCTs were of short duration so that an estimation of long-term effects of treatment-emergent SD is not possible. We also included RCTs that did not report any baseline assessment of SD. Thus, the reported rates of SD in these trials might have been inflated. Furthermore, only a small number of trials included in the network meta-analysis reported sex-specific rates, so we did not perform sex-specific analyses. Although type, severity, and clinical course of SD associated with antidepressant treatment can vary by gender [88], we were not able to assess the potential impact of gender on estimated SD adverse events. Results of both the network meta-analyses and the descriptive analyses should therefore be interpreted with caution. Network meta-analysis is a method that combines direct and indirect information across a network of RCTs and provides estimates of the (adverse) effect of each intervention relative to each other, whether or not they have been directly compared in trials, yet the key assumption is consistency between direct and indirect estimates of effect [89]. We cannot completely rule out that observed differences across trials might be due to violations of consistency assumptions. Still, in the absence of sufficient head-to-head evidence, network meta-analysis can serve as an additional tool to synthesize multiple treatments.

The onset of treatment-emergent SD or aggravation of a pre-existing SD may add to the distress of a patient with MDD, diminish the patient's quality of life, lead to the discontinuation of antidepressant treatment, and threaten the doctor–patient relationship, particularly if the patient has not been fully informed of such adverse events of SGAD [90]. Since evidence suggests that SGADs largely have similar efficacy, onset of action and specific adverse event profiles should guide a clinician's choice of a specific drug for an individual patient. Given the impact of SD on a patient's quality of life, clinicians should provide patients with all relevant information on possible sexual adverse events of a particular antidepressant and discuss patients' preferences and values before initiating antidepressant therapy. If patients are concerned about maintaining normal sexual functioning (e.g., younger patients), choosing an antidepressant that is less likely to be associated with SD should be discussed.

5 Conclusions

Based on the findings of this review using data from RCTs and observational studies on adverse events and SGADs, the comparative risk of SD associated with a specific antidepressant cannot be precisely determined. Nevertheless, we observed three main patterns in our network meta-analysis, with bupropion having a statistically significantly lower risk of SD than some other SGADs, and both escitalopram and paroxetine showing a statistically significantly higher risk of SD than some other SGADs. Clinicians should routinely discuss the possibility of SD as adverse events of SGADs and take into account patients' preferences when selecting an antidepressant and monitoring treatment. Further, we found inconsistencies and shortcomings in methods to determine and report adverse events of SD in many of the studies included in this

review, thus potentially contributing to biased estimates. Future studies on SGADs should be adequately powered to provide complete, reliable, accurate, and gender-specific information on adverse events and should be designed and conducted using systematic and valid methods to assess SD adverse events. Furthermore, reporting quality of adverse events of SD in published trials should be improved to help researchers better appraise the results of such trials and to help clinicians inform patients accordingly.

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