Review

Strategies for managing antidepressant-induced sexual dysfunction: Systematic review of randomised controlled trials

Matthew J. Taylor *, Lisa Rudkin, Keith Hawton

University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

Abstract

Background: This review was undertaken to assess the effectiveness of management strategies for sexual dysfunction caused by antidepressant medication.

Methods: Electronic databases and reference lists were searched, and pharmaceutical companies and experts contacted to identify randomised controlled trials comparing management strategies for antidepressant-induced sexual dysfunction.

Results: Fifteen trials involving 904 people were included. One trial involving 75 people with sexual dysfunction due to sertraline assessed changing antidepressant. Switching to nefazodone was significantly less likely to result in the re-emergence of sexual dysfunction than restarting sertraline (RR 0.34, 95% CI 0.15 to 0.6). Meta-analysis of two trials involving 113 men with erectile dysfunction found that the addition of sildenafil resulted in less sexual dysfunction at endpoint on rating scales including the International Index of Erectile Function (IIEF) (WMD 19.36, 95% CI 15.00 to 23.72). Another trial found the addition of bupropion led to improved scores on the Changes in Sexual Functioning Questionnaire desire–frequency subscale (WMD 0.88, 95% CI 0.21 to 1.55). In a further study the addition of tadalafil was associated with greater improvement in the erectile function domain of the IIEF than placebo (WMD 8.10; 95% CI 4.62 to 11.68). Other augmentation strategies failed to show statistically significant improvements in sexual dysfunction compared with placebo.

Discussion: The currently available evidence is rather limited, with small numbers of trials assessing each strategy. However, while further randomised data is awaited, for men with antidepressant-induced erectile dysfunction, the addition of sildenafil appears to be an effective strategy.

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* Corresponding author. Tel.: +44 1865 223635; fax: +44 1865 251076.
  E-mail address: matthew.taylor@psych.ox.ac.uk (M.J. Taylor).

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1. Introduction

The reported incidence of sexual dysfunction associated with all antidepressants varies considerably, but several studies have indicated that such problems are common (Baldwin et al., 1997; Balon, 1993). These sexual side effects can considerably affect a person's lifestyle, and where this results in reduced compliance with medication, lead to less effective treatment of the primary psychiatric disorder.

The types of sexual dysfunction related to antidepressants can be classified as follows:

1. Altered sexual desire, including loss or lack of desire
2. Orgasmic and ejaculatory dysfunction, including anorgasmia, hyperorgasmia, painful orgasm and inhibited ejaculation
3. Erectile problems, including erectile dysfunction (impotence), priapism and painful erection

4. Other problems, including problems of sexual arousal, reduced sexual satisfaction, lubrication, dyspareunia and vaginismus.

Identifying antidepressant induced sexual dysfunction can be complicated by the association of sexual dysfunction with some disorders that antidepressants are used to treat. For example, depression is associated with increased rates of reported sexual dysfunction even when no treatment is being received (Angst, 1998).

Sexual dysfunction has been reported with all classes of antidepressant. Reported rates of sexual dysfunction are typically underestimates, as sexual side effects are often not specifically asked about in drug trials, while direct questioning can reveal higher rates than are spontaneously reported (Montejo-Gonzalez et al., 1997). A recent review of the prevalence of antidepressant-induced sexual dysfunction (Montgomery et al., 2002) found a number of methodological problems with the identified studies. These included the frequent absence of comparison groups or baseline assessments, and inconsistent definitions of sexual dysfunction between studies, with only one study using a validated rating scale.

The majority of studies directly comparing rates of sexual dysfunction between different antidepressants have involved selective serotonin reuptake inhibitors (SSRIs). Generally, trials have reported no significant differences among SSRIs in rates of sexual dysfunction, with rates of 54–65% reported in one study (Montejo-Gonzalez et al., 1997). In randomised trials, nefazodone and bupropion have been associated with less sexual dysfunction than the SSRI sertraline (Feiger et al., 1996; Croft et al., 1999), and reboxetine with greater sexual satisfaction than the SSRI fluoxetine (Clayton et al., 2003). The monoamine oxidase inhibitor (MAOI), moclobemide, was more commonly associated with increased sexual desire than the tricyclic antidepressant, doxepin (Philipp et al., 1993). Further information on rates of sexual dysfunction with antidepressants can be found elsewhere (Montgomery et al., 2002; Gregorian et al., 2002).

Best estimates suggest that around 5% of the UK adult population take an antidepressant (Donoghue and Tylee, 1996; Jick et al., 1995), with similar prescribing rates in the USA (Grunebaum et al., 2004).

Given the wide variation in the prevalence figures reported, it is impossible to give an overall figure for sexual side effects with antidepressant treatment. However, if, at a conservative estimate, the incidence of serious sexual side effects was 10%, then over one million people in the UK and USA are potentially affected.

The mechanisms by which antidepressants cause sexual dysfunction involve complex multi-system interactions, which are not entirely understood, and psychological factors must also be considered. The main neurotransmitters involved are serotonin, acetylcholine, noradrenaline, and dopamine. The adverse sexual effects may be caused centrally or peripherally and may result from the change in function of one or more neurotransmitter.

Many management strategies have been tried to treat antidepressant-induced sexual dysfunction, including avoiding the use of the antidepressant, waiting, stopping or reducing the drug, switching to another class such as mirtazapine, or adding in a further drug. However, these management strategies themselves may have their own side effects and tolerability problems, or adversely affect the primary psychiatric disorder. Since other types of therapies, e.g. psychological treatments or mechanical devices (Hawton, 1995; Canadian Urological Association Guidelines, 2002), are also used for sexual dysfunctions in general, they might also be of use here.

This review aims to summarise the current evidence regarding potential strategies for managing antidepressant induced sexual dysfunction, in terms of both how well the sexual dysfunction responds, and also the risks such as side effects or worsening of the condition for which the antidepressant was initially prescribed. This should assist patients and their clinicians in deciding how best to manage these common problems.

2. Methods

2.1. Search strategy

Searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Group Controlled Trials Register, the Cochrane Controlled Trials Register, MEDLINE, CINAHL, EMBASE, and PsycINFO

were performed. Reference lists in identified trials and in other articles on sexual side effects, including relevant conference proceedings, were checked. Experts in sexology (J. Bancroft, R. Basson, J. Heiman, R. Rosen) and pharmaceutical companies were contacted for advice on possible further trials.

2.2. Study characteristics

Included studies were randomized controlled trials of patients with sexual dysfunction as a result of being treated with an antidepressant (except mood stabilisers) on any dose regime, comparing any management strategy for the dysfunction–pharmacological, psychological or otherwise–to any alternative strategy, including use of placebo. The primary outcome measure was changes, or post-treatment differences, in the severity of the identified sexual dysfunction. Secondary outcomes were changes, or post-treatment differences, in sexual satisfaction and functioning, dropout rates of specific therapies as a measure of their acceptability, and change, or post-treatment differences, in the primary psychiatric condition for which the antidepressant was being prescribed (based on symptom ratings). Study quality was assessed using a rating scale (Moncrieff et al., 2001). The processes of trial selection, quality assessment, and data extraction were each performed by two reviewers independently.

2.3. Statistical analysis

Data was analysed using Review Manager 4.2 software (Cochrane Collaboration, Oxford, UK). For binary efficacy outcomes, a pooled relative risk (with 95% confidence intervals), calculated using a fixed effects model, is reported. For continuously distributed outcomes, the weighted mean difference was calculated. We used intention-to-treat data when available. Where this was not possible, endpoint data for trial completers was used. Non-quantitative data are presented descriptively.

Statistical heterogeneity between studies was assessed using the Q statistic (Dersimonian and Laird, 1986). The analyses are based on trial endpoint data except where specified. Differences between trials in the times of assessment are reported. For trials of a cross-over design where only pooled data from both periods were available these were used.

3. Results

Fifteen studies were identified which met the inclusion criteria for this review (see Fig. 1). Thirteen studies were of parallel group design, and two studies used a crossover design (Nelson et al., 2001; Meston, 2004). Two studies (Nurnberg et al., 2001; Segraves et al., 2004) were individual patient meta-analyses of several previous parallel group trials, assessing efficacy in the subgroup receiving antidepressants. The total number of participants randomized in the 15 studies was 904. Characteristics of the included studies are summarized in Table 1.

Four studies (Michelson et al., 2000, 2002; Meston, 2004; Jespersen et al., 2004) included only female participants, and four studies (Ginsberg et al., 2001; Nurnberg et al., 2001, 2003; Segraves et al., 2004) included only male participants. The remaining seven studies recruited both male and female participants. Two studies (Nurnberg et al., 2001; Segraves et al., 2004) specified a single sexual dysfunction, erectile dysfunction. All other studies included participants with more than one type of sexual dysfunction. Two studies (Nurnberg et al., 2001; Segraves et al., 2004) did not specify that the erectile dysfunction was due to the antidepressant medication; they reported pooled data from trial participants who were taking antidepressant medication when recruited to the studies with sexual dysfunction. This might therefore be considered antidepressant-associated sexual dysfunction.

In the majority of studies, the participants had wholly or partially recovered from the disorder for which antidepressants had been prescribed, most commonly depression. Participants in two studies were diagnosed with depression at inclusion (Kang et al., 2002; Landen et al., 1999) and for two studies insufficient details were available to clarify this point (DeBattista et al., 2001; Segraves et al., 2004).

3.1. Intervention

The range of intervention types assessed was limited. The majority of studies assessed the addition of further medication to ongoing antidepressant treatment using a placebo control. In two studies (Michelson et al., 2000, 2002) there was more than one active treatment arm in addition to the placebo arm of the trial. The additional medications assessed comprised
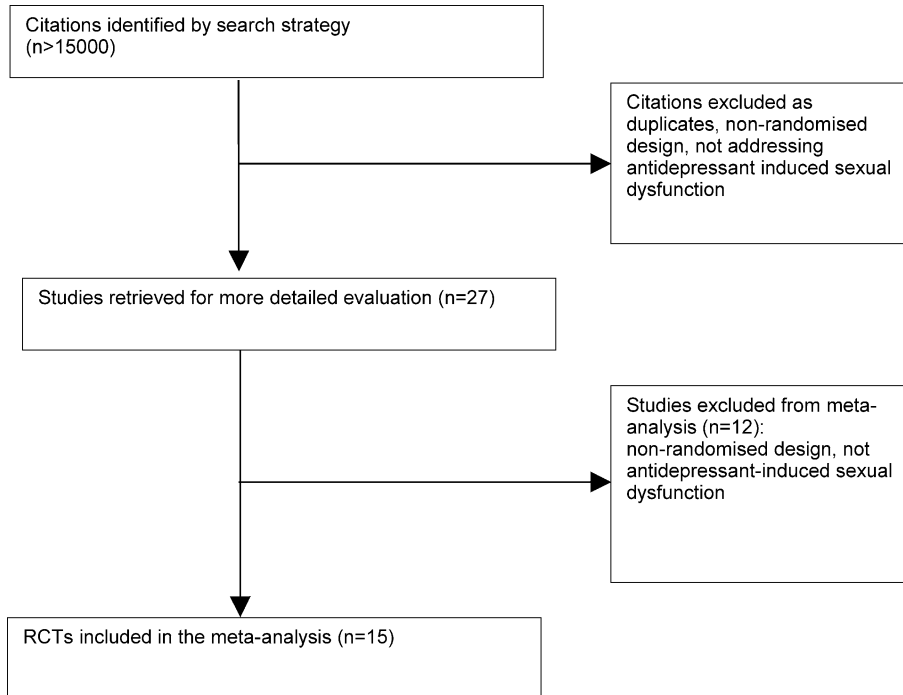
Fig. 1. Flow diagram of trial flow (see QUOROM statement; Moher et al., 1999).

antidepressants with differing modes of action (bupropion, mirtazapine), phosphodiesterase inhibitors (sildenafil, tadalafil), other agents affecting the serotonin, noradrenaline, and dopamine systems (amantadine, buspirone, ephedrine, granisetron, olanzapine, yohimbine), and *Ginkgo biloba*.

One study (Ferguson et al., 2001) assessed changing from an SSRI to an antidepressant with a different mode of action, nefazodone. No studies were identified which assessed the use of drug holidays, psychological interventions, or mechanical devices to treat the sexual dysfunction.

3.2. Outcome measures

A variety of outcome measures was used to assess initial sexual function and response to treatment. These included both self-assessment and externally rated measures, not all of which had independent publications reporting their psychometric properties. Measures of psychiatric symptoms were more consistent, and included the Hamilton Rating Scale for Depression (HAM-D, Hamilton, 1960), the Beck Depression Inventory (Beck et al., 1961), the Hamil-

ton Rating Scale for Anxiety (Hamilton, 1959) and the State-Trait Anxiety Inventory (Spielberger et al., 1983).

3.3. Methodological quality of included studies

3.3.1. Allocation and blinding

Of the 15 included studies, all used randomized allocation, although one (Landen et al., 1999) was a subgroup analysis of a larger randomized trial, and two others (Nurnberg et al., 2001; Segraves et al., 2004) were subgroup analyses of the pooled results of several trials of the same design. Little information was given in the published reports regarding the methods used to maintain concealment of allocation. All included studies report the use of blinding for subjects and assessors.

3.3.2. Reporting of withdrawals and dropouts

The majority of included studies did not include or did not report inclusion of withdrawals or dropouts in analyses. In five of the studies (Ferguson et al., 2001; Ginsberg et al., 2001; Michelson et al., 2002; Nurnberg et al., 2001, 2003) withdrawals and dropouts

Table 1
Characteristics of included studies

Study	Design	Number of participants	Antidepressant used	Primary psychiatric disorder	Interventions	Duration (weeks)
Clayton 2004	Double blind, parallel arm, multicentre (3 sites)	55 (48 women, 7 men)	SSRI >2/12	Hamilton Rating Scale for Depression<11	Bupropion SR 150 mg twice daily or placebo twice daily, in addition to SSRI	4
DeBattista 2001	Double blind, parallel arm	42	SSRI	Unclear	Bupropion SR 150 mg once daily or placebo; in addition to current SSRI	Unclear
Ferguson 2001	Double blind, parallel arm, multicentre (9 sites)	75 (34 women, 38 men)	Sertraline	Judged clinically stable and able to discontinue sertraline	Nefazodone 100mg twice daily increasing to 200 mg after 1 week or sertraline 50 mg once daily increasing to 100 mg after 1 week and placebo at night	10
Ginsberg 2001	Double blind, parallel arm	23 men	SRI	Clinically recovered mood or anxiety disorder	Sildenafil 50–100 mg once daily or placebo for 8 weeks	8
Jespersen 2004	Double blind, parallel arm	12 women	Unclear	Past diagnosis of depression by Mini International Neuropsychiatric Interview. Clinical Global Impression score of 1 or 2	Granisetron (dose not specified) or placebo	2
Kang 2002	Double blind, parallel arm, single centre	37 (10 women, 27 men)	Unclear	Depressive disorder (without psychotic features) or anxiety disorder	*Ginkgo biloba* 120 mg/day increasing to 160 mg/day after 2 weeks, and increasing to 240 mg/day after 4 weeks, or placebo	8
Landen 1999	Subanalysis of one double blind, parallel arm, multicentre (12 centres)	47 (27 women, 20 men) (from total of 119 randomised)	Citalopram or paroxetine	DSM-IV major depressive episode, failed to respond	Buspirone 20–60 mg od or placebo, in addition to fixed dose usual SSRI	4
Masand 2001	Double blind, parallel arm	31	SSRI (>6/52)	Hamilton Rating Scale for Depression score <10	Bupropion SR 150 mg or placebo, in addition to SSRI	3
Meston 2004	Double blind, crossover design	29 women	SSRI >10/52	Treatment of depression successful	Ephedrine 50mg once daily or placebo	8

Michelson 2000	Double blind, parallel arm, multicentre (3 sites)	67 women	Fluoxetine	Hamilton Rating Scale for Depression less than 11	Buspirone 10 mg twice daily increasing to 15 mg, or amantadine 50 mg once daily increasing to 50mg twice daily, or placebo twice daily, in addition to fluoxetine	12
Michelson 2002	Double blind, parallel arm. Multicentre (12 centres)	148 women	Fluoxetine	Condition for which fluoxetine prescribed responded satisfactorily	Mirtazapine 15 mg once daily increasing to 30 mg, or yohimbine 5.4 mg once daily increasing to 10.8 mg, or olanzapine 2.5 mg once daily increasing to 5 mg, or placebo, in addition to fluoxetine	10
Nelson 2001	Double blind, crossover design	38 (18 women, 2 men, 18 gender not stated)	SSRI	Hamilton Rating Scale for Depression score less than 10	Granisetron 1–2 mg as required or placebo, in addition to SSRI	6
Nurnberg 2001	Retrospective subanalysis of 10 double-blind, parallel-arm trials	98 men (from total of 3414 randomised)	Unclear	No uncontrolled psychiatric illness	Sildenafil 5–200 mg once daily or placebo once daily	12–26
Nurnberg 2003	Double blind, parallel arm. Multicentre (3 centres)	90 men	SSRI	DSM-IV major depressive disorder in remission, Hamilton Rating Scale for Anxiety score less than 11, Hamilton Rating Scale for Depression score less than 11	Sildenafil 50 mg as required increasing to 100 mg as required or placebo. In addition to SSRI	6
Segraves 2004	Retrospective subanalysis of 11 double blind, Multicentre (174 centres). 12 weeks	111 men (from total of 2102 randomised)	Unclear	Unclear	Tadalafil 10 mg or 20 mg or placebo	12

SSRI—Selective Serotonin Reuptake Inhibitor; SRI—Serotonin Reuptake Inhibitor; DSM—Diagnostic and Statistical Manual of the American Psychiatric Association.

were included in analyses by carrying forward prior observations.

3.4. Treatment comparisons

The 15 included studies comprised 16 different treatment comparisons. Further information was provided by the authors of six studies (Clayton et al., 2004; Ferguson et al., 2001; Ginsberg et al., 2001; Michelson et al., 2002; Nurnberg et al., 2003; Segraves et al., 2004). Measures of sexual function and satisfaction are reported below. Differences in dropout rates between groups, where reported (see Table 2), did not reach statistical significance, except for an increased dropout rate with mirtazapine compared with both placebo and yohimbine in one study (Michelson et al., 2002). Psychiatric symptoms following treatment were reported in three studies (see

Table 2
Overall dropout rates

Comparison	Studies	Relative risk of dropout (95% confidence interval)
Nefazodone vs. sertraline	Ferguson 2001	0.83 (0.43 to 1.60)
Sildenafil vs. placebo	Ginsberg 2001 Nurnberg 2003	0.72 (0.28 to 1.86)
Bupropion vs. placebo	Masand 2001 Clayton 2004	2.1 (0.78 to 5.72)
Buspirone vs. placebo	Landen 1999 Michelson 2000	2.09 (0.32 to 13.59)
Granisetron vs. placebo	Jespersen 2004	6.67 (0.39 to 114.78)
Olanzapine vs. placebo	Michelson 2002	3.59 (0.80 to 16.21)
Mirtazapine vs. placebo	Michelson 2002	6.5 (1.56 to 27.07)*
Yohimbine vs. placebo	Michelson 2002	2.23 (0.43 to 11.43)
Amantadine vs. placebo	Michelson 2000	1.11 (0.07 to 16.47)
Ginkgo biloba vs. placebo	Kang 2002	1.33 (0.51 to 3.43)
Amantadine vs. buspirone	Michelson 2000	0.55 (0.05 to 5.62)
Olanzapine vs. mirtazapine	Michelson 2002	0.55 (0.25 to 1.25)
Olanzapine vs. yohimbine	Michelson 2002	1.61 (0.52 to 5.04)
Mirtazapine vs. yohimbine	Michelson 2002	2.92 (1.04 to 8.18)*

* Higher dropout rate in mirtazapine arm ($p < 0.05$).

Table 3
Endpoint ratings of mental state

Comparison	Study	Measure	Difference (95% confidence interval)
Nefazodone vs. sertraline	Ferguson 2001	Endpoint HAM-D	−0.32 (−1.64 to 0.99)
Sildenafil vs. placebo	Nurnberg 2003	Endpoint HAM-D	−2.00 (−3.43 to −0.57)*
Bupropion vs. placebo	Clayton 2004	Endpoint HAM-D	−0.60 (−2.62 to 1.42)

HAM-D (Hamilton, 1960)—Hamilton rating scale for depression.
* Lower scores in sildenafil arm ($p < 0.05$).

Table 3). A statistically significant difference between groups was seen in only one of these studies, where the result favoured sildenafil (Nurnberg et al., 2003).

3.4.1. Nefazodone vs. sertraline

One trial (Ferguson et al., 2001) compared the effect of changing antidepressant to nefazodone to the effect of restarting sertraline after a 2-week washout period in which sertraline-induced sexual dysfunction had resolved. On a physician rated measure, sexual dysfunction was significantly less likely to re-emerge on treatment with nefazodone compared with restarting sertraline, Relative Risk (RR) 0.34 (95% confidence interval (CI) 0.19 to 0.60). This means the Number Needed to Treat (NNT) with nefazodone for one additional person to avoid re-emergence of sexual dysfunction was 2 (95% CI 2 to 4). This benefit of using nefazodone was seen by the end of the first week of treatment. However, differences in patient rated overall sexual satisfaction did not achieve statistical significance: weighted mean difference (WMD) 17.22 (95% CI −4.57 to 39.01).

3.4.2. Sildenafil vs. placebo

Three trials (Nurnberg et al., 2001, 2003; Ginsberg et al., 2001) were identified that compared the effect of augmenting antidepressant treatment in men with sildenafil or placebo.

Pooled data from Nurnberg et al. (2003) and Ginsberg et al. (2001) (see Fig. 2) indicate that participants receiving sildenafil had less sexual dysfunction at trial endpoint when rated by the International Index of Erectile Function (IIEF, Rosen et al., 1997) (WMD 19.36, 95% CI 15.00 to 23.72), or the Arizona Sexual Experiences Scale (ASEX, McGahuey et al., 2000) (WMD −4.62, 95% CI −6.29 to −2.95). Results
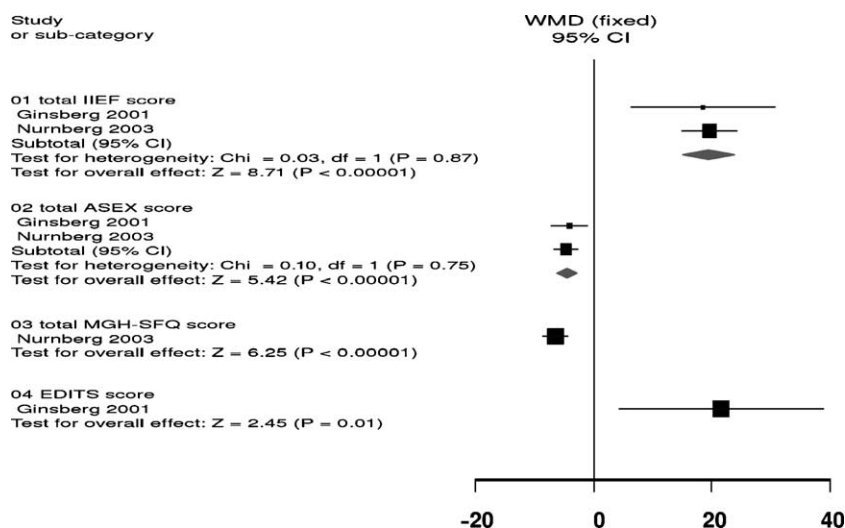
Fig. 2. Sildenafil vs. placebo; continuous outcome measures of sexual function. Weighted mean difference (WMD) with 95% confidence intervals.

from the individual studies also favoured sildenafil on the Massachusetts General Hospital—Sexual Functioning Questionnaire (MGH-SFQ, Labbate and Lare, 2001) (WMD −6.70, 95% CI −8.80 to −4.60 (Nurnberg et al., 2003)), and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS, Althof et al., 1999) (WMD 21.60, 95% CI 4.30 to 38.90 (Ginsberg et al., 2001)). This effect does not appear to have been limited to a reduction in erectile dysfunction alone, since in Nurnberg et al. (2003) improvements were seen on all subscales of both the patient-rated ASEX scale, and the clinician-rated MGH-SFQ. On two items of the IIEF on which data was available from both Nurnberg et al. (2001, 2003), there was no statistically significant heterogeneity in the results ($p > 0.2$).

In Nurnberg et al. (2003), participants randomized to sildenafil were less likely to rate their sexual function as other than much or very much improved after 6 weeks of treatment (RR 0.48, 95% CI 0.34 to 0.66). This means the Number Needed to Treat with sildenafil for one additional person to rate their sexual function as much or very much improved was 2 (95% CI 2 to 4). In Ginsberg et al., the number of men with continuing sexual dysfunction defined by the ASEX scale at trial endpoint tended to favour sildenafil, but a benefit of placebo was not excluded (RR, 0.18, 95% CI 0.03 to 1.30).

3.4.3. Bupropion vs. placebo

Three trials compared the effect of augmenting antidepressant treatment with bupropion or placebo (Clayton et al., 2004; DeBattista et al., 2001; Masand et al., 2001). In one trial (Clayton et al., 2004) endpoint Changes in Sexual Functioning Questionnaire (CSFQ, Clayton et al., 1997) desire–frequency scores favoured bupropion (WMD 0.88, 95% CI 0.21 to 1.55). In a second trial (Masand et al., 2001) there was no significant difference in the numbers of participants failing to achieve 50% improvement on ASEX by the trial endpoint (RR 1.07, 95% CI 0.94 to 1.23). A preliminary report of the third trial (DeBattista et al., 2001) indicates an improvement in sexual arousal on treatment with bupropion, but the details of treatment effect and rating methodology are unclear.

3.4.4. Buspirone vs. placebo

Two trials compared the effect of augmenting antidepressant treatment with buspirone or placebo (Landen et al., 1999; Michelson et al., 2000). In one study of men and women who had failed to respond to antidepressant treatment for depression (Landen et al., 1999) there was no statistically significant difference between the two groups in the numbers failing to achieve remission of sexual dysfunction at 4 weeks (RR 0.60, 95% CI 0.35 to 1.01), although the trend favoured buspirone. The other study (Michelson et al.,

2000) of women who had recovered from depression found no statistically significant difference in patient rated overall function (sexual) between the treatment and placebo groups (WMD 3.1, 95% CI −38.33 to 44.53).

3.4.5. Granisetron vs. placebo

Two trials (Jespersen et al., 2004; Nelson et al., 2001) compared augmentation of antidepressant treatment with granisetron to the addition of placebo. Data from Nelson et al. (2001) are derived from both crossover periods of the trial. There was no statistically significant difference in change from baseline on Sexual Side Effects Scale (SSES) scores between the two groups in one trial (WMD 0.10, 95% CI −2.22 to 2.42; Nelson et al., 2001). The other trial reported no statistically significant difference in endpoint scores on the Arizona Sexual Experience Scale or Feiger Sexual Function and Satisfaction Questionnaire (ASEX WMD 7.90 95% CI −1.87 to 17.67; FSFSQ; Feiger et al., 1996, WMD 1.60 95% CI −5.46 to 8.66; Jespersen et al., 2004).

3.4.6. Tadalafil vs. placebo

In a single comparison of the effect of treatment with tadalafil or placebo alongside antidepressant medication (Segraves et al., 2004), men receiving tadalafil had a greater improvement in scores on the erectile function domain of the International Index of Erectile Function than those receiving placebo (WMD 8.10; 95% 4.62 to 11.58). Those receiving tadalafil were also less likely to fail to report improvement in erections at trial endpoint (RR 0.28; 95% CI 0.17 to 0.47).

3.4.7. Amantadine vs. placebo

In the study of buspirone augmentation noted above, Michelson et al. (2000) also compared augmentation of antidepressant treatment in females with amantadine or placebo. There was no statistically significant difference in overall function (sexual) as rated by visual analogue scale (WMD 13.0, 95% CI −29.02 to 55.02).

3.4.8. Amantadine vs. buspirone

The same trial (Michelson et al., 2000) allows analysis comparing augmentation of antidepressant treatment in females with amantadine or buspirone.

There was no statistically significant difference in overall function (sexual) rated by visual analogue scale between the groups (WMD 9.90, 95% CI 31.52 to 51.32). There was also no significant difference in dropout rates between groups (RR 0.55, 95% CI 0.05 to 5.62).

3.4.9. Olanzapine vs. placebo

From a separate study comparing four treatments as augmentation of antidepressant treatment in females (Michelson et al., 2002), a number of pairwise comparisons can be made. First comparing olanzapine with placebo, the group receiving olanzapine reported a greater improvement on a scale of overall sexual satisfaction completed at interview (WMD −0.70, 95% CI −1.17 to −0.23). However, there was no significant difference on diary ratings of overall sexual functioning (WMD 0.90, 95% CI −4.06 to 5.86).

3.4.10. Mirtazapine vs. placebo

Michelson et al. (2002) also allows comparison of the effect of augmentation of antidepressant treatment in females with mirtazapine or placebo. There was no improvement in sexual dysfunction with the addition of mirtazapine, whether rated at interview (WMD 0.10, 95% CI −0.29 to 0.49) or by diary (WMD −1.30, 95% CI −5.71 to 3.11).

3.4.11. Yohimbine vs. placebo

In a further comparison, Michelson et al. (2002) evaluated augmentation of antidepressant treatment in females with either yohimbine or placebo. There was no improvement in sexual dysfunction with the addition of yohimbine, whether rated at interview (WMD −0.30, 95% CI −0.79 to 0.19) or by diary (WMD 1.20, 95% CI −3.24 to 5.64).

3.4.12. Olanzapine vs. mirtazapine

The same trial (Michelson et al., 2002) provides data for comparisons of augmentation of antidepressant treatment in females with olanzapine or mirtazapine. The group receiving olanzapine reported a greater improvement on a scale of overall sexual satisfaction completed at interview (WMD −0.80, 95% CI −1.25 to −0.35). However, there was no significant difference on diary ratings of overall sexual functioning (WMD 2.20, 95% CI −2.59 to 6.99).

3.4.13. Olanzapine vs. yohimbine

In a further comparison, Michelson et al. (2002) evaluated augmentation of antidepressant treatment in females with olanzapine or yohimbine. There was no statistically significant difference found in sexual dysfunction between the groups, whether assessed at interview (WMD -0.40, 95% CI -0.94 to 0.14), or by diary (WMD -0.30, 95% CI -5.11 to 4.51).

3.4.14. Mirtazapine vs. yohimbine

Finally, Michelson et al. (2002) compared augmentation of antidepressant treatment in females with mirtazapine or yohimbine. There was no significant difference in sexual dysfunction assessed at interview at trial endpoint (WMD 0.40, 95% CI -0.08 to 0.88), although the baseline values for the groups had differed, with less initial sexual dysfunction in the mirtazapine group (WMD -0.80, 95% CI -0.97 to -0.63). There was also no significant difference on diary ratings of sexual dysfunction at trial endpoint (WMD -2.50, 95% CI -6.74 to 1.74).

3.4.15. G. biloba vs. placebo

Kang et al. (2002) compared the effect of augmenting antidepressant treatment with *G. biloba* or placebo. There was no significant difference in sexual dysfunction, assessed by questionnaire, between the groups on most subscales. On the 'satisfaction to orgasm' subscale, scores were better in the placebo arm (WMD -1.12, 95% CI -2.00 to -0.24).

3.4.16. Ephedrine vs. placebo

Meston (2004) compared the effect of augmenting antidepressant treatment with ephedrine or placebo. Data are derived from both crossover periods of the trial. There were no statistically significant differences at the end of treatment between the two groups on several measures derived from the Brief Index of Sexual Functioning for Women (Taylor et al., 1994).

4. Discussion

We identified 15 randomized trials assessing management strategies for sexual dysfunction induced by antidepressant medication. No trials were found that assessed the benefits of psychological interventions, mechanical devices, or changes to antidepressant medication regime such as dose reduction or drug holidays. This review was performed using the methods of the Cochrane Collaboration (Alderson et al., 2004), and focuses on evidence from randomized trials since it is generally accepted that this study design yields the most reliable estimates of effects. Methodological choices, such as the broad search strategy and the incorporation of unpublished data where possible, aim to minimize the effects of biases, particularly publication bias, on the results.

One challenge in this area is clearly separating sexual dysfunction induced by an antidepressant with sexual dysfunction due to some other cause that is coincidentally associated with the taking of antidepressant medication. The trials described here vary in the approach taken on this issue, from at one extreme Ferguson et al. (2001), where participants with suspected sertraline-induced dysfunction demonstrated recovery from sexual dysfunction on withdrawal of sertraline before entry to the study, and at the other Segraves et al. (2004), where participants were included on the basis of taking an antidepressant while experiencing erectile dysfunction. Equally, the range of types of sexual dysfunction that can result from antidepressant use means that apparent treatment efficacy in a broadly defined group may result from a change in a particular subgroup, or perhaps more likely, apparent lack of efficacy could be seen despite benefits for some kinds of dysfunction. At present there is insufficient data for any one intervention to establish whether these diagnostic factors affect estimates of treatment effect.

4.1. Adverse effects

We hypothesised that management strategies for antidepressant-induced sexual dysfunction might differ in acceptability or be associated with a worsening of the condition for which antidepressants were being taken. We have identified no data for any of the strategies assessed here indicating they lead to a worsening of psychiatric symptoms. However, the relatively small numbers assessed for each intervention means that the possibility of such an effect cannot be confidently excluded.

Only one intervention, mirtazapine augmentation (Michelson et al., 2002), was associated with an

increase in people dropping out of the study: rates of dropouts attributed to adverse effects were higher than with both placebo and yohimbine. However, the analysis of this four-arm study does not correct for the multiple statistical comparisons that result, and therefore the 95% confidence intervals presented may over-estimate the confidence with which this effect has been shown. Further randomized trial data may reduce this uncertainty.

4.2. Addition of further medication

There is some evidence that for men with antide-pressant-induced erectile dysfunction, the addition of sildenafil is of benefit in improving sexual function, and that this strategy is not associated with increased numbers of people dropping out from the study. This evidence comes from randomisation of 211 people. Where equivalent data are reported there is no statistically significant heterogeneity between the trials. Interestingly, the estimates of treatment effect observed are similar to those reported for its use in erectile dysfunction due to other causes (Fink et al., 2002).

The related treatment, tadalafil, has shown some evidence of benefit in a retrospective subgroup analysis, but it is unclear what proportion of those analysed had erectile dysfunction due to antidepressant use, and in what proportion there was another cause. Further randomized data in a population where erectile dysfunction is more clearly antidepressant-induced would improve confidence in estimates of effect. However, again the treatment effect observed here is similar to that seen in its use in erectile dysfunction due to other causes (Carson et al., 2004). Taken together, these data are consistent with the interpretation that the coincidental use of antide-pressants does not appear to interfere with the efficacy of phosphodiesterase inhibitors for erectile dysfunction (Tignol et al., 2004).

At present it is unclear if the addition of bupropion or buspirone is of benefit. Although it has been reported that use of bupropion as monotherapy for depression is associated with lower rates of sexual dysfunction than use of an SSRI (Croft et al., 1999), of the two trials assessing its use as an augmentation strategy that have been fully published, one (Clayton et al., 2004) showed some evidence of benefit, while

the other, using a lower dose (Masand et al., 2001), did not. The third trial, of which only preliminary details are available, also used the lower dose (DeBattista et al., 2001). For buspirone augmentation, again available data from one trial showed some evidence of benefit (Landen et al., 1999), and another trial using a lower dose range did not (Michelson et al., 2000). The use of different outcome measures between trials limits the possibility of pooling data between studies to improve the estimate of effect. At present the evidence does not demonstrate either significant benefit or significant harm from the addition of olanzapine, mirtazapine, yohimbine, granisetron, amantadine, *G. biloba*, or ephedrine to ongoing antidepressant medication. However, it should be noted that the majority of these interventions have only been assessed in single, relatively small, randomized trials that may have been underpowered to demonstrate small treatment effects. It remains possible they may prove to be efficacious in the future, perhaps in different dosages.

4.3. Changing antidepressant

There is some evidence that switching antidepressant to nefazodone is of benefit where sertraline has led to sexual dysfunction. This strategy was not associated with increased numbers of people dropping out from the study. This evidence of benefit comes from only one trial (Ferguson et al., 2001), and while a statistically significant effect was found on a physician rated measure, patient ratings did not exclude a lack of benefit. The existence of only one or two negative or neutral trials would have a substantial effect on the estimate of effect, and it is not known how well these results can be generalised to sexual dysfunction due to other antidepressants. On a practical level, Serzone (nefazodone) has been discontinued in Europe, which will limit the availability of this strategy to many people.

4.4. Implications for practice

The currently available evidence is limited, with small numbers of trials assessing each intervention. Further randomized data may be required before clinicians or patients can be confident of the benefits of any one intervention. However, at present the evidence base for the use of sildenafil for men with

antidepressant-induced erectile dysfunction is the largest and most consistent.

4.5. Implications for research

Further randomised trials are required. There is an absence of randomised data assessing the role of psychological or mechanical interventions, or of techniques such as drug holidays. Potentially promising strategies for which estimates of effect need to be improved include the addition of bupropion, tadalafil, and buspirone.

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