Pharmacotherapy for post-traumatic stress disorder – a systematic review and meta-analysis

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Background. Post-traumatic stress disorder (PTSD) is a prevalent and disabling condition. Evidence that PTSD is characterised by specific psychobiological dysfunctions has contributed to a growing interest in use of medication in its treatment.

Objectives. To assess the effects of medication in the treatment of PTSD.

Design. Systematic review of randomised controlled trials (RCTs) following the Cochrane Collaboration guidelines. A more detailed version of the review is published in the Cochrane Database of Systematic Reviews.

Methods. We searched the Cochrane Depression, Anxiety and Neurosis Group specialised register, the Cochrane Central Register of Controlled Trials (Cochrane Library issue 4, 2004), MEDLINE (January 1966 - December 2004), PsycINFO (1966 - 2004), the National PTSD Center Pilots database, and the meta register module of the Controlled Trials database. Reference lists of retrieved articles were searched for additional studies.

Two raters independently assessed RCTs for inclusion in the review, collated trial data, and assessed trial quality. Investigators were contacted to obtain missing data. Summary statistics were stratified by medication class, and by medication agent for the selective serotonin re-uptake inhibitors (SSRIs). Dichotomous and continuous measures were calculated using a random effects model, heterogeneity was assessed, and subgroup/sensitivity analyses were done.

Main results. Thirty-five short-term (14 weeks or less) RCTs were included in the analysis (4 597 participants). Symptom severity for 17 trials was significantly reduced in the medication groups, relative to placebo (weighted mean difference (WMD) = –5.76, 95% confidence interval (CI): –8.16 - –3.36, $N = 2\ 507$). Similarly, summary statistics for responder status from 13 trials demonstrated overall superiority of a variety of medication agents compared with placebo (relative risk (RR) = 1.49, 95% CI: 1.28, 1.73, number needed to treat (NNT) = 4.85, $N = 1\ 272$). Medication and placebo response occurred in 59.1% ($N = 644$) and 38.5% ($N = 628$) of patients, respectively. Of the medication classes, evidence of treatment efficacy was most convincing for the SSRIs.

Medication was also effective in reducing the severity of the PTSD re-experiencing/intrusion, avoidance/numbing, and hyperarousal symptom clusters in 9 trials ($N = 1\ 304$). In addition, medication was superior to placebo in reducing co-morbid depression and disability. Medication was also less well tolerated than placebo. A narrative review of the 3 maintenance trials suggested that long-term medication may be required in treating PTSD.

Conclusion. Medication treatments can be effective in treating PTSD, acting to reduce its core symptoms, as well as associated depression and disability, and should be considered as part of the treatment of this disorder. The findings of this review support the status of SSRIs as first-line agents in the pharmacotherapy of PTSD, as well as their value in long-term treatment. However, there remain important gaps in the evidence base, and there is a continued need for more effective agents in the management of PTSD.

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Although the phenomenon of post-traumatic stress disorder (PTSD) has long been recognised (for example as 'shell shock' or 'combat neurosis'), it is only relatively recently that this disorder has been officially recognised in the psychiatric nomenclature.[1] The personal, social and economic burden of PTSD has become increasingly apparent owing to the prevalence (estimated at lifetime rates of between 5% and 10% of the adult population[2]) and chronicity of the condition, and

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because of the high psychiatric and medical co-morbidity and impaired quality of life associated with it.

PTSD is defined in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*[3] as the psychological sequela of exposure to 'actual or threatened death or serious injury, or threat to the physical integrity of self or others', and in which 'the person's response involved intense fear, helplessness or horror'. PTSD symptoms can be grouped into the following symptom clusters: intrusive/re-experiencing (e.g. flashbacks, nightmares), avoidant/numbing (e.g. loss of interest, detachment), and hyperarousal (e.g. irritability and difficulty concentrating and sleeping).

Psychotherapy has traditionally been the treatment of choice for PTSD. Nevertheless, a rationale for the use of medication treatments can be found in the increasing recognition that this disorder is characterised by specific psychobiological dysfunctions and the lack of evidence for the effectiveness of

certain commonly employed psychotherapeutic interventions (such as psychological debriefing[4]). In addition, several psychiatric disorders are often found co-morbid with PTSD disorders,[2] and certain of these are known to respond to medication.

Systematic review of the pharmacotherapy studies may be useful in tackling several questions. First, is pharmacotherapy in fact an effective form of treatment in PTSD? Given the preponderance of psychological models and evidence for the efficacy of certain forms of psychotherapy in treating PTSD,[5,6] the role of pharmacotherapy remains debatable for many.

Second, are particular medication classes more effective in the treatment of symptoms and/or more acceptable to the patient in terms of adverse events than others? Some sources[7] have suggested that the serotonin re-uptake inhibitors (SSRIs) nefazodone and venlafaxine are first-line medications for the treatment of PTSD, with benzodiazepines and mood-stabilisers having a role to play in treating patients with certain kinds of symptoms. Others have highlighted paroxetine and mirtazapine.[6]

Third, can a systematic review of randomised controlled trials (RCTs) provide information on the most important factors affecting pharmacotherapy response? Treatment response may be affected by clinical factors (e.g. duration of symptoms, the kind of pre-existing trauma (e.g. combat-related), and the presence of co-morbid depression), as well as methodological factors (e.g. medication dosage and trial duration).

This review represents a systematic attempt to answer these questions through adhering to the guidelines prescribed by the Cochrane Collaboration. A more detailed version of this review is published in the Cochrane Database of Systematic Reviews.[8]

Methods

Identification of clinical trials

We considered for inclusion all RCTs on the pharmacotherapy of PTSD in which patients diagnosed with this condition were randomised to either a medication or a comparison group (placebo or other medication). Candidate trials were identified through searching MEDLINE (January 1966 - December 2004), the Cochrane Central Register of Controlled Trials (issue 4, 2004), the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, PsycINFO (1966 - 2004), the National PTSD Center Pilots database and the metaRegister module (mRCT) of the Controlled Trials database (please refer to the Cochrane Review[8] for the queries used). Reference lists of retrieved articles were searched for additional studies.

RCTs identified from the search were independently assessed for inclusion by two raters, based on information included in the trial report. Any disagreements in assessment and collation were resolved by discussion. A flow chart of the trial inclusion procedure is provided in Fig. 1.
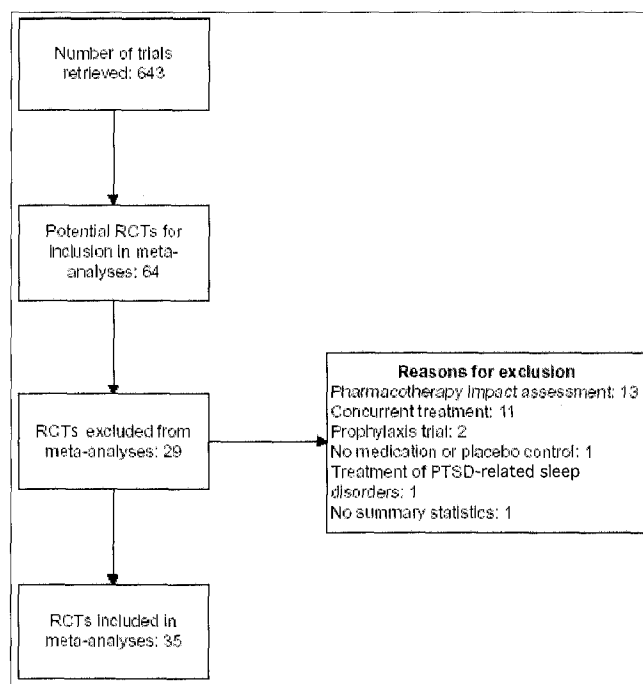

Fig. 1. Flow chart of trial inclusion in meta-analyses.

Data extraction, collation, and synthesis

Outcome measures were decided on an *a priori* basis, so as to minimise bias. Primary outcomes included the reduction in total symptom severity and the number of treatment responders. PTSD symptom severity was determined from the total score on the Clinician Administered PTSD Scale (CAPS),[9] a measure increasingly used in RCTs of PTSD. Treatment response was determined from the Clinical Global Impressions scale-Improvement item (CGI-I),[10] or a closely related measure.

Secondary outcomes included reduction of the severity of PTSD symptom clusters (assessed using the respective CAPS subscales), and the response of co-morbid depression (measured using scales such as the Beck Depression Inventory (BDI)[11] and the Hamilton Depression scale (HAM-D)[12]). Quality of life and functional disability measures were also included when provided, to address the question of medication effectiveness. The total proportion of participants who withdrew from the RCTs because of treatment-emergent adverse events were included as a measure of medication acceptability.

Descriptive and outcome summary statistics for each trial were captured on customised data-collection forms, and subsequently exported to the Review Manager software (RevMan version 4.2.8)[13] for analysis. Where information was missing, the reviewers contacted investigators by e-mail in an attempt to obtain this information.

Data analysis

Weighted mean differences (WMDs) for continuous measures

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and relative risks (RRs) for categorical outcomes were obtained from a random effects model and were expressed in terms of average effect size for each subgroup, as well as by means of 95% confidence intervals (CIs). The number needed to treat (NNT) was also calculated. The NNT provides an indication of the number of patients who require treatment with medication, relative to a control, before a single additional patient in the medication group responds to treatment. The standardised mean difference (SMD) was used instead of the WMD for comparisons in which a range of scales were employed.

In recognition of the possibility of differential effects for different types of medication, all of the comparisons were stratified by medication class. Medications that could not be classified as SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) or reversible inhibitors of monoamine oxidase (RIMAs) were placed in a separate category, labelled 'Other medication'. In addition, it was decided, on the basis of the large number of SSRI trials included in the review, to stratify the primary outcome measure and drop-out comparisons by individual SSRI agents. In the case of data from trials employing multiple fixed doses of medication, the endpoint mean scores and standard deviations (SDs) were pooled across all of the treatment arms as a function of the number of participants in each arm.

Cross-over trials were only included in the calculation of summary statistics when it was: (i) possible to extract medication and placebo/comparator data from the first treatment period; or (ii) when the inclusion of data from both treatment periods was justified through a wash-out period of a duration sufficient to minimise the risk of carry-over effects (a minimum of 2 weeks or longer in the case of trials assessing the efficacy of agents with extended half-lives, such as the SSRI, fluoxetine[14]).

Quality of included studies

Trial quality was assessed by collating data for trial characteristics that have been recognised as a potential source of systematic bias. These include the method of concealing treatment allocation (categorised on a scale from A to C, depending on whether the method used was adequate, unclear, or inadequate, respectively), as well as whether outcome assessment was blinded (A: yes, B: no, C: unclear).

Heterogeneity

Heterogeneity of treatment response was assessed at the 0.1 level of significance by means of the chi-square statistic. Differences on continuous measures between groups on this statistic were assessed by means of Deeks' stratified test of heterogeneity.[15] Differences in treatment response on the CGI-I were determined by overlap in the CIs for the effect sizes for the subgroups tested.

Subgroup analyses were undertaken in order to determine the degree to which methodological and clinical differences

between trials might have systematically influenced differences observed in the primary treatment outcomes.

Criteria used in grouping the trials included: (i) whether or not they were conducted at single or multiple centres; (ii) whether or not the trials included combat veterans; and (iii) whether patients diagnosed with major depressive disorder (MDD) were included in the sample. Combat veterans are generally regarded as being more resistant to treatment, while controlling for the presence of patients with MDD would help to determine the extent to which the efficacy of medication in combating PTSD is mediated by the antidepressant properties of the drugs used.

Results

Description of studies

The review included 35 short-term RCTs of PTSD (4 597 participants), 3 of which contained a maintenance component (Table I). Of the 35 trials, 30 were published, and all of these publications were in English. A placebo comparison group was employed in all but 4 of the trials.[16-19]

Quality of included studies

The majority of the trial reports did not provide sufficient information to determine the quality of the studies. Of the 35 short-term trials, only 6 characterised the assessment of outcome as blinded, with 2 comparative RCTs not employing any form of blinding.[17,18] Even fewer trials described the allocation sequence that was used in assigning group membership to participants (N = 5).

Failure to provide sufficient information for the calculation of summary statistics prevented the inclusion of data from the 4 acute cross-over RCTs in the meta-analysis.[20-23] However this is unlikely to have had a significant effect on estimates of treatment efficacy as these trials were all small.

In analysing data from the placebo-controlled trial of phenelzine and imipramine,[24] only data from the imipramine arm were included in the meta-analyses. This reduced the disparity in the number of MAOI and TCA trials in the review, in keeping with the a priori decision to restrict data inclusion from multi-arm trials to the less well-represented medication classes, so as to avoid the potential bias of comparing summary statistics for multiple medication groups against the same placebo control. In the multi-arm trials comparing the SRIs citalopram[25] and venlafaxine (unpublished trials, Table I) with the SSRI sertraline, the former agents were given preference as less well-represented medication agents, for the same reason.

Primary outcomes

Patients who received medication in the 17 trials providing data on the CAPS displayed significantly less severe PTSD symptoms at trial endpoint than those who received placebo (WMD = −5.76, 95% CI: −8.16 - −3.36, number of participants (N) = 2 507). Evidence was detected for the efficacy of the SSRIs

Table I. Placebo-controlled randomised studies included in the review

Medication agents	First author*	Year	Duration (weeks)	No. of sites	Sample size	Baseline severity§	% Males	% War trauma	% MDD
MAOIs									
Phenelzine	Shestatzky[23]	1988	5	1	13	–	–	30.8	15.4
Phenelzine	Kosten[24]	1991	8	3	41	–	100	100	0
RIMAs									
Brofaromine	Baker[31]	1995	12	12	114	83.40	80.7	60.5	–
Brofaromine	Katz[32]	1995	14	9	45	81.94	75.6	17.8	–
SSRIs									
Sertraline	Brady[33]	2000	12	14	187	75.90	26.7	5.9	33.2
Sertraline	Brady[26]	2005	12	1	94	58.90	54.3	0.0	–
Fluoxetine	Connor[34]	1999	12	1	54	–	9.3	0.0	–
Sertraline	Davidson[28]‡	2001	12/28	12	208	73.69	22.1	4.8	–
Fluoxetine	Eli Lilly†	–	12	–	411	–	–	–	–
Fluoxetine	Hertzberg[35]	2000	12	1	12	–	100	100	66.7
Paroxetine	Marshall†‡	–	10/12	1	52	83.53	32.7	0	57.7
Paroxetine	Marshall[36]	2001	12	59	376	74.85	32.2	–	66
Fluoxetine	Martenyi[27]‡	2002	12/24	18	301	80.70	81.4	48.2	–
Sertraline	Pfizer588†	–	11	16	189	–	25.39	0	–
Sertraline	Pfizer589†	–	10	–	169	–	79.88	71	–
Paroxetine	Bryson†	–	12	–	322	–	46.3	–	–
Paroxetine	Tucker[37]	2001	12	37	323	73.74	34.2	6.5	33.4
Citalopram	Tucker[25]	2003	10	1	35	91.91	28.6	2.9	77.8
Fluoxetine	v. d. Kolk[38]	1994	5	2	64	87.02	65.6	43.8	53.1
Fluoxetine	v. d. Kolk†	–	8	1	59	–	13.6	–	–
Sertraline	Zohar[39]	2002	10	3	42	72.03	88.1	76.2	–
TCAs									
Amitriptyline	Davidson[40]	1990	4/8	1	46	–	100	100	19.6
Desipramine	Reist[22]	1989	4	1	18	–	100		33.3
Other									
Olanzapine	Butterfield[41]	2001	10	2	15	–	6.7	13.3	53.3
Alprazolam	Braun[20]	1990	5	1	16	–	–	25.0	12.5
Mirtazapine	Davidson[42]	2003	8	1	26	–	–	15.4	73.1
Venlafaxine	Davidson†	–	12	1	352	–	–	–	–
Nefazodone	Davis[43]	2004	12	1	42	81.79	97.6	95.2	38.1
Lamotrigine	Hertzberg[44]	1999	12	1	15	–	64.3	66.7	–
Inositol	Kaplan[21]	1996	4	2	–	–	61.5	–	0
Risperidone	Reich[45]	2004	8	1	21	64.40	0	–	61.9

*Number next to first author refers to number of study citation.
†Unpublished data.
‡Maintenance trials.
§Baseline severity on CAPS.
MDD = major depressive disorder; MAOIs = monoamine oxidase inhibitors; RIMAs = reversible inhibitors of monoamine oxidase; SSRIs = selective serotonin re-uptake inhibitors; TCAs = tricyclic antidepressant; – = data not provided.

(N = 12, WMD = –5.59, 95% CI: –8.6 - –2.58, N = 1 909), with this class of medication making the largest contribution to the overall effect size (weight = 82.4%).

Comparison of the efficacy of particular SSRIs in reducing PTSD symptom severity provided evidence for the efficacy of both paroxetine (N = 4, WMD = –10.49, 95% CI: –13.87 - –7.11, N = 940) and to a lesser extent, sertraline (N = 6, WMD = –3.78, 95% CI: –6.9 - –0.65, N = 875). There was no indication that brofaromine was more effective than placebo, while the single trials of the novel antidepressant nefazodone, the antipsychotic risperidone, the selective norepinephrine re-uptake inhibitor (SNRI) venlafaxine, and the SSRIs citalopram and fluoxetine failed to provide evidence for the efficacy of these medications in reducing symptom severity (Fig. 2).

Neither the two head-to-head comparisons of nefazodone and sertraline, nor the single unpublished comparison of venlafaxine and sertraline, detected a difference in the efficacy of medication agents in reducing symptom severity. The investigators in the only trial to compare mirtazapine and sertraline directly[17] were unable to detect a difference in efficacy when comparing these groups on the total CAPS score. The RCT of sertraline in treating concurrent PTSD and co-morbid alcoholism[26] was not able to detect a difference in the efficacy of medication and placebo in reducing symptom severity on the CAPS.

Patients who received medication in the 13 short-term trials providing treatment response data on the CGI-I or a related measure were significantly more likely to be responders than those who received placebo (RR = 1.49, 95% CI: 1.28 - 1.73, N = 1 272). Response to medication occurred in 59.1% of subjects (N = 644), while response to placebo was seen in 38.5% of subjects (N = 628). The short-term efficacy of medication treatment was observed for the SSRIs as a group (N = 7, RR = 1.59, 95% CI: 1.39 - 1.82, N = 999).

The pattern of treatment response on the CGI-I for the separate SSRI medications was similar to that observed for symptom severity, with both paroxetine (N = 3, RR = 1.62, 95% CI: 1.38 - 1.9, N = 719) and sertraline (N = 2, RR = 1.71, 95% CI: 1.22 - 2.4, N = 215) demonstrating efficacy (Fig. 3). There was insufficient evidence to determine whether fluoxetine or the MAOI brofaromine was effective in increasing the number of responders, relative to placebo. None of the trials of the TCA amitriptyline, the novel antidepressant mirtazapine, the antipsychotic olanzapine, or the anticonvulsant lamotrigine was significantly more effective than placebo in increasing treatment response.

The NNT analysis revealed that approximately 5 additional patients would need to be treated with medication over an average period of 11 weeks to achieve 1 additional response, relative to placebo (NNT = 4.85). The equivalent number of
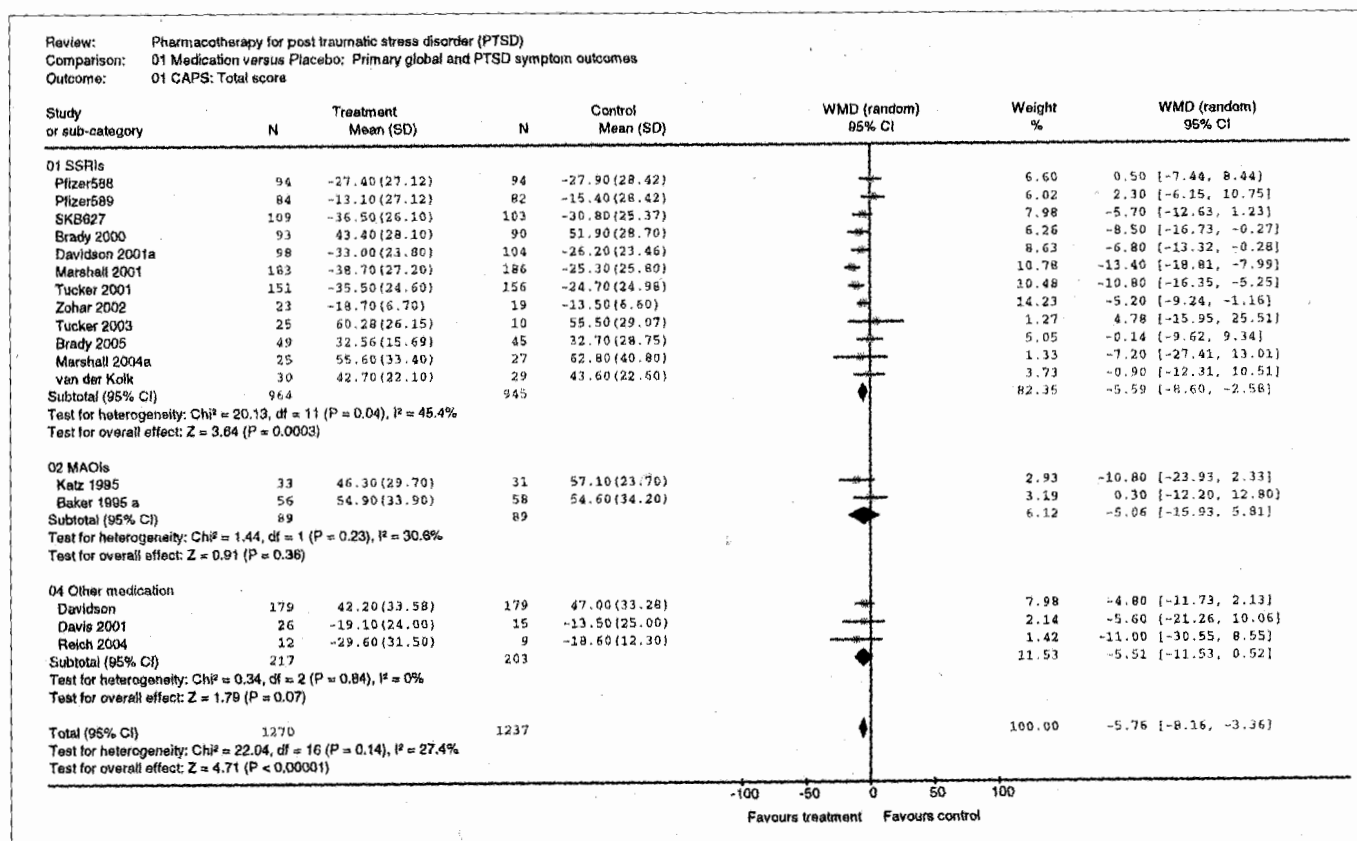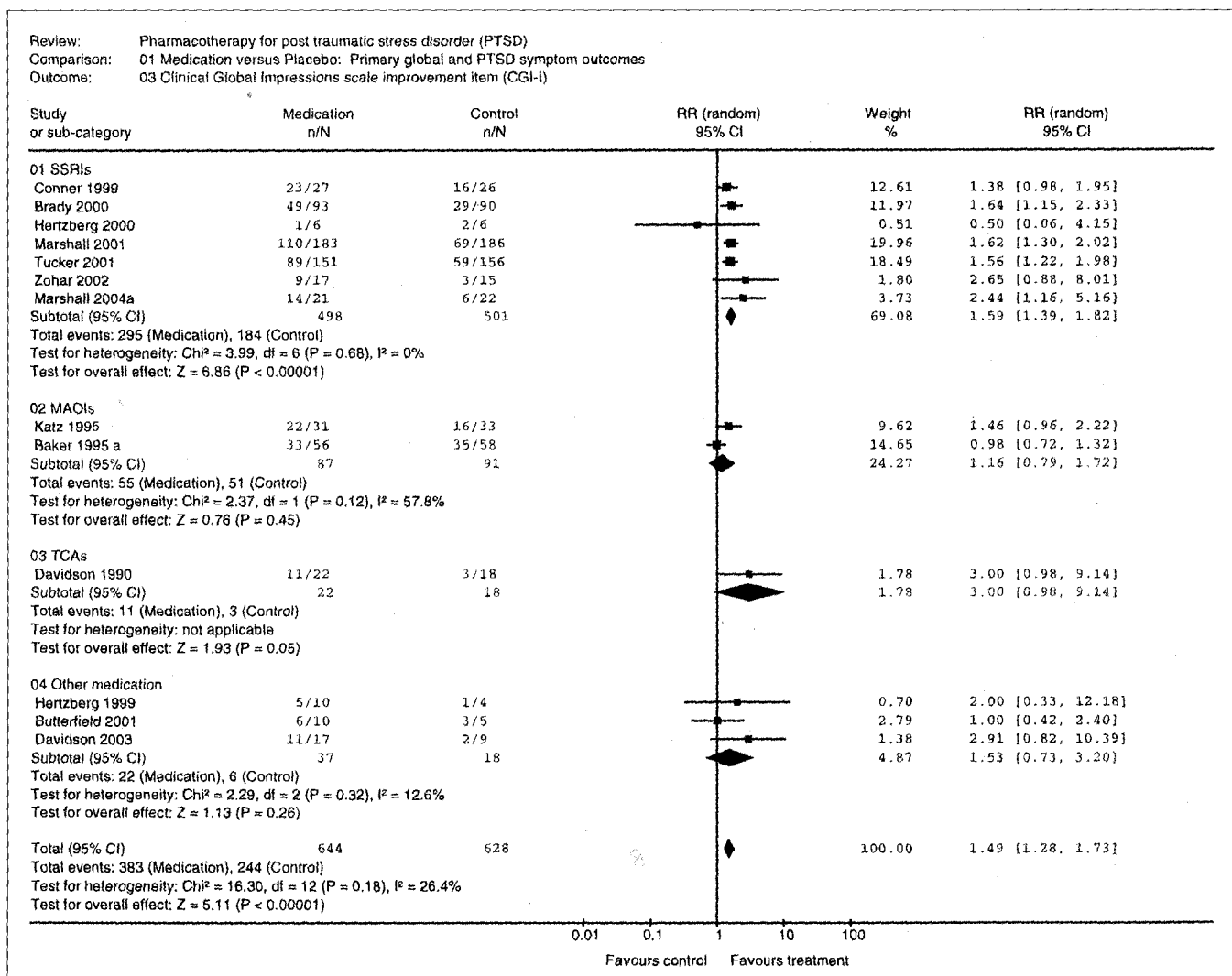

Review: Pharmacotherapy for post traumatic stress disorder (PTSD)
Comparison: 01 Medication versus Placebo: Primary global and PTSD symptom outcomes
Outcome: 01 CAPS: Total score

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 SSRIs							
Pfizer588	94	-27.40 (27.12)	94	-27.90 (28.42)		6.60	0.50 [-7.44, 8.44]
Pfizer589	84	-13.10 (27.12)	82	-15.40 (28.42)		6.02	2.30 [-6.15, 10.75]
SKB627	109	-36.50 (26.10)	103	-30.80 (25.37)		7.98	-5.70 [-12.63, 1.23]
Brady 2000	93	43.40 (28.10)	90	51.90 (28.70)		6.26	-8.50 [-16.73, -0.27]
Davidson 2001a	98	-33.00 (23.80)	104	-26.20 (23.46)		8.63	-6.80 [-13.32, -0.28]
Marshall 2001	183	-38.70 (27.20)	186	-25.30 (25.80)		10.78	-13.40 [-18.81, -7.99]
Tucker 2001	151	-35.50 (24.60)	156	-24.70 (24.98)		10.48	-10.80 [-16.35, -5.25]
Zohar 2002	23	-18.70 (6.70)	19	-13.50 (6.60)		14.23	-5.20 [-9.24, -1.16]
Tucker 2003	25	60.28 (26.15)	10	55.50 (29.07)		1.27	4.78 [-15.95, 25.51]
Brady 2005	49	32.56 (15.69)	45	32.70 (28.75)		5.05	-0.14 [-9.62, 9.34]
Marshall 2004a	25	55.60 (33.40)	27	62.80 (40.80)		1.33	-7.20 [-27.41, 13.01]
van der Kolk	30	42.70 (22.10)	29	43.60 (22.60)		3.73	-0.90 [-12.31, 10.51]
Subtotal (95% CI)	964		945			82.35	-5.59 [-8.60, -2.58]
Test for heterogeneity: Chi² = 20.13, df = 11 (P = 0.04), I² = 45.4%							
Test for overall effect: Z = 3.64 (P = 0.0003)							
02 MAOIs							
Katz 1995	33	46.30 (29.70)	31	57.10 (23.70)		2.93	-10.80 [-23.93, 2.33]
Baker 1995 a	56	54.90 (33.90)	58	54.60 (34.20)		3.19	0.30 [-12.20, 12.80]
Subtotal (95% CI)	89		89			6.12	-5.06 [-15.93, 5.81]
Test for heterogeneity: Chi² = 1.44, df = 1 (P = 0.23), I² = 30.6%							
Test for overall effect: Z = 0.91 (P = 0.36)							
04 Other medication							
Davidson	179	42.20 (33.58)	179	47.00 (33.28)		7.98	-4.80 [-11.73, 2.13]
Davis 2001	26	-19.10 (24.00)	15	-13.50 (25.00)		2.14	-5.60 [-21.26, 10.06]
Reich 2004	12	-29.60 (31.50)	9	-18.60 (12.30)		1.42	-11.00 [-30.55, 8.55]
Subtotal (95% CI)	217		203			11.53	-5.51 [-11.53, 0.52]
Test for heterogeneity: Chi² = 0.34, df = 2 (P = 0.84), I² = 0%							
Test for overall effect: Z = 1.79 (P = 0.07)							
Total (95% CI)	1270		1237			100.00	-5.76 [-8.16, -3.36]
Test for heterogeneity: Chi² = 22.04, df = 16 (P = 0.14), I² = 27.4%							
Test for overall effect: Z = 4.71 (P < 0.00001)							

-100   -50   0   50   100
Favours treatment   Favours control

Fig. 2. PTSD symptom severity.

Review: Pharmacotherapy for post traumatic stress disorder (PTSD)
Comparison: 01 Medication versus Placebo: Primary global and PTSD symptom outcomes
Outcome: 03 Clinical Global Impressions scale improvement item (CGI-I)

Study or sub-category	Medication n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 SSRIs					
Conner 1999	23/27	16/26		12.61	1.38 [0.98, 1.95]
Brady 2000	49/93	29/90		11.97	1.64 [1.15, 2.33]
Hertzberg 2000	1/6	2/6		0.51	0.50 [0.06, 4.15]
Marshall 2001	110/183	69/186		19.96	1.62 [1.30, 2.02]
Tucker 2001	89/151	59/156		18.49	1.56 [1.22, 1.98]
Zohar 2002	9/17	3/15		1.80	2.65 [0.88, 8.01]
Marshall 2004a	14/21	6/22		3.73	2.44 [1.16, 5.16]
Subtotal (95% CI)	498	501		69.08	1.59 [1.39, 1.82]
Total events: 295 (Medication), 184 (Control)					
Test for heterogeneity: Chi² = 3.99, df = 6 (P = 0.68), I² = 0%					
Test for overall effect: Z = 6.86 (P < 0.00001)					
02 MAOIs					
Katz 1995	22/31	16/33		9.62	1.46 [0.96, 2.22]
Baker 1995 a	33/56	35/58		14.65	0.98 [0.72, 1.32]
Subtotal (95% CI)	87	91		24.27	1.16 [0.79, 1.72]
Total events: 55 (Medication), 51 (Control)					
Test for heterogeneity: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.8%					
Test for overall effect: Z = 0.76 (P = 0.45)					
03 TCAs					
Davidson 1990	11/22	3/18		1.78	3.00 [0.98, 9.14]
Subtotal (95% CI)	22	18		1.78	3.00 [0.98, 9.14]
Total events: 11 (Medication), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.05)					
04 Other medication					
Hertzberg 1999	5/10	1/4		0.70	2.00 [0.33, 12.18]
Butterfield 2001	6/10	3/5		2.79	1.00 [0.42, 2.40]
Davidson 2003	11/17	2/9		1.38	2.91 [0.82, 10.39]
Subtotal (95% CI)	37	18		4.87	1.53 [0.73, 3.20]
Total events: 22 (Medication), 6 (Control)					
Test for heterogeneity: Chi² = 2.29, df = 2 (P = 0.32), I² = 12.6%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	644	628		100.00	1.49 [1.28, 1.73]
Total events: 383 (Medication), 244 (Control)					
Test for heterogeneity: Chi² = 16.30, df = 12 (P = 0.18), I² = 26.4%					
Test for overall effect: Z = 5.11 (P < 0.00001)					

0.01   0.1   1   10   100

Favours control   Favours treatment

Fig. 3. Treatment response.

patients for the individual SSRIs was 4.31 for paroxetine, 4.49 for sertraline, and 6.07 for fluoxetine.

Continued reduction of symptom severity on the CAPS was observed in the 10-week extension of the 12-week placebo-controlled RCT of paroxetine (Marshall RD, Lewis-Fernandez R, Blanco C, *et al.* – unpublished data). An increased rate of relapse was observed in those patients randomised to placebo after responding to a 12-week trial of fluoxetine.[27] Davidson and colleagues[28] found that over half of the 96 outpatients who had initially responded to 6 months of treatment with sertraline experienced worsening of symptoms once switched over to placebo, with patients in this group being 6.35 times more likely to relapse than those participants who remained on medication.

Across trials there was little variation in the effectiveness of medication in reducing symptom severity (chi-square = 16.3, df = 12, p = 0.18) or treatment response. However, separation of the effects of the SSRIs by agent revealed that paroxetine was

more effective in reducing symptom severity than sertraline (Q_b = 8.86, $p < 0.01$). Indeed, the reduction of symptom severity was more than twice as great for paroxetine as for all the other medications combined (WMD = -10.49 versus -4.07).

No effect of medication was observed on the symptom severity and treatment response outcome measures used in any of the placebo-controlled cross-over trials of alprazolam, desipramine, inositol, and phenelzine.

Secondary outcomes

The finding of a significant effect of medication on the re-experiencing/intrusion (WMD = -2.06, 95% CI: -3.02 - -1.1, N = 1 304), avoidance/numbing (WMD = -4.06, 95% CI: -5.41 - -2.7, N = 1 304), and hyperarousal (WMD = -3.1, 95% CI: -4.1 - -2.1, N = 1 304) symptom subscales of the CAPS can largely be attributed to the data from the 7 SSRI trials. The remaining trials of nefazodone (N = 1) and risperidone (N = 1)

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provided no evidence of efficacy on any of the symptom clusters.

With regard to co-morbidity, medication demonstrated greater efficacy in alleviating the symptoms of depression than placebo, as assessed by a range of depression scales ($N = 7$, SMD $= -0.34$, 95% CI: $-0.57 - -0.10$, $N = 459$). The only head-to-head comparison of nefazodone with sertraline for which co-morbidity summary statistics were available demonstrated that these medications were equally effective in reducing symptoms of depression. This was also the case for the single trial comparing mirtazapine and sertraline.

Quality of life was significantly improved by pharmaco- therapy ($N = 5$, WMD $= -2.54$, 95% CI: $-3.68 - -1.41$, $N = 752$), according to summary statistics on the Sheehan Disability Scale (SDS). Once again, this was primarily due to the SSRI interventions, with only 1 of the 4 trials in this class not demonstrably superior to placebo in improving functioning. Patients receiving medication were more likely to withdraw from treatment because of side-effects experienced than those who received placebo ($N = 21$, RR $= 1.44$, 95% CI: $1.04 - 2$, $N = 2\ 116$). However this finding could not be attributed to the poor tolerability of any particular medication class.

Subgroup analyses

Symptom severity was reduced to a greater extent when multiple centres participated in a trial ($N = 6$) than when the trial was conducted at a single centre ($N = 8$) ($Q_b = 2.8$, $p = 0.09$, df = 13). However this difference was not observed with regard to treatment response for the comparison of single versus multi-centre trials.

Symptom severity decreased to an equivalent extent ($Q_b = 0.5$, $p = 0.48$) in trials that included depressed participants ($N = 9$) and those that did not ($N = 2$). RCTs that included few combat veterans ($N = 8$, average proportion of war veterans = 3%) demonstrated a significantly greater reduction in symptom severity

following medication treatment ($Q_b = 4.12$, $p = 0.04$) than trials with a large percentage of participants with combat-related trauma ($N = 4$, average proportion = 61.1%). The difference between these groups was not detected with regard to treatment response.

Discussion

This review provides evidence of the effectiveness of medication in the short-term treatment of PTSD, as assessed on the primary outcome measures of responder status and symptom severity. Medication was significantly more effective than placebo across the three symptom clusters that characterise PTSD. In addition, the administration of medication resulted in a reduction in co-morbid symptoms, and improvement in quality of life measures. These findings hold despite the clinical heterogeneity of PTSD subjects included in the reviewed trials (Tables I and II).

The current evidence base of RCTs is unable to demonstrate superior efficacy or acceptability for any particular medication class, despite suggestions that the SSRIs are more effective and tolerable than older antidepressants.[29] Nevertheless, the fact that the SSRI trials constitute the bulk of the evidence for the efficacy of medication in treating PTSD suggests that it is reasonable to support the expert consensus[30] that SSRIs constitute the first-line medication choice in PTSD.

Indeed, it is unlikely that all medications are equally effective in treating PTSD. While there is evidence that paroxetine and sertraline are effective in reducing the severity of PTSD symptoms, and although the two mirtazapine trials provide some support for the efficacy of this agent, none of the alprazolam, brofaromine, desipramine, lamotrigine and olanzapine trials demonstrated efficacy with regard to treatment response or symptom reduction. The question of whether benzodiazepines are useful immediately after trauma or in PTSD remains debated, although recent

Table II. Comparative randomised studies included in the review

Medication agents	First author	Year	Duration (wks)	Number of sites	Sample size	Baseline severity†	% Males	% War trauma	% MDD
Mirtazapine and sertraline	Chung[17]	2004	6	1	113	96.19	100	100	15
Nefazodone and sertraline	McRae[16]	2004	12	2	37	71.38	23.1	0	–
Nefazodone and sertraline	Saygin[19]	2002	24	1	60	–	75.9	0	8.3
Paroxetine, sertraline and venlafaxine	Smajkic[18]	2001	6	1	40	43.8	0	0	–

*Number next to first author refers to number of study citation.
†Baseline severity on CAPS.
MDD = major depressive disorder; – = no data provided.

expert consensus panels have suggested caution in use of these agents.[7,30]

The finding that treatment over the longer term results in further improvements in efficacy and prevents relapse is consistent with the recommended duration of medication treatment of 6 - 12 months for acute PTSD,[7] and treatment of at least 12 months for chronic PTSD.[7,30]

Given the heterogeneous phenomenology of PTSD, it remains crucial to conduct further research into the factors, such as age and co-morbidity, that may predict response to medication. For instance, this review found some evidence that war veterans experience less reduction in symptom severity following pharmacotherapy than other patient groups. The failure to find a similar difference in treatment efficacy for patients with and without co-morbid major depression suggests that these medications are unlikely to exert their effects indirectly in PTSD via a reduction in depressive symptoms.

Finally, the inherent problems of meta-analyses should also be borne in mind; the quality of a meta-analysis is only as good as that of its constituent trials. The context of clinical practice also differs from controlled trials in many respects, such as the inclusion in the former of patients with more complex symptom presentations and the possible need of polypharmacy in a subgroup of patients with PTSD.

Conclusion

Implications for practice

Medication can be effective in treating PTSD, acting to reduce its core symptoms, and should be considered as part of the treatment of this disorder. The bulk of evidence for the efficacy of medication has, to date, been with the SSRIs and supports expert consensus guidelines that these medications constitute first-line agents in treating PTSD. The findings of maintenance trials support the value of long-term treatment in improving efficacy and preventing relapse.

Implications for research

Additional good-quality controlled trials would help to answer questions regarding the differential efficacy and acceptability of medication classes, as well as factors predicting response. Further research on the value of medication in treating PTSD in different trauma and age groups, and in co-morbid and treatment-resistant patients, is needed. Clinical trials to determine the possible benefits of early, combined (with psychotherapy), and long-term intervention in PTSD may also be valuable.

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