Trazodone for erectile dysfunction: a systematic review and meta-analysis

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Evidence-based medicine is an important way of allowing the reader to judge clearly whether a treatment has a place in a particular condition, and to see what faults were present in the various trials of its efficacy. It is often rather unsettling to read in a meta-analysis or in a systematic literature review how poorly constructed many trials are. The authors from Minneapolis have carried out such a study into the use of trazodone in male erectile dysfunction. They draw attention to the poor quality of many of the trials and give their reasons for this observation. They suggest that trazodone may be helpful in men with this condition, possibly at higher doses and in men with psychogenic erectile dysfunction.

OBJECTIVE

To determine the efficacy and safety of trazodone in the treatment of erectile dysfunction (ED) in a meta-analysis.

METHODS

The data sources used were Medline and the Cochrane Library databases (January 1966 to May 2002), bibliographies of retrieved articles and review articles, and conference proceedings and abstracts. Trials were eligible for inclusion in the review if they included men with ED, compared trazodone with a control, were randomized, of ≥7 days' duration and assessed clinically relevant outcomes. Two reviewers independently evaluated study quality and extracted data in a standardized fashion.

RESULTS

Six trials (comprising 396 men) met the inclusion criteria; they consisted of heterogeneous populations, were small, brief and in some cases methodologically weak. Three of the six trials showed an apparently clinically meaningful benefit of trazodone for ED compared with placebo, the differences being statistically significant in two. In pooled results, trazodone monotherapy appeared more likely than placebo to lead to a 'positive treatment response', although this difference was not statistically significant (37% vs 20%; relative benefit increase, 1.6; 95% confidence interval, CI, 0.8–3.3). Subgroup analyses suggested that men with psychogenic ED might be more likely to benefit from trazodone than those with mixed or physiological ED. The efficacy of trazodone also appeared greater at higher doses (150–200 vs 50 mg/day). Men randomized to trazodone were not significantly more likely than those receiving placebo to withdraw for any reason or for an adverse event, or to have specific adverse events, but wide CIs could not exclude a greater risk of these adverse outcomes with trazodone. Specific adverse events with trazodone included dry mouth (19%), sedation (16%), dizziness (16%) and fatigue (15%).

CONCLUSION

Trazodone may be helpful in men with ED, possibly more so at higher doses, and in men with psychogenic ED. Future high-quality trials should compare trazodone with placebo and other therapies in men with depression and psychogenic ED.

KEYWORDS

erectile dysfunction, trazodone, impotence, meta-analysis, treatment outcome, adverse events

INTRODUCTION

Erectile dysfunction (ED) is defined as 'the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.' [1] While ED is not life-threatening, it may result in withdrawal from sexual intimacy and reduced quality of life [2,3]. Estimates of the prevalence of ED in different populations vary, with differences probably caused partly by study-related differences in the definition of ED, and cultural perceptions of ED. In Wales (UK) complete ED was reported by 7% of men aged 55–60 years, 13% of men aged 61–65 and 22% of those aged 66–70 [4]. In Olmstead County in the USA, < 1% of men aged 40–49 and 27% of men aged ≥70 years reported complete ED, with some degree of ED present in 23% and 82% for these age groups, respectively [5]. Besides increased age, other factors independently associated with ED include diabetes, heart disease, hypertension, depression and use of certain medications [6,7]. In most cases, ED is thought to be multifactorial.

There are various treatment options for ED, although men strongly prefer oral therapies [8]. Among oral treatments for ED the selection of a specific agent may involve considering associated adverse effects and possible contraindications because of patient comorbidity or drug interactions. For these reasons among others, it is important for patients with ED to have a variety of available treatment options that are both effective and safe.

Trazodone hydrochloride is an oral antidepressant agent that also has anxiolytic and sedative/hypnotic effects. Because of reports of increased libido and sexual function associated with its use, trazodone is also sometimes used to treat ED [9]. Annually there are nearly 0.5 million prescriptions for trazodone in the UK and ≈13.6 million in the USA [10,11]; no data are available on trazodone prescriptions by indication. The mechanism of action by which trazodone has its antidepressant effects may involve the selective inhibition of serotonin re-uptake in the brain. The effect of trazodone on erectile function may be related to its antagonism of α2-adrenergic receptors [12,13]. Antagonism of these receptors in penile vascular and corporal smooth muscle may relax the tissues, enhance arterial inflow and thereby produce erection. Administered in adults for depression, trazodone may be initiated at 150 mg/day in divided doses, with a maximum dose of 600 mg/day. When used as a hypnotic or in the elderly, trazodone usually is initiated at 25–50 mg at bedtime, with a maximum dose of ≤200 mg/day. There is no generally accepted dose of trazodone for treating ED.

Multiple randomized trials have evaluated trazodone for treating men with ED. We conducted a systematic review and meta-analysis of randomized, placebo-controlled trials to more precisely estimate the magnitude of treatment benefits and adverse effects associated with trazodone treatment in men with ED.

METHODS

Trials were identified by searching the Medline computer database (1 January 1966 to 31 May 2002) using an optimally sensitive Cochrane Collaboration search strategy [14]. The search strategy included the terms 'trazodone', 'antiserotoninergic agents' and 'adrenergic α-antagonists', combined with 'impotence' and 'erectile dysfunction', and including all subheadings. In addition, bibliographies of retrieved trials and review articles were reviewed, and AUA national meeting abstracts from January 1995 to May 2002 were hand-searched. The Cochrane Library and the Prostatic Diseases and Urologic Malignancies Group specialized registry were screened for additional trials. There were no language restrictions.

SELECTION CRITERIA

Trials were eligible for inclusion if they: (i) included men with ED; (ii) were randomized; (iii) compared trazodone with placebo or active control; (iv) were at least 7 days in duration; and (v) assessed clinical outcomes related to ED (e.g. success of sexual intercourse attempts, participants' overall assessment of treatment). For each trial, two reviewers independently assessed study eligibility, and differences in eligibility assessment were resolved by discussion.

OUTCOME MEASURES

For each trial, information on trial characteristics, patient demographics, inclusion and exclusion criteria, withdrawals, treatment efficacy, and adverse events were extracted by two independent reviewers in a standard fashion. Discrepancies were resolved by discussion.

Previously we judged successful sexual intercourse to be the most clinically relevant measure of the efficacy of treating ED [15]. Therefore, 'successful sexual intercourse attempts' was considered the primary outcome measure in any trial for which it was available. Secondary outcome measures included a sexual function questionnaire domain or overall scores, overall assessments of improved erections, and other patient reports of 'positive treatment response'. For adverse effects, we examined the percentage of men reporting side-effects and the percentage of men withdrawing from the trial. Missing or additional information was sought from authors.

ASSESSMENT OF METHODOLOGICAL QUALITY

We assessed the quality of concealment of randomized treatment allocation according to a scale developed by Schulz *et al.* [16], assigning 1 to the poorest quality and 3 to the best. Also, we assessed whether trial participants and investigators were unaware of the treatment provided, whether trials used an intention-to-treat analysis, and the percentage of subjects who withdrew or were lost to follow-up.

STATISTICAL ANALYSIS

To assess categorical treatment outcomes, we determined the percentage of men achieving each outcome according to treatment assignment. For measures of efficacy, because no two eligible trials used the same outcome measure, results are initially presented for individual trials without pooling. Subsequently, study results were pooled by comparing the increase in the proportion of subjects with a 'positive treatment response' between trazodone and control subjects by calculating the weighted relative benefit increases (RBI) and their 95% CI using software [17]. For adverse events and treatment withdrawals, the increase in the proportion of subjects treated with trazodone with adverse events was compared to that of control subjects by calculating the weighted relative risk increases (RRI) and their 95% CI. Weighted RBIs and RRIs were estimated using random effects meta-analytical models to allow for heterogeneity among the trials.

TABLE 1 Characteristics of the included trazodone trials

Study	N (Wd)*	Design	Trazodone dose mg/day (N)	Control regimen(s) (N) mg × daily	Treatment, weeks	Characteristics of participants	Exclusion criteria
Trazodone monotherapy							
[23]	79 (0)	Parallel	150 (21)	Placebo (18) TU 120 (20) Hypnotic suggestion (20)	4†	Turkish men, mean age 38	Any organic cause of ED
[21]	51 (3)	Crossover	50 once (48)	Placebo (48)	13	American men mean age 65 Variable causes of ED, ED for ≥ 3 months	Significant cardiac disease
[18]	34 (1)	Parallel	150–200 × 1 (16)	Placebo (18)	4	Belgian men, mean age 48, ED for ≥4 months + stable heterosexual relationship for ≥6 months	Any organic cause of ED (except diabetes) history of MI, PTCA or CABG in past 3 months; ejaculation disorder; use of medication known to possibly cause ED.
[19]	100 (15)	Parallel	50 mg ×3 (25)	Placebo (25) Ketanserin 20 ×2 (25) Mianserin 10 × 3 (25)	4	Turkish men, mean age 47 ED ≥6 months sufficient libido and +ve papaverine test	Any organic cause of ED; chronic or recent psychological problem; ejaculatory disorder; recent trauma that could interfere with erections
[22]	69 (11)	Parallel	150 × 1 (32)	Placebo (37)	4	Dutch men, mean age 55. Variable causes of ED	Severe kidney or liver disease; use of medication known to possibly cause ED
Combination therapy							
[20]	63 (8)	Partial crossover	50 × 1, with yohimbine 5 × 3 (28)‡	Placebo (27)†	8	Italian men, mean age 43. Psychogenic ED, ED for ≥3 months	Use of medication known to possibly cause ED

**Withdrawals, referring to all randomized subjects not completing the trial, including those excluded after randomization. The number of withdrawals for crossover studies represents the number of treatment arms that were not completed; TU, testosterone undecanoate; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft. †Patients followed for 16 weeks, but outcome data only reported at 4 weeks. ‡Includes participant data only from the first arm of the crossover, as the second arm did not include a placebo group and thereby was unblinded.*

A clinical decision was made to include in the meta-analyses only trials that compared trazodone monotherapy and placebo. Among these trials, all but one [18] presented outcome data in a manner that permitted meta-analytical pooling, as described above. Results were tested for heterogeneity at a significance level of $P < 0.10$.

RESULTS

Six trials involving 396 men (range 34–100) met all eligibility criteria and were included in this systematic review (Table 1); all trials were published in peer-reviewed, English-language journals [18–23]. All trials indicated that they were randomized, but only one reported an adequate method of random allocation and concealment of treatment assignment [21]. Five trials reported that they were double-blind, while one did not state whether or not it was blinded [23]. Five trials evaluated trazodone monotherapy, while one evaluated a trazodone-yohimbine combination; the most common dose of trazodone assessed was 150 mg/day (range 50–200). All trials were placebo-controlled.

Four trials used a parallel treatment group design and one a crossover design, with the remaining trial using a partial crossover design; only data collected before the crossover were considered for the present analysis, because there was no placebo control group in the arm after crossover [20]. The treatment duration with assessment of outcome was 4–13 weeks. The most common trial inclusion criterion was ED of at least 3–6 months' duration. Exclusion criteria used in more than one trial included recent or significant cardiac disease, presence of an ejaculatory disorder, and

the use of medication known to possibly cause ED.

Two trials defined a positive treatment response as whether participants achieved successful sexual intercourse during treatment [19,20]. The others trials used a study-specific sexual function questionnaire [18,21] or an overall definition of treatment response, e.g. whether or not subjects were 'happy and had no problem with sexual activity' [23], whether erections were 'improved' [21], or to what degree the medication 'works' [22].

TABLE 2
Positive treatment response by aetiology of ED, trazodone monotherapy vs placebo

Study	N/total (%) Trazodone	Placebo	RBI (95% CI)
Psychogenic ED			
[23]	14/21 (67)	7/18 (39)	1.7 (0.9–3.3)
[19]	15/25 (60)	3/25 (12)	5.0 (1.7–15.2)
Subtotal	29/46 (63)	10/43 (23)	2.7 (0.9–8.0)
Physiological ED			
[21]	5/26 (19)	6/26 (23)	0.8 (0.3–2.3)
Mixed aetiology ED			
[22]	4/32 (13)	5/37 (14)	0.9 (0.3–3.2)
Total	38/104 (37)	21/105 (20)	1.6 (0.8–3.3)

DEMOGRAPHICS

Men in these trials had a mean age of 48 years, the range of study means being 38–65 years (Table 1). The mean duration of ED was reported for only two trials [20,21], in which it was 8 and 36 months, respectively. No trials provided information on the severity of ED in enrolled subjects. About 80% of men had definite or probable psychogenic ED, whereas 9% had a vascular aetiology, 5% had ED attributed to diabetes, and 6% had another, mixed or unknown cause for their ED. No data were available on the prevalence of specific comorbid conditions in trial participants.

EFFICACY OUTCOME

Only two trials used 'successful sexual intercourse attempts' as an efficacy outcome measure (Table 2). Kurt *et al.* [19], in a study comprising men with psychogenic ED, found that those randomized to trazodone 150 mg/day were significantly more likely to have three or more successful attempts at sexual intercourse during treatment than those allocated to placebo (Table 2). In another trial consisting entirely of men with psychogenic ED, Montorsi *et al.* [20] reported that trazodone 50 mg/day combined with yohimbine 5 mg three times daily was significantly more likely to bring about a 'complete return to satisfactory sexual functioning, with the occurrence of erections sufficient for penetration' (50% vs. 11% for placebo; RBI 4.5; 95% CI 1.5–13.9).

The remaining trials, all of which compared trazodone monotherapy with placebo, used what we judged to be less clinically relevant efficacy outcome measures. Aydin *et al.* [23], in a study of men with psychogenic ED, reported that subjects were more likely to report 'no problem with sexual activity' with 150 mg/day of trazodone than with placebo, although the treatment difference was not statistically significant (Table 2). In a trial by Meinhardt *et al.* [22], subjects with heterogeneous causes of ED were no more likely to report that treatment 'works well' for their erectile function with trazodone 150 mg/day than with placebo (Table 2). In a study of subjects with physiological ED, Costabile *et al.* [21] reported that treatment with trazodone 50 mg/day was no more likely than placebo to improve erections (Table 2) or to increase scores on the study-specific Index of Sexual Satisfaction. Last, in a study population of men with psychogenic ED, Enzlin *et al.* [18] found no statistically significant difference between trazodone 200 mg/day and placebo for the outcomes of sexual desire or a study-specific sexual functioning inventory.

When results were pooled from trials that compared trazodone monotherapy with placebo, men randomized to trazodone appeared more likely to have a positive treatment response, although this difference was not statistically significant (Table 2).

While no data were available for specific patients, several study-level subgroup analyses of trials comparing trazodone monotherapy with placebo suggested patterns that might be clinically meaningful. In a subgroup analysis in which trials were categorized by the aetiology of ED, men with psychogenic ED appeared to have an improvement in sexual function with trazodone (Table 2). The results of treatment appeared to be less favourable for trazodone in single trials of men with a mixed aetiology for ED or with physiological ED (Table 2). In a second subgroup analysis, the improvement with trazodone monotherapy relative to placebo appeared greater in trials that used 150–200 mg/day (42% for trazodone vs 19% for placebo; RBI 2.0; 95% CI 0.9–4.6) than in the single trial that used 50 mg/day [21] (Table 2). Finally, the data also suggested the possible importance of methodological quality on study results. There was no difference between trial results as a function of whether trials were double-blinded or whether concealment of the random treatment allocation scheme was judged to be adequate, but the two trials that used what we considered a more clinically relevant efficacy outcome measure, successful sexual intercourse attempts, were also the only two to find a statistically significant benefit for trazodone over placebo.

ADVERSE EVENTS

Discontinuations and adverse events were not reported for all trials (Table 3); among trials reporting data, men randomized to trazodone monotherapy were no more likely than those allocated to placebo to withdraw for any reason or to withdraw because of an adverse event (Table 3), although the wide CIs cannot exclude a substantial increased risk of these adverse outcomes with trazodone. Data on specific adverse events were not reported uniformly in all trials. Therefore, unless a specific adverse event was explicitly reported to have not occurred in one or both treatment groups in a trial, we assumed that no data on this given adverse event were available from the trial. The most commonly reported adverse events in men allocated to trazodone were dry mouth (19% vs 11% for placebo), sedation (16% vs 6%), dizziness (16% vs none) and fatigue (15% vs 8%). Although point estimates suggested a greater rate of all of these adverse events with trazodone than with placebo, no differences were statistically significant. The pooled rates presented here may be overestimates of true rates if, in trials

TABLE 3 Discontinuations and adverse events

Study	N/total (%) Trazodone	Placebo	No. of studies reporting	RRI (95% CI)
Trazodone monotherapy				
Discontinuations				
For any reason	8/94 (9)	9/98 (9)	4	1.0 (0.4–2.5)
For adverse event(s)	8/78 (10)	3/80 (4)	3	2.6 (0.8–8.6)
Adverse events				
Sedation	20/126 (16)	8/128 (6)	4	2.1 (0.97–4.4)
Dry mouth	14/73 (19)	8/73 (11)	2	1.6 (0.8–3.5)
Fatigue	7/48 (15)	4/48 (8)	1	1.8 (0.6–5.6)
Dizziness	5/32 (16)	0/37 (0)	1	12.7 (0.7–220.6)
Nausea	3/57 (5)	2/62 (3)	2	1.2 (< 0.1–42.8)
Headache	3/32 (9)	1/37 (< 1)	1	3.5 (0.4–31.7)
Priapism	1/25 (4)	0/25 (0)	1	3.0 (0.1–70.3)
Combination therapy*				
Discontinuations				
For any reason	6/28 (21)	2/27 (7)	1	2.9 (0.6–13.1)
For adverse event(s)	6/28 (21)	2/27 (7)	1	2.9 (0.6–13.1)
Adverse events†	NA	NA	NA	NA

**One trial used trazodone together with yohimbine, comparing the combination to placebo; †Data for incidence of specific adverse events were not reported except for discontinuations for adverse events; NA, not available.*

not reporting occurrences of these adverse events, there were in fact no such events. Priapism was noted in one man treated with trazodone in one trial, but not in the placebo group.

DISCUSSION

This systematic review summarizes the available evidence from randomized controlled clinical trials for the efficacy and safety of trazodone for treating ED. There were relatively few treatment trials and the trials comprised heterogeneous patient populations, were small, brief and in some cases methodologically weak.

Of six trials identified, three reported what appeared to be clinically meaningful benefits with trazodone for ED when compared with placebo, with these differences being statistically significant in two of the trials. When results were pooled, trazodone appeared more likely to be beneficial than was placebo. However, this pooled difference was not statistically significant. Furthermore, subgroup analyses suggested that patient population, trazodone dose and trial methodological quality may have been important factors influencing the results. First, trazodone appeared possibly more effective than placebo in men with psychogenic ED, but not in men with physiological ED or ED of mixed aetiology. Next, trazodone appeared possibly superior to placebo when given at 150–200 mg/day but not at 50 mg/day. Last, trials that used 'successful sexual intercourse' as their primary measure of treatment efficacy were more likely to report the superiority of trazodone over placebo than trials that used a less rigorous primary efficacy measure.

Safety data from the trials in this systematic review suggest that adverse events appear to occur more frequently with trazodone than with placebo, consistent with data reported in its package insert (Desyrel, Apothecon, Princeton, NJ 1998). That no differences were statistically significant in this review is most probably a consequence of the limited number of subjects for whom adverse event data were available.

As previously noted, the likelihood of ED is increased in men with depression. Because many antidepressant medications have adverse effects on ED it may be difficult in depressed patients with ED to determine whether their ED is caused by antidepressant treatment, depression, or some other cause. Similarly, it is difficult in such patients, and impossible from the trials included in this review, to determine whether trazodone has any effect on ED independent of its effect on depressive symptoms.

The findings of this review must be considered cautiously given the relatively few primary studies and the limited size and quality of some of them. Further, all subgroup analyses must be considered exploratory. Nevertheless, the evidence from this systematic review and meta-analysis suggests that trazodone may have a beneficial effect on ED, particularly in specific subgroups of men. These results should be investigated further in high-quality randomized trials. For example, men with mild to moderate untreated depression and psychogenic ED might be randomized to trazodone, sildenafil, a selective serotonin reuptake inhibitor, psychotherapy or placebo. Outcome measures should include the proportion of successful sexual intercourse attempts, a validated depression scale and adverse events.

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Abbreviations: **ED**, erectile dysfunction; **RBI**, relative benefit increase; **RRI**, relative risk increase.