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Erectile and Ejaculatory Dysfunction Associated with Use of Psychotropic Drugs: A Systematic Review

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ABSTRACT

Background: Sexual dysfunction may be a side effect of treatment with antipsychotics, antidepressants, and other psychotropic drugs.

Aim: To review the evidence concerning male sexual dysfunctions in patients taking psychotropic drugs to provide specific information to nonpsychiatric physicians for the management of these dysfunctions.

Methods: A systematic search of Medline and Embase databases was performed up to October 15th, 2020. We included randomized controlled trials comparing the effects of psychotropic drugs versus placebo or versus another drug of the same class, for at least 5 weeks.

Outcomes: We considered studies whose male population could be evaluated separately from the female population and with a separate analysis of the different phases of the male sex cycle.

Results: We included 41 studies in the final review. There was a significant association between sexual dysfunction and antidepressant drug therapy, compared to placebo (decreased libido OR 1.89, 95% CI:1.40 to 2.56, 22 series, 11 trials, 7706 participants; erectile dysfunction OR = 2.28, 95% CI: 1.31 to 3.97; 11 trials, 3008 participants; ejaculatory dysfunction OR = 7.31, 95% CI: 4.38 to 12.20,19 trials, 3973 participants). When the effects of selective serotonin reuptake inhibitors (SSRIs) were evaluated separately from those of serotonin/norepinephrine reuptake inhibitors (SNRIs), the use of SNRIs but not that of SSRIs was characterized by significantly higher odds of erectile dysfunction compared to placebo. Only limited data were found regarding the effects of antipsychotics on the phases of the male sexual cycle, as it was shown that aripiprazole and risperidone showed lower and higher odds for erectile or ejaculatory dysfunction, respectively, compared to other atypical antipsychotics.

Clinical Implications: Treatment of male sexual dysfunction in patients taking psychotropics requires a basic knowledge of the different drugs that affect sexual function with different mechanisms.

Strengths & Limitations: The effects of psychotropic drugs on erectile function and ejaculation were evaluated separately. The great variability of the mechanisms of action makes it difficult to make comparisons between the effects of the different classes of psychotropic drugs.

Conclusions: Administration of antipsychotics affects male sexual function with different mechanisms, although the increase in prolactin values associated with the administration of first-generation antipsychotics and some atypical, such as risperidone, seems to play a primary role in determining male sexual dysfunction. Most antidepressants cause decreased libido, ejaculatory and erectile dysfunction, however the administration of SNRIs appears to be possibly associated with a specific risk of erectile dysfunction. **Trinchieri M, Trinchieri M, Perletti G, et al. Erectile and Ejaculatory Dysfunction Associated with Use of Psychotropic Drugs: A Systematic Review. J Sex Med 2021;18:1354–1363.**

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INTRODUCTION

Urologists and other nonpsychiatric physicians are sometimes consulted for the treatment of sexual dysfunction by patients on treatment with psychotropic drugs. The approach to these patients requires a basic knowledge of the mechanisms of action and side effects of psychotropic drugs.[1] Psychotropic drugs may be classified according to their therapeutic actions as antipsychotics, antidepressants, anxiolytics and mood stabilizers.[1]

Psychotropic drugs more frequently associated with sexual dysfunction are antipsychotics and antidepressants. Quality meta-analyses evaluated the evidence related to the presence of sexual dysfunction in patients taking antipsychotic and antidepressant drugs.[2-4] However, in most of these reviews, a separate analysis for the two sexes was not carried out and the effects of the drugs on the different phases of the male sexual cycle were not evaluated. The purpose of this study was to review the results of studies that evaluated the sexual dysfunction in male patients taking psychotropic drugs.

MATERIALS AND METHODS

This review was conducted in accordance with PRISMA checklist criteria.

PubMed and Embase databases were searched using the following MeSH terms: (Orgasm OR Ejaculation OR Erectile dysfunction OR Sexual dysfunction, Physiological) AND Psychotropic drugs; and the following filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review. The search was assessed as up to date on October 15, 2020. Handsearching was performed by screening for additional studies previously cited in published meta-analyses or systematic reviews[2-4] that analyzed the effects of psychotropic drugs on sexual function.

Screening of the retrieved records (by title and abstract first, and by full-text reading thereafter) and data extraction (using identical extraction tables) was performed by three independent reviewers.

In this systematic review we included randomized controlled trials (RCTs), with an open-label or single/double blinded design, which enrolled patients treated with antipsychotic or antidepressant drugs or other psychotropic drugs.

We included study reports, written in English, in which the effect of administering a single psychotropic drug was compared with that of a placebo or other drug of the same category. Only studies that included data concerning male subjects that could be considered separately from the female population were included. An inclusion criterion for this review was the availability of information concerning the onset of sexual dysfunction during treatment.

Non-controlled studies, observational studies and case-control studies were excluded.

The primary outcome considered for this review was the appearance of a dysfunction of one of the components of the male sex cycle (desire, erectile, ejaculation or orgasmic dysfunction).

Alterations in sexual desire were analyzed when described in the studies included in the review, even if male and female patients were not considered separately.

Studies reporting the occurrence of "sexual dysfunction" and lacking any detail of the dysfunction apart from this generic term, were excluded.

The quality of included studies was assessed by two independent reviewers. The risk of bias (ROB) was graded as high, low or unclear using the Cochrane Collaboration tool.[5]

Quantitative analysis of data was performed using the RevMan 5.4 software provided by Cochrane Collaboration. Meta-analysis was performed using a random−effects model.

Dichotomous data (presence/absence of decreased desire, erectile, ejaculatory or orgasmic dysfunction at specific study time points) and number of per-protocol or intent-to-treat patients were extracted to calculate odds ratio (OR), confidence intervals (CI) to odds-ratios and Z statistics according to Mantel-Haenszel methods.

Heterogeneity was assessed by calculating the I^2 value.

Publication bias was analyzed by visual inspection of funnel plots and by performing the Egger's regression and Begg's/Mazumdar correlation tests, using the MetaEssentials 1 software. The 'trim and fill' missing study imputation approach was applied to funnel plots and adjusted overall effect sizes were calculated.

RESULTS

A total of 238 records were retrieved from Medline, 144 from Embase, and 128 records by hand-searching. After de-duplication, 472 abstracts were subjected to title/abstract screening, and 223 records were rated as eligible. After full text reading, 41 RCTs met the inclusion criteria for this systematic review (either qualitative or quantitative analysis) (Figure 1).

The list of studies included in the review and a summary of their characteristics and outcomes are included in the Supplementary Materials 1.

Antipsychotics

Two studies (4 comparisons in total) were included in the quantitative analysis of the effect on erection and ejaculation of aripiprazole in comparison to other atypical antipsychotics and

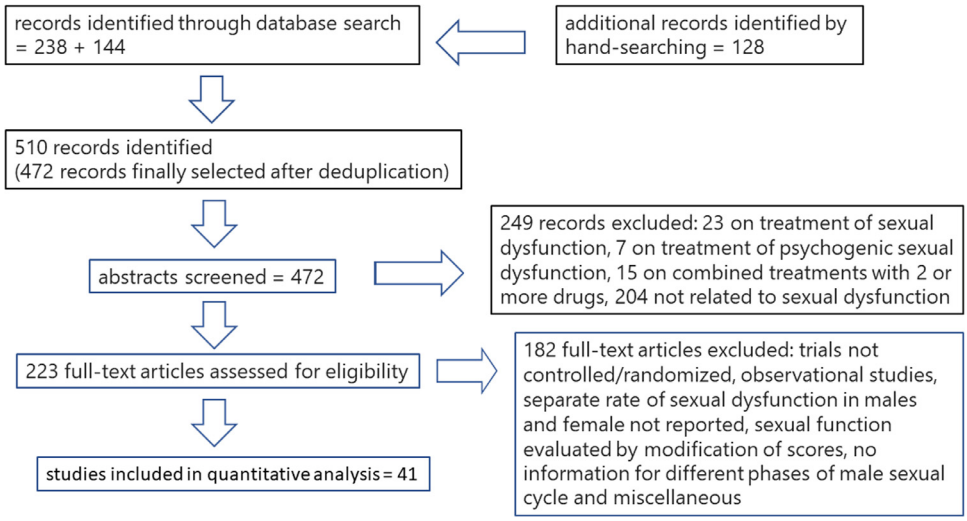

Figure 1. Flow diagram of the study selection process.

three studies in the analysis of the effect on erection or ejaculation of risperidone compared to other atypical antipsychotics.

Aripiprazole was associated with a lower odds for erectile (OR = 0.23, 95% CI: 0.08 to 0.66; 2 trials, 266 participants, I^2 = 0% Z = 2.75, $P < .006$) and ejaculatory (OR = 0.23, 95% CI: 0.08 to 0.67; 2 trials, 4 comparisons, 266 participants, I^2 = 0%, Z = 2.71, $P < .007$) disorders compared to other atypical antipsychotic agents. On the contrary, the odds ratio was not significant for loss of libido. Such evidence is to be considered preliminary due to the low number of included studies.

Risperidone showed a higher odds for erectile or ejaculatory dysfunction (composite endpoint) than other atypical antipsychotics (olanzapine and perospirone)(OR = 3.90, 95% CI: 1.32 to 11.56, 3 trials, 274 participants, I^2 = 0%, Z = 2.46, $P < .01$).

One study assessed the effects on sexual function of different dosages of quetiapine compared to placebo in patients with generalized anxiety disorder showing rates of erectile dysfunction progressively higher from 1 to 2.3% as the dosage of the drug increased. Similarly, loss of libido was observed at increasing rates in relation to the dose of quetiapine, while ejaculatory dysfunction was not associated with the dose of the drug.

Antidepressants Versus Placebo

Twenty-two studies were considered for the evaluation of the effect of antidepressants on sexual desire, erection and ejaculation in comparison to placebo.

Increased odds for decreased libido (OR = 1.89, 95% CI:1.40 to 2.56, 11 trials, 22 comparisons, 7706 participants, I^2 = 0%, Z=4.13, P=.0001), erectile dysfunction (OR = 2.28, 95% CI: 1.31 to 3.97; 11 trials, 20 comparisons, 3008 participants, I^2 = 5%, Z = 2.92, $P < .004$) and ejaculatory dysfunction (OR = 7.31, 95% CI: 4.38 to 12.20; 19 trials, 31 comparisons, 3973 participants, I^2 = 0%, Z = 7.62, $P < .00001$) was observed in patients subjected to antidepressant treatment compared to placebo (Figure 2, 3 and 4).

It is noticeable that in some series an increase in sexual desire has been episodically described in some cases after treatment with antidepressants.

Subgroup analysis was performed to separately assess the risk of decrease of sexual desire and erectile and ejaculatory dysfunction during treatment with different classes of antidepressants.

Use of serotonin/norepinephrine reuptake inhibitors (SNRIs) was characterized by significantly higher odds of erectile dysfunction compared to placebo (OR 6.96, 95% CI, 2.68 to 18.08, 1041 participants, 6 studies, 9 comparisons, I^2 = 0%, Z = 3.99, $P < .0001$) whereas selective serotonin reuptake inhibitors (SSRIs) were not associated with significant higher odds than placebo (OR 1.25, 95% CI, 0.63 to 2.46, 1889 participants, 5 studies, 10 comparisons, I^2 = 4%, Z = 0.64, $P = .52$). Conversely, both SSRIs (OR 5.65, 95% CI, 2.85 to 11.19, 2733 participants, 11 studies, 18 comparisons, I^2 = 0%, Z = 4.96, $P < .00001$) and SNRIs (OR 10.16, 95% CI, 4.70 to 21.97, 1198 participants, 9 studies, 12 comparisons, I^2 = 0%, Z = 5.89, $P < .00001$) presented higher odds of ejaculatory dysfunction when compared to placebo.

Odds for decreased libido was also significantly higher in both patients receiving SSRIs (OR = 2.05, 1.37 to 3.08, 5559 participants, 9 studies, 16 comparisons, I^2 = 0%, Z = 3.48, $P = .0005$) and SNRIs (OR = 1.69, 1.05 to 2.70, 1584 participants, 4 studies, 6 comparisons, I^2 = 0%, Z = 2.17, $P = .03$) compared to placebo.

Comparison Between Antidepressants

Thirteen studies dealt with various comparisons between different antidepressants drugs. Paroxetine showed higher odds for ejaculatory dysfunction compared to other SSRIs and the odds

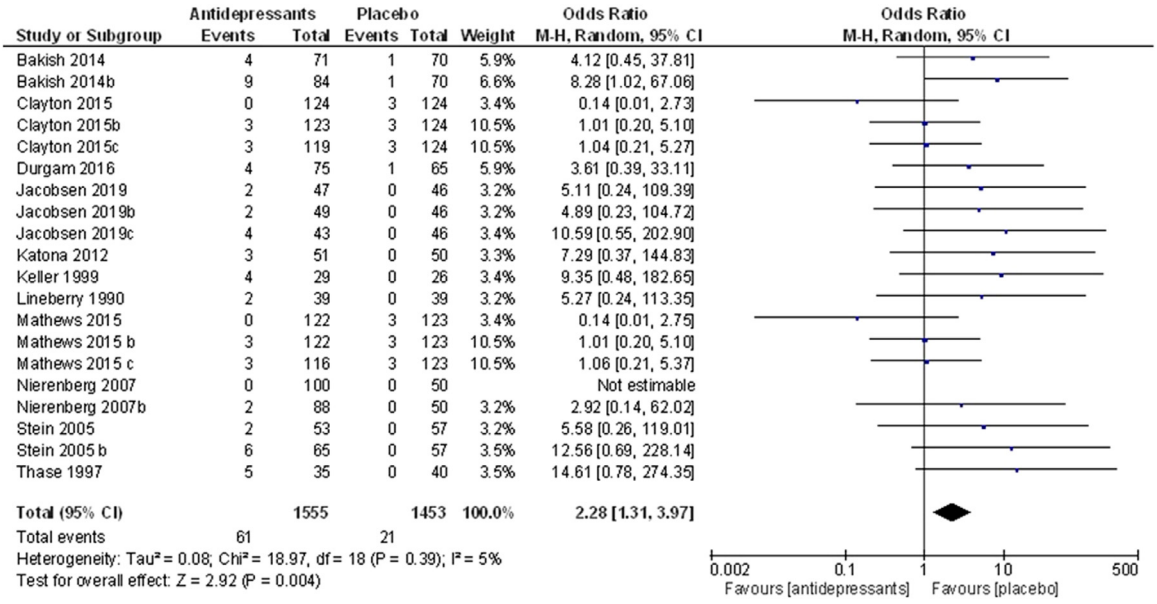

Figure 2. Forest plot Antidepressants versus Placebo: pooled analysis of randomized, placebo-controlled studies investigating the association between erectile dysfunction and antidepressant treatment, compared to placebo. The number of subjects allocated to treatment arms, the number of cases showing erectile dysfunction, the odds ratios, the 95% confidence intervals, the Z value for the overall effect, the significance of the pooled comparisons, and heterogeneity data (Chi^2 and I^2) are shown. Data to the right of the vertical no-effect line of the Forest plot represent increased odds for sexual dysfunction for antidepressants, and a more favorable performance of placebo. The diamond represents the overall effect size extending to the limits of the 95% confidence interval of the pooled odds-ratio. The risk of bias analysis for each included study is also shown.

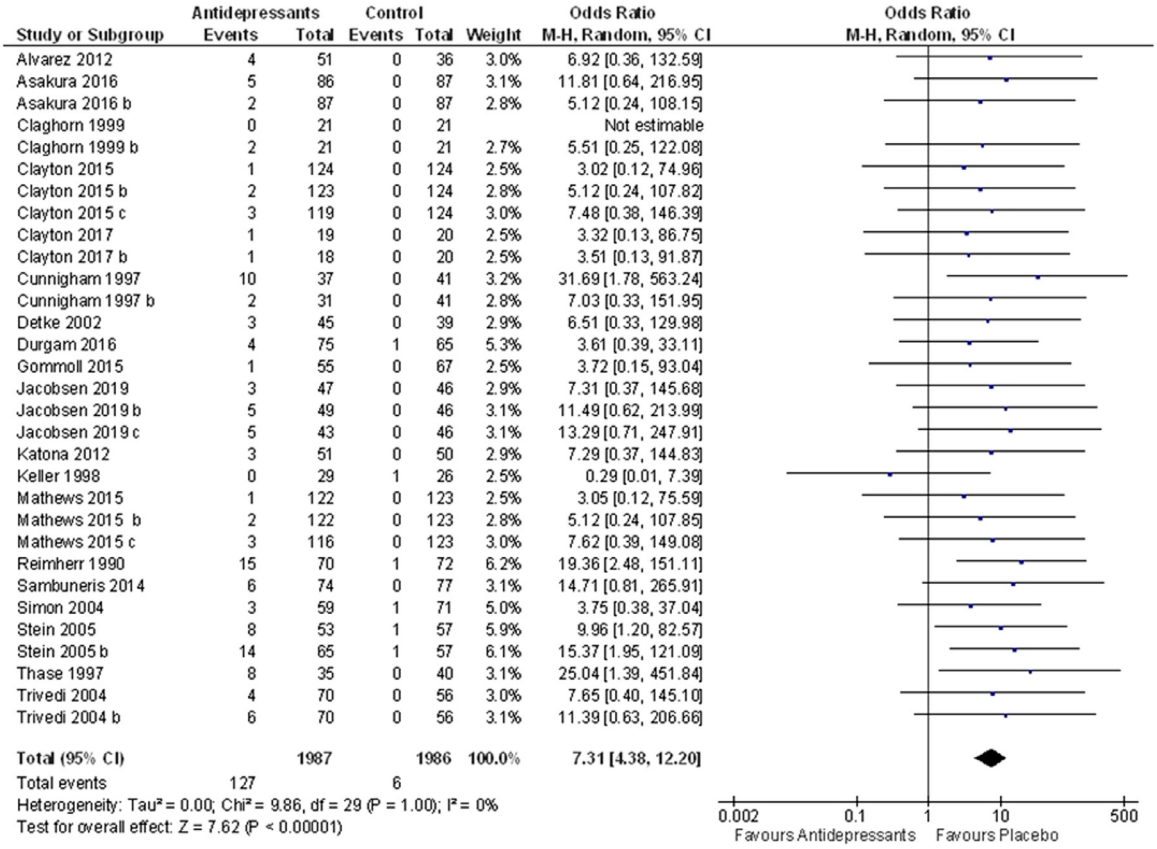

Figure 3. Forest plot Antidepressants versus Placebo: pooled analysis of randomized, placebo-controlled studies investigating the association between ejaculatory dysfunction and antidepressant treatment, compared to placebo.

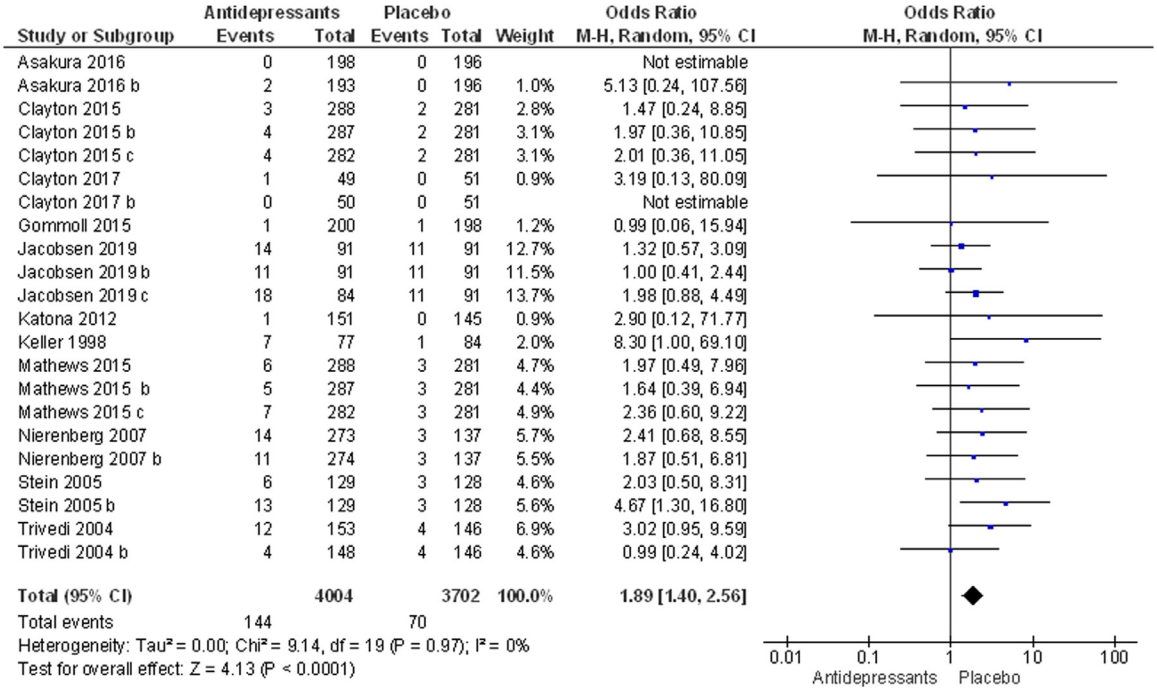

Figure 4. Forest plot Antidepressants versus Placebo: pooled analysis of randomized, placebo-controlled studies investigating the association between decreased sexual desire and antidepressant treatment, compared to placebo. Data to the right of the vertical no-effect line of the Forest plot represent increased odds for libido impairment upon exposure to antidepressant drugs.

ratio was statistically significant (OR 2.69, CI 1.34-5.39, 387 participants, 5 series from 4 studies, I^2 = 0%, Z = 2.79, *P* = .005). The same comparison did not result in a significant odds ratio for the erectile dysfunction (OR 1.27, CI 0.41-3.94, 204 participants, 2 series from 2 studies, I^2 = 0%, Z = 0.41, *P* = .69). In contrast to paroxetine, sertraline did not show significantly increased odds for ejaculatory dysfunction (OR 0.71, CI 0.28-1.79, 374 participants, 5 series from 4 studies, I^2 = 48%, Z = 0.73, *P* = .46). Administration of atypical antidepressants was associated with decreased odds for erectile dysfunction compared to SSRIs, and the odds ratio was statistically significant (OR 0.14, CI 0.02-0.80, 171 participants, 3 series from 3 studies, I^2 = 0%, Z = 2.20, *P* = .03). No difference in the odds for decreased sexual desire was observed between different antidepressants.

Risk of Bias

The evaluation of risk of bias demonstrated a good quality of studies included in the review (Supplementary Materials 1). Randomization methods were well reported and randomization sequences were adequately generated in 22 studies (22/41; low ROB), and the ROB was rated as unclear in 19 studies. In most studies on antidepressant drugs, the treatment allocation was adequately concealed (16/35) and blinding of participants and personnel (25/35) and blinding of outcome assessors (25/35) were adequate. In the remaining studies on antidepressants, randomization or blinding modalities were unclear, except for one study showing a high risk of bias. In contrast, all studies on antipsychotic drugs presented a high risk of bias due to inadequate concealment of allocations and blinding. In most studies (26/41) incomplete outcome data were adequately addressed and balanced across groups. The risk of selective reporting bias was considered low in most studies included in the analysis (unclear in 8 studies).

Finally, a possible other factor of bias could be the lack of specific questionnaires for measuring sexual function. Only 8 studies have been specifically designed for the evaluation of the emergence of sexual dysfunction and used validated questionnaires for its evaluation. This prompted us to apply a conservative random-effects model for meta-analysis. The main outcome of most studies was the evaluation of the effectiveness of treatment of psychiatric conditions, which was measured by specific questionnaires. The emergence of erectile or ejaculatory or orgasmic dysfunction was recorded among side effects that were evaluated by non-structured interviews or non-specific checklists. For this reason, the emergence of sexual dysfunction may have been underestimated in some studies.

Publication bias Funnel plots were generated to assess the presence of publication bias (Supplementary Materials 2). Visual inspection of the funnel plot of the meta-analysis comparing the association between treatment with any antidepressant and ejaculatory disfunction, compared to placebo, suggested asymmetry of the data distribution, which was confirmed by the Egger's and Begg's tests (Egger's, *P* = .015; Begg's, *P* < .0001). Significant

asymmetry was also detected for the comparison between SSRIs and placebo (Egger's, $P = .04$; Begg's, $P < .0001$). The Egger's and Begg's tests did not reach statistical significance when applied to other funnel plots. As a caveat to the interpretation of these asymmetry assessments, it should be kept in mind that whereas both Egger's and Begg's tests applied to the comparisons of antidepressants vs. placebo (endpoints: ejaculatory and erectile dysfunction) appear to be sufficiently powered, caution should be used when evaluating the significance of tests applied to comparisons which included a low number of studies, namely the comparisons between apiprazole or risperidone vs. other antipsychotics. The 'trim and fill' method applied to the funnel plot of the comparison between any antidepressant and placebo (erectile dysfunction endpoint) imputed 4 missing studies, and the adjusted estimate of the overall effect size was slightly reduced and lost statistical significance (OR: 1.76, 95% CI: 0.98 to 3.18), compared to the non-adjusted original effect size (OR: 2.28, 95% CI: 1.31 to 3.97). *Summary of findings* Tables of Supplementary Materials 3 include a summary of findings for each pooled comparison, and list illustrative comparative risks, relative effects and an evaluation of the quality of the evidence according to GRADE criteria. In almost all cases the quality of the evidence was rated as moderate or high. In the case of any antidepressant vs. placebo comparison (erectile dysfunction endpoint), the quality of the evidence was rated as low. Reasons for downgrading were mainly the presence of risk of bias that may affect the effect size and the presence of publication bias. In pooled analyses of few studies including a low number of patients, downgrading included the risk of imprecision of the results. The absence of heterogeneity in all meta-analyses (I^2 = 0, I^2 < 0) suggested that the quality of the evidence should not be downgraded for inconsistency in any case. The main reason for upgrading of the quality of the evidence in most cases was the magnitude of the effect, according to GRADE criteria. For the decrease/loss of libido endpoint, the quality of evidence was rated as low. This was mostly due to the presence of risk of bias and by the indirectness of evidence, due to the applicability of the findings obtained from meta-analysis of a mixed men-women population.

DISCUSSION

Sexual dysfunction in males can have several presentations as erectile, ejaculatory or orgasmic dysfunction or as a combination of two or all of these disorders. The physiology of the male sexual cycle is complex with separate pathways for the regulation of each of its phases that however are coordinated with each other in a complex way. The evaluation of the male patient with sexual dysfunction requires to distinguish the different alterations of the sexual cycle to recognize their pathological mechanisms and to plan an adequate treatment. Patients with mental disorders experience sexual dysfunction as result of psychopathology per se or as result of pharmacological treatment. The assessment of the prevalence of sexual dysfunction in psychiatric patients is difficult because patients tend to under-report their sexual discomfort, which often must be actively sought by the therapist. In patients hospitalized in psychiatric wards, the frequency of sexual dysfunction was described to be as high as 40%, with higher rates in patients with bipolar disorder and schizophrenia and lower rates in patients with substance abuse or anxiety disorders.[6] Sexual dysfunction in patients with schizophrenia may arise from negative symptoms (avolition, apathy) that limit the capability to establish interpersonal and sexual relationships.[7] In bipolar disorders, sexual dysfunction is related to the illness phase. In depressive episodes, patients experience reduction of sexual desire whereas manic or hypomanic episodes can intensify hypersexuality, with an increased incidence of risky sexual behaviors.[8] Sexual dysfunction can also be associated with anxiety, eating and personality disorders.[9]

Finally, sexual dysfunction may be a side effect of treatment with antipsychotics, antidepressants, mood stabilizers, and benzodiazepines.

Antipsychotics

Sexual disorders associated with antipsychotics in men include the reduction of the ability to obtain and maintain an erection, disorders of ejaculation (reduced volume, absence) and reduced intensity of orgasm. The main mechanism of action of antipsychotics is the blockage of dopamine receptors. Typical or first-generation antipsychotic drugs are defined by their ability to block dopamine (D2) receptors. When typical antipsychotics are administered, all D2 receptors are blocked, not only the ones located in the mesolimbic area, treating psychotic symptoms, but unfortunately also those in other areas of the brain. D2 antagonism in nigrostriatal pathways can be responsible for extrapyramidal side effects while D2 antagonism in mesocortical pathway can result in cognitive side effects and can be responsible for the exacerbation of negative symptoms like apathy and abulia, nuclear symptoms of schizophrenia. Finally, also tuberoinfundibular pathway is not spared by D2 antagonism, resulting in elevated levels of prolactin (PRL).[10] The mechanism of action of second-generation antipsychotics has been attributed to the combination of the D2 antagonism with the serotonin 5-HT2A antagonism which stimulates dopamine release in a range of pathways, thus reducing the side effects that a typical dopamine block would cause.[10] Sexual dysfunction may depend on direct action on dopaminergic receptors but may be affected by other possible effects of antipsychotic drugs that can also have anticholinergic, alpha-adrenergic and histaminic actions, that can increase sedation and reduce peripheral vasodilatation. Evidence-based knowledge of the effects of antipsychotic drugs on sexual function is limited by the difficulty to perform placebo-controlled studies in these patients. Instead, some randomized controlled studies comparing the effects of different antipsychotics are available. Both conventional and new−generation antipsychotic drugs can impair sexual function although conventional antipsychotics and risperidone have been associated with an

increased risk of sexual dysfunction compared to clozapine, olanzapine, quetiapine, and aripiprazole.[11] In fact, conventional antipsychotics and some second-generation antipsychotics such as risperidone and paliperidone increase PRL secretion, whereas clozapine and other atypical antipsychotics can successfully treat psychosis without increasing or even decreasing PRL levels.[12] A small meta-analysis of two studies did not show any variation in the risk of erectile dysfunction between first-generation antipsychotics and risperidone[13] whereas a second meta-analysis[3] demonstrated that typical antipsychotic agents as haloperidol and thioridazine but also some atypical agents as risperidone, clozapine and olanzapine were associated with higher rates of sexual dysfunction (40−60%) than quetiapine, ziprasidone, perphenazine, and aripiprazole (16−27%). A third meta-analysis demonstrated that risperidone may cause more sexual dysfunction than olanzapine (RR for abnormal ejaculation 4.36, RR for impotence 2.43).[14] Our pooled analyses confirmed that aripiprazole has a lower odds and risperidone higher odds of erectile or ejaculatory dysfunction, compared to other atypical antipsychotics. This finding could be explained by the pharmacological characteristics of risperidone as strong binding affinity for dopaminergic D2 receptors with secondary hyperprolactinemia and high affinity for $\alpha 1-$ and $\alpha 2-$adrenergic receptors. On the contrary, lower odds of sexual dysfunction associated with aripiprazole is explained by its partial D2 agonist activity and its lower affinity for $\alpha 1$ receptors.[10,15]

Antidepressants Antidepressant drugs may affect male sexual function by decreasing libido, delaying orgasm and less frequently causing arousal difficulties. First-generation antidepressants (tricyclic antidepressants and nonselective monoamine oxidase inhibitors) are associated with a high risk of sexual dysfunction. Antidepressants with serotonergic activity, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are also frequently associated with sexual dysfunction.[16] In fact, serotonergic activity interferes with dopaminergic transmission via serotonin receptors in the mesolimbic area, which is primarily associated with sexual desire and orgasm. Other possible causes of sexual dysfunction related to treatment with antidepressants are the reduction of nitric oxide synthetase and the anticholinergic action of some antidepressant drugs. Mirtazapine, bupropion and agomelatine have been associated with less sexual dysfunction compared with SSRIs. Some of these drugs (bupropion, mirtazapine) and buspirone, a non-benzodiazepine anxiolytic, have even demonstrated enhancement of sexual function in certain individuals. For this reason, they have been proposed as augmentation agents (antidotes) or substitution agents in patients with emerging sexual dysfunction after treatment with antidepressants.[17] Previously, three systematic reviews evaluated the effects of antidepressant drugs on sexual function.[2,4,18] A meta-analysis[2] showed that the rate of treatment-emergent sexual dysfunction among patients in antidepressant therapy was higher than placebo for first-generation antidepressants (imipramine, phenelzine) but also for many selective serotonin reuptake inhibitors (SSRIs) (sertraline, citalopram, paroxetine, fluoxetine, escitalopram and fluvoxamine) and for some serotonin and norepinephrine reuptake inhibitors (SNRI)(venlafaxine, duloxetine). On the contrary, it was demonstrated that sexual dysfunction rate associated with other antidepressants as agomelatine, amineptine, bupropion, moclobemide, mirtazapine, and nefazodone was not higher than in controls treated with placebo. Another meta-analysis[4] of 63 studies with more than 26,000 patients treated with second-generation antidepressants demonstrated a similar risk of sexual dysfunction for most drugs included in the study. Only bupropion showed a significantly lower risk of sexual dysfunction than other second-generation antidepressants, while the highest risk of dysfunction was observed for escitalopram and paroxetine (secondary to their well-known effect on nitric oxide synthetase).[19] The low rate of sexual side effects associated with bupropion treatment was confirmed by a review that included double-blind trials, open-label trials and anecdotal reports. The same review found limited evidence, mainly based on open-label studies, that bupropion can reverse SSRI-induced sexual side effects.[18] Information on the effects of antidepressants in the two sexes is more limited as well as data on the effects of antidepressants on different stages of the sexual cycle. When male patients were separately evaluated, Reichenpfader et al[4] demonstrated the highest weighted mean rates associated with sertraline (15.80%) and paroxetine (15.10%) followed by venlafaxine (12.30%) and duloxetine (10.80%) while other SSRIs (escitalopram, fluoxetine) had rates less than 10%. Unfortunately, their meta-analysis did not provided differentiation of results according to the different stages of the sexual cycle, although the increased relevance of SNRIs in male patients compared to their more limited effect on the whole population, including both males and females, could imply that SNRIs play a specific role in male-specific sexual dysfunctions as erectile dysfunction. Serretti and Chiesa[2] evaluated the effects of antidepressants on different stages of the sexual cycle showing that the drugs with the greatest effect on the arousal phase were citalopram, venlafaxine and paroxetine. When the effects on sexual dysfunction were assessed separately in males and females, venlafaxine was associated with the highest rate of dysfunction of arousal. This reappraisal of data from previous systematic reviews suggested us the hypothesis of a specific effect of SNRIs on erectile dysfunction. Our meta-analysis confirms that treatment with second generation antidepressants is associated with both erectile and ejaculatory dysfunction compared to placebo.

Similarly, odds for decreased sexual desire is higher in patients on treatment with second generation antidepressants compared to placebo. However, it should be noticed that the evaluation of the effect of psychotropic drugs on libido is a complex issue because many depressed patients experience a loss of sexual interest even when they are not taking any antidepressant medication.

On the other hand, depression and sexual desire are strictly interconnected and, whatever is cause-and-effect relationship between them, the treatment of one condition could improve

the other. Not surprisingly, an increase of sexual desire after antidepressant therapy was described in some patients.

When SSRIs and SNRIs were analyzed separately, a specific effect of SNRIs on erectile dysfunction was observed. In fact, odds for ejaculatory dysfunction and for loss of libido were higher in both patients treated with SSRIs or SNRIs compared to placebo, while odds for erectile dysfunction compared to placebo was higher for SNRIs but not for SSRIs. An explanation for this finding could be the increased adrenergic stimulus of cavernous bodies resulting from the inhibition of adrenaline reuptake. In fact, it has been shown that inhibition of norepinephrine reuptake can potentiate sympathetic vasoconstriction in a dosage-dependent fashion and cardiovascular effects of some SNRIs have also been reported.[20,21] This effect could alter the balance between vasoconstrictor agents that cause cavernosal smooth muscle contraction reducing blood inflow and vasodilators that relax smooth muscle promoting erection.[22]

Other Psychotropic Agents

Our database search has not recovered randomized studies on the effects of mood stabilizers or other psychotropic agents on sexual function, although, in the literature, lithium (in combination with benzodiazepines), some mood stabilizers, gabapentin and pregabalin and some benzodiazepines were associated with sexual dysfunction.[23]

Prevention and Therapy

Management of erectile or ejaculatory dysfunctions in patients treated with psychotropic drugs requires close collaboration between psychiatrist and urologist or andrologist, which implies a good knowledge of the mechanisms of action and the effects on the different stages of the male sexual cycle of psychotropic drugs.

The potential impact of pharmacological therapy on sexual function should be considered, although this is not easily predictable as it depends on the psychopathology and genetic characteristics of the individual.[24] Patients should be counselled on potential adverse effects of the drugs and regularly interviewed about the appearance of sexual dysfunction.

In patients on antipsychotic therapy, serum prolactin levels should be measured. In the presence of hyperprolactinemia, the psychiatrist should assess whether a dose reduction or switching to a prolactin-sparing antipsychotic is appropriate. First-generation antipsychotics, risperidone, paliperidone and amisulpride can be considered prolactin-inducing drugs, while clozapine, quetiapine, ziprasidone and aripiprazole are included among prolactin-sparing drugs.[25] Use of PDE5 inhibitors in patients on antipsychotic therapy has been shown to be effective and well tolerated.[26,27] In patients on antidepressant therapy with sexual dysfunction, discontinuation of treatment could involve serious risks; consequently, the non-psychiatric physician must be cautious in communication with the patient to avoid unintentionally encouraging the patient to self-suspend the drug. The psychiatrist should assess whether it is appropriate to withdraw treatment, temporary discontinue treatment (weekend holydays), reduce dosing or replace the drug. Our review confirmed that no erectile dysfunction was reported in patients on nefazodone or bupropion. Other studies not included in the review have previously shown the absence of sexual dysfunction after administration of agomelatine.[28,29] PDE-5 inhibitors (sildenafil, vardenafil, and tadalafil) have also been proven to be effective and well tolerated in the treatment of sexual dysfunction secondary to treatment with antidepressants.[30,31] It is always important to combine pharmacotherapy with psychotherapy providing a relational space of expression to assist the patient while elaborating a condition of psychological distress.

Limitations

A strength of our study was the separate evaluation of the effects of psychotropic drugs on erectile function and ejaculation. A limitation was the retrieval of a limited number of studies designed to have as main outcome the evaluation of the sexual side effect, being most studies primarily aimed to evaluate the efficacy of drugs on mental disorders. The presence of sexual dysfunction had been investigated by self-reporting of patients or by interview based on open questions or checklists, without using specific questionnaires for evaluation and scoring of sexual dysfunctions. This approach could underestimate the incidence of sexual disorders that could need to be actively researched. On the other hand, this limitation is common to all meta-analysis on this subject. Reichenpfader et al[4] reported that only 60% of the studies included in their review provided information on the method used to collect information of sexual dysfunction and only a few used a standardized validated tool to establish sexual dysfunction. On the other hand, some well-designed studies did not provide information to be used in the pooled analysis according to our criteria. Another limitation was the difficulty to make comparisons between the effects of the different classes of psychotropic drugs due to the great variability of the mechanisms of action .

CONCLUSIONS

Our systematic review did not retrieve any randomized placebo study to confirm the risk of sexual dysfunction after administration of antipsychotics. Antipsychotics, and in particular the latest atypical antipsychotics, have a complex mechanism of action depending on their variable affinity for dopaminergic, serotoninergic and adrenergic receptors. However, the increase in circulating prolactin, secondary to the administration of conventional and some atypical antipsychotics such as risperidone and paliperidone, has a primary role in conditioning sexual function in patients treated with antipsychotics as confirmed by our finding of higher odds of sexual

dysfunction of risperidone compared to other atypicals. The association of antidepressant treatment with erectile and ejaculatory dysfunction has been confirmed by placebo-controlled studies. The negative effect of both SSRIs and SNRIs on ejaculatory function has also been confirmed, while erectile function appeared to be mostly affected by the administration of SNRIs probably for peripheral adrenergic stimulation. This unexpected finding needs to be confirmed by studies specifically designed to study erectile function with validated questionnaires in patients treated with these drugs.

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Margherita Trinchieri: Conceptualization, Data Curation, Writing—original Draft Preparation; Martina Trinchieri: Conceptualization, Data Curation, Writing—Original Draft Preparation; Gianpaolo Perletti: Methodology, Formal Analysis, Writing—Review and Editing; Vittorio Magri: Data Curation; Konstantinos Stamatiou: Data Curation; Tommaso Cai: Data Curation; Emanuele Montanari: Supervision; Alberto Trinchieri: Conceptualization, Methodology, Formal Analysis, Writing—Original Draft Preparation, Writing—Review and Editing.

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SUPPLEMENTARY MATERIALS

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