BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"For adults with Post-Traumatic Stress Disorder (PTSD) greater than 3 months duration, what is the most effective pharmacological intervention for decreasing PTSD symptoms?"

Clarification of question using PICO structure

Patients:	Adults with Post-Traumatic Stress Disorder (PTSD) greater than 3 months duration
Intervention:	Any pharmacological intervention
Comparator:	Any
Outcome:	PTSD symptoms

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Clinical and research implications

There is some very limited evidence, from very small trials with substantial methodological flaws, to suggest that antipsychotic drugs (specifically olanzapine and risperidone) may be effective in treating the symptoms of chronic PTSD with non-combat origins. Similarly, evidence from one very small, poor quality trial indicated that nefazodone may be effective in treating combat veterans with chronic PTSD. Two larger trials reported consistent results indicating that paroxetine may be effective in reducing both primary PTSD symptoms and depression symptoms in patients chronic PTSD with a variety of trauma sources. No studies reported comparisons of active treatments and it was therefore not possible to assess the relative effectiveness of different treatment options.

Further high quality research is needed particularly to compare the effectiveness of different active treatments and to assess the effectiveness of treatments in patients with combat-related trauma.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified eight randomised controlled trials which were considered relevant to this evidence summary.[1-8] All of the identified studies were placebo controlled trials; there were no studies comparing active treatments and hence there is no basis for assessing which pharmacological treatment option is most effective. All studies were conducted in adults with chronic PTSD. Four studies were conducted in veterans with combat trauma; two assessed divalproex,[3,4] one assessed fluoxetine,[5] and one assessed nefazodone.[2] Two studies were conducted in non-combat populations, both of which assessed the effectiveness of antipsychotic drugs, olanzapine[1] and risperidone.[7] The remaining two studies were conducted in mixed populations that included combat and other sources of trauma; both of these studies assessed the effectiveness of the SSRI paroxetine.[6,8] Studies reported a variety of outcome measures including measures of PTSD symptoms, trauma, depressive symptoms, disability and functioning.

Main Findings

Of the four studies conducted in veterans with combat trauma, only the study of nefazodone found any statistically significant treatment effects; this study found that nefazodone was associated with a reduction in PTSD symptoms and symptoms of depression compared to placebo, however the study was small (n=42) and had a dropout rate of approximately 43%.[2] The two studies that assessed the effectiveness of antipsychotic drugs in populations with non-combat-related trauma found that both olanzapine[1] and risperidone[7] were associated with improvements in PTSD symptoms compared to placebo and that olanzapine was also associated with improvements in trauma symptoms and functioning but had no effect on symptoms of depression;1 both studies were small (n=34,[1] and n=21,[7]) and had high dropout rates. Two large studies, conducted in populations with mixed trauma sources, found that paroxetine was associated with significant reductions in PTSD, trauma and depression symptoms, and reductions in measures of disability compared to placebo.[6, 8]

Authors Conclusions

Carey (2012) - Despite the small sample size, these data suggest that olanzapine may have a role in the treatment of PTSD. These findings warrant replication in a larger sample.

Davis (2004) - This pilot study supports the efficacy of nefazodone for the treatment of PTSD. However, larger placebo-controlled studies in more diverse patient population are warranted.

Davis (2008) - Divalproex monotherapy was not effective in the treatment of chronic PTSD in predominantly older male combat veterans. Further study is needed to determine the efficacy of divalproex in the management of PTSD in women or civilians or in combination with antidepressants.

Hamner (2009) - Divalproex was not superior to placebo in this study. This could be due to lack of effi cacy of divalproex in this population, inadequate sample size to detect differences, or other factors. Further study of divalproex is needed to better clarify the role of this agent in PTSD.

Hertzberg (2000) – Fluoxetine patients did not show a greater response than placebo patients in this small sample of male combat veterans with severe chronic PTSD.

Marshall (2001) – Doses of 20 and 40 mg/d of paroxetine are effective and well tolerated in the treatment of adults with chronic PTSD.

Reich (2004) – The results of this study indicate that low dose risperidone is a safe and effective treatment for intrusive and hyperarousal symptoms in women with chronic PTSD from childhood physical, sexual, verbal and emotional abuse.

Tucker (2001) – Paroxetine in doses of 20 to 50 mg once daily is effective as a treatment for chronic PTSD.

Reliability of conclusions/Strength of evidence

This evidence summary is based on eight randomised controlled trials. Most trails had very small sample sizes and all had substantial methodological weaknesses. All but one had high dropout rates (ranging from 20 to 51%). The evidence base is therefore weak. In addition, all of the studies identified were placebo controlled trials; there were no studies comparing active treatments and hence there is no basis for assessing which pharmacological treatment option is most effective.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines make recommendations as to what is the most effective pharmacological treatment for chronic PTSD.

Date question received: 01/12/2014
Date searches conducted: 05/01/2015
Date answer completed: 26/01/2015

References

1. Carey, P., Suliman, S., Ganesan, K., Seedat, S., & Stein, D. J. (2012). Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. *Human Psychopharmacology: Clinical and Experimental*, *27*(4), 386-391.

2. Davis, L. L., Jewell, M. E., Ambrose, S., Farley, J., English, B., Bartolucci, A., & Petty, F. (2004). A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: A preliminary study. *Journal of Clinical Psychopharmacology*, *24*(3), 291-297.

3. Davis, L. L., Davidson, J. R., Ward, L. C., Bartolucci, A., Bowden, C. L., & Petty, F. (2008). Divalproex in the treatment of posttraumatic stress disorder: A randomized, double-blind, placebo-controlled trial in a veteran population. *Journal of Clinical Psychopharmacology*, *28*(1), 84-88.

4. Hamner, M. B., Faldowski, R. A., Robert, S., Ulmer, H. G., Horner, M. D., & Lorberbaum, J. P. (2009). A preliminary controlled trial of divalproex in posttraumatic stress disorder. *Ann Clin Psychiatry*, *21*(2), 89-94.

5. Hertzberg, M. A., Feldman, M. E., Beckham, J. C., Kudler, H. S., & Davidson, J. R. (2000). Lack of efficacy for fluoxetine in PTSD: A placebo controlled trial in combat veterans. *Annals of Clinical Psychiatry*, *12*(2), 101-105.

6. Marshall, R. D., Beebe, K. L., Oldham, M., & Zaninelli, R. (2001). Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study. *American Journal of Psychiatry*, *158*(12), 1982-1988.

7. Reich, D. B., Winternitz, S., Hennen, J., Watts, T., & Stanculescu, C. (2004). A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *The Journal of Clinical Psychiatry*, *65*(12), 1601-1606.

8. Tucker, P., Zaninelli, R., Yehuda, R., Ruggiero, L., Dillingham, K., & Pitts, C. D. (2001). Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *Journal of Clinical Psychiatry*.

Results

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Carey et al. (2012)	*Participants*: Inclusion criteria: Adults (≥18 years); DSM-IV diagnosis of non-combat-related chronic PTSD (symptoms of at least 3 months duration); ≥50 on the Clinician Administered PTSD Scale (CAPS); free of psychotropic medication for a washout period of 5 days (5 weeks for fluoxetine) prior to randomisation. Exclusion criteria: current major depressive disorder (MADRS score≥20); presence of suicide risk; substance use disorder within past 6 months; history of severe personality disorder; history of psychosis; pregnant, breastfeeding, or female of childbearing age unwilling to use contraception; unstable medical condition; unresolved significant laboratory of ECG findings; previous failure to respond to or intolerance of second generation antipsychotics; failure of two or more trials of an SSRI or SNRI; initiation or change in psychotherapy in	n=34 randomised (n=28 included in the analyses)	This trial aimed to assess the efficacy and tolerability of olanzapine monotherapy for the treatment of non-combat related PTSD. There were no statistically significant between-group differences in measures of symptoms and disease severity at baseline, with the exception of SDS which was higher in the placebo group. No information was reported to allow assessment of between group equivalence with respect to other participant characteristics. Ten of the 34 randomised participants did not complete the study: four were lost to follow-up (groups not reported); one was withdrawn due to poor compliance (group not reported); four were withdrawn due to lack of efficacy or withdrawn consent (groups not reported); one was withdrawn due to severe sedation (olanzapine group). The mean age of the 28 participants included in the analyses was 41.5±11 years and 61% were female. Mean baseline CAPS scores were >75 in both groups. The mean daily dose of olanzapine, over the duration of the study, was not reported. The mean improvement in CAPS score, from baseline to	The study was described as a randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. Appearance matched olanzapine/placebo was supplied by an independent pharmacist. Outcomes were assessed by study clinicians.

	the previous 8 weeks; ECT in the previous 3 months; participation in a clinical trial in the previous 6 months; improvement of ≥2 points on the CGI scale between screening and randomisation. *Intervention*: Olanzapine monotherapy, flexible dose, 8 weeks. All participants started on 5mg/d for 1 week, then 7.5 mg/d for week 2, then 10 mg/d for weeks 3 to 4. This was increased in 2.5mg increments every 2 weeks to a maximum of 15mg/d, as necessary. No concomitant psychoactive medication was permitted during the study. *Comparator*: Placebo, matched appearance. *Outcome*: Primary: Change in PTSD symptoms using the CAPS, from baseline to 8 weeks. Secondary outcomes: clinical symptoms (Clinical Global Impressions Scale; CGI), depression (Montgomery and Asberg Depression Rating Scale; MADRS); trauma symptoms (Davidson Trauma Scale; DTS); functioning (Sheehan Disability Scale; SDS).		end-point (eight weeks), was significantly greater in the olanzapine group (-35.86±19.85) than in the placebo group (-19.29±28.77). When response was defined as >50% CAPS reduction from baseline to endpoint, 71.4% of participants in the olanzapine group and 21.4% of participants in the placebo group were classified as responders. CGI results were consistent with CAPS. Olanzapine was also associated with significant improvements in trauma symptoms (DTS) and functioning (SDS) compared to placebo (change from baseline data not reported). There were no significant between-group differences in depression symptoms (MADRS). Eleven participants in the olanzapine group and five in the placebo group reported sedation. Weight gain was reported by 100% of participants in the olanzapine group and 6/14 experienced substantial weight gain (6 to 10 Kg).	Ten of the 34 participants did not complete the study (dropout rate 29%) and analyses appeared to have been based on data from 28 participants. Baseline and endpoint values were reported for all listed outcome measures.
Davis et al. (2004)	*Participants*: Inclusion criteria: Adults (19 to 75 years); DSM-IV diagnosis of chronic PTSD; stable physical health; negative urine screen for	n=42 (nefazodone n=27; placebo	This trial aimed to assess the effectiveness of nefazodone for the treatment of chronic PTSD. Participants included in the analyses were 40 male veterans	The study was described as a randomised, double-blind, placebo-

	drugs of abuse; free of psychotropic medication in the previous 2 weeks (fluoxetine for 6 months); use of adequate contraception in women of childbearing age. Exclusion criteria: history of bipolar, cognitive, or psychotic disorder; acute suicidality or homicidality; current (previous 4 months) substance abuse/dependence; unstable medical condition; pregnancy or breast feeding; history of sensitivity to nefazodone. *Intervention*: Nefazodone, 12 weeks. 100mg capsule twice daily, increasing in 1 capsule increments every 4 days (as needed) to a maximum of 600 mg/day. *Comparator*: Placebo, matched appearance. *Outcome*: Primary outcome: PTSD symptoms (CAPS). Secondary outcomes: depression (Hamilton Rating Scale for Depression; HAMD), PTSD symptoms (PTSD Checklist; PTSDC), dissociation (Clinician-Administered Dissociative States Scale; CADSS), functioning (Global Assessment of Functioning Scale, GAFS; Clinician Global Impression, CGI).	n=15)	with combat trauma and one female civilian with sexual trauma. The mean age of study participants was approximately 54 years and the mean duration of PTSD was approximately 30 years. There were no clear differences in participant characteristics, duration of illness, or co-morbidities, between the nefazodone and placebo groups; a higher proportion of participants in the nefazodone group had prior exposure to other psychiatric medications. The mean final dose of nefadozone was 435 mg/d. Twelve (46%) of the participants in the nefazodone group and 6 (40%) of the participants in the placebo group did not complete the study. Five participants in the nefazodone group and none in the placebo group discontinued due to adverse events. The mean improvement in CAPS score, from baseline to end-point (12 weeks), was significantly greater in the nefazodone group (-19.1±24) than in the placebo group (-13.5±25); When sub-scales were analysed separately the effect of nefazodone only remained significant for the CAPS-D subscale (hyperarrousal). Similar, though not statistically significant treatment effects were seen for the PTSD symptom checklist and the Clinician-Administered Dissociative States Scale (CADSS). Based on a definition of ≥30% CAPS reduction from baseline to endpoint, 47% of participants in nefazodone group and 42% of participants in the placebo group were classified as responders. Nefazodone was also associated with a statistically significantly greater reduction in symptoms of depression	controlled trial. Participants were randomised in a 2:1 ratio, nefazodone:placebo, but no further details of the randomisation or allocation concealment procedures were reported. Appearance matched nefazodone/placebo was used. No details of outcome assessors were reported. Analyses were reported as intention-to-treat basis. One participant form the nefazodone group was excluded due to

			(HAM-D) score (-3.8±8) than placebo (-1.8±6).	compromised blinding arising from a medical event un-related to the study medication. However, dropout rates were high (46% in the nefazodone group and 40% in the placebo group. Baseline and follow-up values were reported for all listed outcome measures.
Davis et al. (2008)	*Participants*: Inclusion criteria: Adults (19 to 70years); chronic PTSD (DSM-IV) and a total CAPS score ≥45; stable medical condition; use of adequate contraception in women of childbearing age. Exclusion criteria: Substance-use disorder in previous 2 months; any psychotropic medication use in past 2 weeks (fluoxetine for 6 months); history of bipolar, cognitive, or psychotic disorder;	n=85 (divalproex 44, placebo n=41)	This trial aimed to assess the efficacy of divalproex for the treatment of PTSD hyperarousal symptom cluster. Eighty-two participants (41 in each group) received at least one dose of study medication and were included in the analyses. Eighty of these participants were male and all but 4 had combat-related trauma. The mean age of study participants was 55.2±6.8 years and the mean illness duration was 24.4±10.9 years. There were no significant between-group differences in age, sex, trauma type, duration of illness, or baseline measures of symptoms. The	Randomisation was determined by a random-number generator with allocation sequence that was concealed in the pharmacy until the study was completed.

	history of seizures; current suicidality or homicidality; pregnancy or breast feeding; history of sensitivity to divalproex. *Intervention*: Divalproex, 8 weeks. 500mg tablet twice a day, increasing in 500mg increments until maximum therapeutic benefit was achieved (maximum dose 3000mg/d). No other psychotropic medications were allowed during the study, except for low-dose trazodone (50 mg/d), if needed, for insomnia. *Comparator*: Placebo, matched appearance. *Outcome*: Primary outcome: PTSD symptoms (CAPS). Secondary outcomes: depression (HAMD; MADRS), PTSD treatment outcome (Treatment Outcome PTSD Scale, TOP-8), functioning (Clinical Global Impressions Scale for Severity, CGI-S; Clinical Global Impressions Scale for Improvement, CGI-I), trauma symptoms (DTS).		mean final dose of divalproex was 2309±508 mg/d. Seven patients (17%) from the placebo group and ten (22%) from the divalproex group did not complete the study. Three patients from the divalproex group and one from the placebo group discontinued due to adverse events. There were statistically significant between-group differences in any of the outcome measures assessed.	Appearance matched divalproex/placebo was used. No details of outcome assessors were reported. Analyses used a modified intention-to-treat approach, with all randomised participants who received at least one dose of study medication included. However, the dropout rate was high (approximately 20%). Baseline and follow-up values were reported for all listed outcome measures.
Hamner et al.	*Participants*: Inclusion criteria: Adults (18 to 65 years);	n=29 (divalproex	This trial aimed to assess the efficacy and tolerability of divalproex for the treatment of chronic PTSD.	The study was described as a

(2009)	chronic PTSD (DSM-IV) and a CAPS score ≥50 Exclusion criteria: Unstable medical condition; substance-use disorder within previous 1 month; history of psychosis or bipolar disorder; change in psychotropic medication within 4 weeks of study entry. *Intervention*: Divalproex, 10 weeks. 750 mg/d in divided doses, increased by 250mg every 3-4 days if tolerated, until a positive clinical response was achieved. *Comparator*: Placebo *Outcome*: Primary outcome: PTSD symptoms (CAPS). Secondary outcomes Impact of events (Impact of Events Scale, EIS), functioning (CGI-I), depression (HAMD), anxiety (Leibowitz Social Anxiety Scale, LSAS), sleep quality (Pittsburgh Sleep Quality Index, PSQI; PSQI-A).	n=16, placebo n=13)	Twenty-eight participants received at least one dose of study medication and were included in the analyses; one patient in the divalproex group was excluded. All but one of the study participants was male and the sources of trauma were combat (28) and sexual assault (1). The mean age of study participants was approximately 52 years and the mean illness duration was not reported. There were no significant between-group differences in participant demographic characteristics, comorbidities, clinical history, or medication history, at baseline. The mean final dose of divalproex was 1250±327 mg/d. Seven patients (44%) from the divalproex group and seven (54%) from the placebo group did not complete the study. Two patients from the divalproex group and one from the placebo group discontinued due to adverse events. There were statistically significant between-group differences in any of the outcome measures assessed.	randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. The study was described as double blind but no further details were reported; it was not clear which combination of participants, treating clinicians and outcome assessors was blinded. Analyses used a modified intention-to-treat approach, with all randomised participants who received at least one dose of study medication included.

				However, the dropout rate was high (approximately 51%). Baseline and follow-up values were reported for all listed outcome measures.
Hertzberg et al. (2000)	*Participants*: No inclusion or exclusion criteria were reported. Participants were male veterans with chronic PTSD (DSM-IV). *Intervention*: Fluoxetine, 12 weeks. Starting 10mg/d, increased after 1 week by 10mg/d if tolerated until maximum response was achieved (maximum dose 60mg/d). No concomitant psychotropic medications were allowed during the study. *Comparator*: Placebo *Outcome*: Trauma (DTS), functioning (SDS), clinical symptoms (Structured Interview for PTSD, SIP; Duke Global Rating for PTSD Scale, DGRP).	n=12 (fluoxetine n=6, placebo n=6)	This trial aimed to assess the effects of fluoxetine in male combat veterans with severe chronic PTSD. The mean age of study participants was 46 years (range 44 to 48) and all were male combat veterans. There were no significant between-group differences in age, compensation status, ethnicity, or duration and severity of illness, at baseline. The mean fluoxetine dose at week 12 was 48 mg/d. One participant in the fluoxetine group did not complete the study due to adverse events (activation symptoms). Based on Duke improvement scores, one fluoxetine patient and two patients in the placebo group responded. There were statistically significant between-group differences in trauma (DTS), functioning (SDS), or PTSD symptoms (SIP).	The study was described as a randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. The study was described as double blind but no further details were reported; it was not clear which combination of

				participants, treating clinicians and outcome assessors was blinded. All participants appear to have been included in the analyses. Baseline and follow-up values were reported for all listed outcome measures.
Marshall et al. (2001)	*Participants*: Inclusion criteria: adults (≥18 years); chronic PTSD (DSM-IV); CAPS score ≥50; concurrent affective and anxiety disorders were allowed if PTSD was the primary diagnosis; use of adequate contraception and negative pregnancy test for females of childbearing age. Exclusion criteria: receipt of disability payments or involvement in litigation relating to PTSD or any other psychiatric illness; alcohol/substance abuse/dependence within 6 months of entry; taking psychotropic medication	n=563; n=551 included in the analyses (placebo n=186; 20 mg/d paroxetine n=183; 40 mg/d paroxetine n=182)	This trial aimed to assess the efficacy and safety of paroxetine for the treatment of patients with chronic PTSD. The mean age of study participants was 41.8±11.6 years and there were approximately twice as many women as men in the study. The most common types of trauma were physical or sexual assault (48 to 54%), witnessing injury or death (17 to 16%), serious accident or injury (6 to 12 %), and combat (5 to 8%). The mean time from index trauma was 15.7±14.8 years. Participant characteristics and baseline symptoms did not differ significantly across the three groups. Sixty-eight (36%) participants from the placebo group, 66	The study was described as a randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. The study was described as double blind but no further

	within 2 weeks of entry (4 weeks for fluoxetine); psychotherapy or ECT within 12 weeks of entry; suicide or homicide risk; intolerant to paroxetine or any other SSRI; serious medical conditions. *Intervention*: (1) Paroxetine, 20mg/d, for 12 weeks; (2) Paroxetine, 40mg/d (started on 20 mg/d and increased to 40 mg/d by beginning of week 3), for 12 weeks. *Comparator*: Placebo. *Outcome*: Primary outcome: PTSD symptoms (CAPS-2; CGI). Secondary outcomes: trauma (DTS), depression (MADRS).		participants (35%) from the paroxetine 20 mg/d group, and 74 participants (40%) from the paroxetine 40 mg/d group did not complete the study. Eighteen participants from the placebo group, 21 participants from the paroxetine 20 mg/d group, and 28 participants from the paroxetine 40 mg/d group discontinued due to adverse events; there were no significant differences in the rate of discontinuation due to adverse events between the groups. Paroxetine, at both doses, was associated with significantly greater reductions in PTSD symptoms (CAPS-2) from baseline to 12 weeks than placebo; the mean change from baseline was -37.9±28.7 for the 40 mg/d paroxetine group, -39.6±25.7 for the 20 mg/d paroxetine group, and -25.3±25.8 for the placebo group. Treatment effects remained significant for all three CAPS subscales (re-experiencing, avoidance and hyper arousal). Paroxetine, at both doses, was associated with significantly greater reductions in trauma symptoms (DTA) from baseline to 12 weeks than placebo; the mean change from baseline was -36.0±30.9 for the 40 mg/d paroxetine group, -38.5±29.6 for the 20 mg/d paroxetine group, and -25.1±29.4 for the placebo group. Treatment effects remained significant for all three DTS subscales (intrusion, avoidance and hyper arousal). Paroxetine, at both doses, was associated with significantly greater reductions in depression symptoms (MADRS) from	details were reported; it was not clear which combination of participants, treating clinicians and outcome assessors was blinded. Analyses included all randomised participants who had at least one post-treatment assessment, however, the dropout rate was high (approximately 37%). Change from baseline values were reported for all listed outcome measures.

			baseline to 12 weeks than placebo; the mean change from baseline was -11.3±10.9 for the 40 mg/d paroxetine group, -12.2±11.2 for the 20 mg/d paroxetine group, and -5.7±10.6 for the placebo group. Paroxetine, at both doses, was associated with significantly greater reductions in disability (SDS) from baseline to 12 weeks than placebo; the mean change from baseline was -6.4±8.1 for the 40 mg/d paroxetine group, -7.0±7.6 for the 20 mg/d paroxetine group, and -4.5±7.9 for the placebo group.	
Reich et al. (2004)	*Participants*: Inclusion criteria: Adult women (18 to 64 years) with chronic PTSD (DSM-III-R) related to childhood physical, sexual, verbal or emotional abuse; caps score ≥50 Exclusion criteria: organic mental disorder or psychosis in the last 6 months; substance dependence within the past 60 days; unstable general medical condition; previous treatment of risperidone for 1 week or more; treatment with another antipsychotic or mood stabiliser; significant risk of suicide or homicide; psychotherapy within past 3 months; group therapy in the previous month; pregnancy or nursing. Participants could be taking one antidepressant or hypnotic,	n=21 (risperidone n=12, placebo n=9)	This trial aimed to assess the effectiveness of risperidone for the treatment of women with chronic PTSD from childhood physical, sexual, verbal and emotional abuse. The mean age of study participants was approximately 27 years. There were no significant between-group differences in participant demographic or socioeconomic characteristics, abuse history, or symptom score at baseline. The overall mean daily dose of risperidone prescribed during the study was 1.41 mg. Three patients from the risperidone group and 2 from the placebo group did not complete the study. Treatment emergent adverse events were reported by four participants in the risperidone group and one participant in the placebo group. Risperidone was associated with significantly greater	The study was described as a randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. The study was described as double blind but no further details were reported; it was not

	but the dose was required to have been stable for at least 1 month prior to study entry. *Intervention*: Risperidone, 8 weeks. Flexible daily dosages in the range of 0.5-0.8mg. *Comparator*: Placebo. *Outcome*: PTSD symptoms (CAPS 1-month version, CAPS1; CAPS 1-week version CAPS2).		reductions in PTSD symptoms (CAPS-2) from baseline to eight weeks than placebo; the mean change from baseline was -29.6±31.5 for the risperidone group and -18.6±12.3 for the placebo group. Treatment effects remained significant for intrusive and hyper arousal subscales of CAPS-2, but not for the avoidance subscale.	clear which combination of participants, treating clinicians and outcome assessors was blinded. All participants appear to have been included in the analyses, but the dropout rate was high (approximately 24%). Full results were reported for CAPS-2
Tucker et al. (2001)	*Participants*: Inclusion criteria: Adult (≥18 years) outpatients; chronic PTSD (DSM-IV). Exclusion criteria: Comorbid bipolar disorder, dissociative disorder, or psychosis; formal psychotherapy or ECT within past 12 weeks, substance dependence/abuse within past 12 weeks; receiving disability payments or involved in litigation for any psychiatric disorder; alcohol/drug dependence in the previous 12 months (DSM-IV); psychoactive herbal medications (e.g., St John's wort).	n=323; n=307 included in the analyses (paroxetine 151, placebo 156)	This trial aimed to assess the efficacy and safety of paroxetine in outpatients with PTSD. The mean age of study participants was approximately 41 years and 34% were male. The mean time since index trauma was approximately 15 years. The most common traumas were physical or sexual assault (49%), witnessing injury or death (19%), serious accident or injury (10%), and combat (7%). The treatment groups were similar with respect to age, gender and race distribution, time since index trauma, trauma types, and baseline symptoms. The mean dose of paroxetine during the study was 27.6±6.72	The study was described as a randomised, double-blind, placebo-controlled trial, but no details of the randomisation or allocation concealment procedures were reported. The study was

	Comorbid mood and anxiety disorders were allowed, if PTSD was the primary disorder. Psychotropic medications were discontinued prior to the baseline assessment, with appropriate washout periods defined. *Intervention*: Paroxetine, 12 weeks; 20 mg/d for the first two weeks, then two weekly increases of 10 mg/d at the discretion of the treating clinician up to a maximum of 50mg/d. *Comparator*: Placebo. *Outcome*: Primary outcomes PTSD symptoms (CAPS; CGI). Secondary outcomes: trauma (DTS), PTSD treatment outcome (TOP-8), functional impairment (SDS), depression (MADRS).		mg/d. Twelve participants from the paroxetine group and four from the placebo group were lost to follow-up after baseline assessment. Paroxetine was associated with significantly greater reductions in PTSD symptoms (CAPS-2) from baseline to 12 weeks than placebo (adjusted mean difference -10,6 (95% CI: -16.2 to -5.0)); a significant treatment effect remained across all three domains of CAPS-2 (re-experiencing, avoidance and hyperarousal). A significant treatment effect was also seen for PTSD symptoms measured using TOP-8 (adjusted mean difference -3.8 (95% CI: -5.6 to -1.9)). Paroxetine was associated with significantly greater reductions in trauma symptoms (DTA) from baseline to 12 weeks than placebo (adjusted mean difference -12.6 (95% CI: -18.8 to -6.4)). Treatment effects remained significant for all three DTS subscales (intrusion, avoidance and hyper arousal). Paroxetine was associated with significantly greater reductions in depression symptoms (MADRS) from baseline to 12 weeks than placebo (adjusted mean difference -3.8 (95% CI: -6.4 to-1.2)). Paroxetine was associated with significantly greater reductions in disability (SDS) from baseline to 12 weeks than placebo (adjusted mean difference -2.6 (95% CI: -4.4	described as double blind but no further details were reported; it was not clear which combination of participants, treating clinicians and outcome assessors was blinded. The analyses included all randomised participants who had at least one post-baseline efficacy assessment. The dropout rate appeared to be approximately 5%. Full results were reported for all listed outcome measures.

			to -0.7)).	

Risk of Bias:

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Carey et al. (2012)	?	?	☺	☺	☹	☺
Davis et al. (2004)	?	?	☺	?	☹	☺
Davis et al. (2008)	☺	☺	☺	?	☹	☺
Hamner et al. (2009)	?	?	?	?	☹	☺
Hertzberg et al. (2000)	?	?	?	?	☺	☺
Marshall et al. (2001)	?	?	?	?	☹	☺
Reich et al. (2004)	?	?	?	?	☹	☺
Tucker et al. (2001)	?	?	?	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	PTSD pharmacological chronic	28	0
DARE	1 (ptsd OR post-trauma* OR (post adj1 trauma*) OR (stress* adj1 disorder*) OR (combat adj1 disorder*) or trauma*) IN DARE 1248 Delete 2 MeSH DESCRIPTOR Stress Disorders, Post-Traumatic EXPLODE ALL TREES 124 Delete 3 #1 OR #2 1284 Delete 4 (((serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj (uptake or reuptake or re-uptake))) IN DARE 346 Delete 5 ((antiadrenergic or anti-adrenergic)) IN DARE 1 Delete 6 (5-hydroxytrypotophan or Acetylcarnitine or Alaproclate or alprazolam or Amersergide or Amiflamine or Amineptine or Amitriptyline) IN DARE 181 Delete 7 (Amoxapine or anticonvulsant* or Antidepress* or antipsychotic* or anxiolytic* or Aripiprazole) IN DARE 1447 Delete 8 (Befloxatone or Benactyzine or Benzodiazepine* or Brofaromine or Bupropion or Butriptyline) IN DARE 348 Delete 9 (Carbazepine or Caroxazone or cck-4 or Chlorimipramine or Chlorphenamidine or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or clonidine or Clorgyline or Clovoxamine or Cyproheptadine or d-Cycloserine) IN DARE 260 Delete 10 (Deanol or Demexiptiline or Deprenyl or Desipramine or Desvenlafaxine or Dibenzipin or Diclofensine or divalproex or dopamin* or Dosulepin or Dothiepin or Doxazosin or Doxepin or Duloxetine) IN DARE 367 Delete 11 (Escitalopramor Etoperidone or Femoxetine or Fenfluramine or flumazenil or Fluotracen or fluoxetine or Fluparoxan or fluphenazine or Fluvoxamine or Furazolidone or Guanfacine) IN DARE 295 Delete 12 (haloperidol or Harmaline or Harmine or hydrocortisone or Idazoxan or Imipramine or inositol or Iprindole or Iproniazid or Isocarboxazid or lamotrigine) IN DARE 454 Delete	111	0

	13 (Lithium carbonate or Lithium compounds or Litoxetine or Lofepramine) IN DARE 40 Delete 14 (MAOI* or Maprotiline or medicat* or Medifoxamine or Melitracen or Metapramine or Metyrapone or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monoamine Oxidase Inhibitor*) IN DARE 2598 Delete 15 (Naloxone or Naltrexone or Nefazodone or Nialamide or Nomifensine or noradrenerg* or Norfenfluramine or Nortriptyline or Noxiptiline or Olanzapine or Opipramol or Oxaflozane or Oxaprotiline or Oxcarbazepine) IN DARE 391 Delete 16 (N-Methyl-3,4-methylenedioxyamphetamine) IN DARE 0 Delete 17 (Pargyline or Paroxetine or pharmacother* or Phenelzine or Pheniprazine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Prazosin or Pregabalin or Procaine or Propranolol or Prosulpride or Protriptyline or psychotropic*) IN DARE 949 Delete 18 (Quetiapine or Quinupramine or Quipazine or Reboxetine or Risperidone or Ritanserin or Rolipram) IN DARE 228 Delete 19 (Selegiline or seroto* or Sertraline or Setiptiline or SNRI* or SSRI* or Sulpiride) IN DARE 538 Delete 20 (Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tiagabine or Tianeptine or Toloxatone or Tomoxetine or Topiramate or Tranylcypromine or Trazodone or tricyclic* or Trimipramine or Tryptophan) IN DARE 349 Delete 21 (Venlafaxine or Viloxazine or Viqualine or Yohimbine or Zimeldine) IN DARE 105 Delete 22 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 4657 Delete 23 #3 AND #22 111 Delete		
Primary studies			
CENTRAL	#1 ptsd or post-trauma* or (post adj1 trauma*) or (stress* adj1 disorder*) or (combat adj1 disorder*) or trauma* 15347 #2 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees 957 #3 (serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj1 (uptake or reuptake or re-uptake) 18 #4 antiadrenergic or anti-adrenergic 45 #5 5-hydroxytrypotophan or Acetylcarnitine or Alaproclate or alprazolam or Amersergide or Amiflamine or Amineptine or Amitriptyline 3485 #6 Amoxapine or anticonvulsant* or Antidepress* or antipsychotic* or anxiolytic* or Aripiprazole	825	8

	20283 #7 Befloxatone or Benactyzine or Benzodiazepine* or Brofaromine or Bupropion or Butriptyline 6114 #8 Carbazepine or Caroxazone or cck-4 or Chlorimipramine or Chlorphenamidine or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or clonidine or Clorgyline or Clovoxamine or Cyproheptadine or d-Cycloserine 5938 #9 Deanol or Demexiptiline or Deprenyl or Desipramine or Desvenlafaxine or Dibenzipin or Diclofensine or divalproex or dopamin* or Dosulepin or Dothiepin or Doxazosin or Doxepin or Duloxetine 9040 #10 Escitalopramor Etoperidone or Femoxetine or Fenfluramine or flumazenil or Fluotracen or fluoxetine or Fluparoxan or fluphenazine or Fluvoxamine or Furazolidone or Guanfacine 5474 #11 haloperidol or Harmaline or Harmine or hydrocortisone or Idazoxan or Imipramine or inositol or Iprindole or Iproniazid or Isocarboxazid or lamotrigine 12714 #12 Lithium carbonate or Lithium compounds or Litoxetine or Lofepramine 878 #13 MAOI* or Maprotiline or medicat* or Medifoxamine or Melitracen or Metapramine or Metyrapone or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monoamine Oxidase Inhibitor* 46054 #14 Naloxone or Naltrexone or Nefazodone or Nialamide or Nomifensine or noradrenerg* or Norfenfluramine or Nortriptyline or Noxiptiline or Olanzapine or Opipramol or Oxaflozane or Oxaprotiline or Oxcarbazepine 7544 #15 N-Methyl-3,4-methylenedioxyamphetamine 105 #16 Pargyline or Paroxetine or pharmacother* or Phenelzine or Pheniprazine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Prazosin or Pregabalin or Procaine or Propranolol or Prosulpride or Protriptyline or psychotropic* 16015 #17 Quetiapine or Quinupramine or Quipazine or Reboxetine or Risperidone or Ritanserin or Rolipram 3460 #18 Selegiline or seroto* or Sertraline or Setiptiline or SNRI* or SSRI* or Sulpiride 10937 #19 Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tiagabine or Tianeptine or Toloxatone or Tomoxetine or Topiramate or Tranylcypromine or Trazodone or tricyclic* or Trimipramine or Tryptophan 4999 #20 Venlafaxine or Viloxazine or Viqualine or Yohimbine or Zimeldine 1795 #21 #1 or #2 15347		

	#22 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 102142 #23 #1 and #2		
PsycINFO	47. PsycINFO; ((serotonin OR norepinephrine OR noradrenaline OR dopamine OR neurotransmitter) adj1 (uptake OR reuptake OR re-uptake)).ti,ab; 8818 results. 48. PsycINFO; ((antiadrenergic OR anti-adrenergic)).ti,ab; 54 results. 49. PsycINFO; (5-hydroxytrypotophan OR Acetylcarnitine OR Alaproclate OR alprazolam OR Amersergide OR Amiflamine OR Amineptine OR Amitriptyline).ti,ab; 3473 results. 50. PsycINFO; (Amoxapine OR anticonvulsant* OR Antidepress* OR antipsychotic* OR anxiolytic* OR Aripiprazole).ti,ab; 57314 results. 51. PsycINFO; (Befloxatone OR Benactyzine OR Benzodiazepine* OR Brofaromine OR Bupropion OR Butriptyline).ti,ab; 11663 results. 52. PsycINFO; (Carbazepine OR Caroxazone OR cck-4 OR Chlorimipramine OR Chlorphenamidine OR Chlorpoxiten OR Cilosamine OR Cimoxatone OR Citalopram OR Clomipramine OR clonidine OR Clorgyline OR Clovoxamine OR Cyproheptadine OR d-Cycloserine).ti,ab; 6957 results. 53. PsycINFO; (Deanol OR Demexiptiline OR Deprenyl OR Desipramine OR Desvenlafaxine OR Dibenzipin OR Diclofensine OR divalproex OR dopamin* OR Dosulepin OR Dothiepin OR Doxazosin OR Doxepin OR Duloxetine).ti,ab; 40883 results. 54. PsycINFO; (Escitalopramor AND Etoperidone OR Femoxetine OR Fenfluramine OR flumazenil OR Fluotracen OR fluoxetine OR Fluparoxan OR fluphenazine OR Fluvoxamine OR Furazolidone OR Guanfacine).ti,ab; 9419 results. 55. PsycINFO; (haloperidol OR Harmaline OR Harmine OR hydrocortisone OR Idazoxan OR Imipramine OR inositol OR Iprindole OR Iproniazid OR Isocarboxazid OR lamotrigine).ti,ab; 15066 results. 56. PsycINFO; (Lithium AND carbonate OR Lithium AND compounds OR Litoxetine OR Lofepramine).ti,ab; 217 results. 57. PsycINFO; (MAOI* OR Maprotiline OR medicat* OR Medifoxamine OR Melitracen OR Metapramine OR Metyrapone OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Monoamine AND Oxidase AND Inhibitor*).ti,ab; 1762 results. 58. PsycINFO; (Naloxone OR Naltrexone OR Nefazodone OR Nialamide OR Nomifensine OR noradrenerg* OR Norfenfluramine OR Nortriptyline OR Noxiptiline OR Olanzapine OR Opipramol OR Oxaflozane OR Oxaprotiline OR Oxcarbazepine).ti,ab; 19022 results. 59. PsycINFO; N-Methyl-3,4-methylenedioxyamphetamine.ti,ab; 5 results.	444	0

	60. PsycINFO; (Pargyline OR Paroxetine OR pharmacother* OR Phenelzine OR Pheniprazine OR Piribedil OR Pirlindole OR Pivagabine OR Pizotyline OR Prazosin OR Pregabalin OR Procaine OR Propranolol OR Prosulpride OR Protriptyline OR psychotropic*).ti,ab; 26652 results. 61. PsycINFO; (Quetiapine OR Quinupramine OR Quipazine OR Reboxetine OR Risperidone OR Ritanserin OR Rolipram).ti,ab; 8526 results. 62. PsycINFO; (Selegiline OR seroto* OR Sertraline OR Setiptiline OR SNRI* OR SSRI* OR Sulpiride).ti,ab; 33256 results. 63. PsycINFO; (Teniloxine OR Tetrindole OR Thiazesim OR Thozalinone OR Tiagabine OR Tianeptine OR Toloxatone OR Tomoxetine OR Topiramate OR Tranylcypromine OR Trazodone OR tricyclic* OR Trimipramine OR Tryptophan).ti,ab; 10751 results. 64. PsycINFO; (Venlafaxine OR Viloxazine OR Viqualine OR Yohimbine OR Zimeldine).ti,ab; 2985 results. 65. PsycINFO; 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64; 156740 results. 66. PsycINFO; POSTTRAUMATIC STRESS DISORDER/ [Limit to: Publication Year 1998-2015]; 18749 results. 67. PsycINFO; (ptsd OR post-trauma* OR (post adj1 trauma*)).ti,ab [Limit to: Publication Year 1998-2015]; 21243 results. 68. PsycINFO; 66 OR 67 [Limit to: Publication Year 1998-2015]; 24578 results. 69. PsycINFO; 65 AND 68 [Limit to: Publication Year 1998-2015]; 1483 results. 70. PsycINFO; CLINICAL TRIALS/ [Limit to: Publication Year 1860-2014]; 8222 results. 71. PsycINFO; random*.ti,ab [Limit to: Publication Year 1860-2014]; 136645 results. 72. PsycINFO; (doubl* adj3 blind*).ti,ab [Limit to: Publication Year 1860-2014]; 18872 results. 73. PsycINFO; (singl* adj3 blind*).ti,ab [Limit to: Publication Year 1860-2014]; 1735 results. 74. PsycINFO; EXPERIMENTAL DESIGN/ [Limit to: Publication Year 1860-2014]; 9414 results. 75. PsycINFO; controlled.ti,ab [Limit to: Publication Year 1860-2014]; 84646 results. 76. PsycINFO; (clinical adj3 study).ti,ab [Limit to: Publication Year 1860-2014]; 8267 results. 77. PsycINFO; trial.ti,ab [Limit to: Publication Year 1860-2014]; 71884 results. 78. PsycINFO; "treatment outcome clinical trial".md [Limit to: Publication Year 1860-2014]; 28582 results. 79. PsycINFO; 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 [Limit to: Publication Year 1860-2014]; 259313 results. 80. PsycINFO; 69 AND 79 [Limit to: Publication Year 1998-2015]; 444 results.		
Embase	3. EMBASE; ((serotonin OR norepinephrine OR noradrenaline OR dopamine OR neurotransmitter) adj1	979	0

	(uptake OR reuptake OR re-uptake)).ti,ab; 21063 results. 4. EMBASE; ((antiadrenergic OR anti-adrenergic)).ti,ab; 655 results. 5. EMBASE; (5-hydroxytrypotophan OR Acetylcarnitine OR Alaproclate OR alprazolam OR Amersergide OR Amiflamine OR Amineptine OR Amitriptyline).ti,ab; 10082 results. 6. EMBASE; (Amoxapine OR anticonvulsant* OR Antidepress* OR antipsychotic* OR anxiolytic* OR Aripiprazole).ti,ab; 131049 results. 7. EMBASE; (Befloxatone OR Benactyzine OR Benzodiazepine* OR Brofaromine OR Bupropion OR Butriptyline).ti,ab; 40854 results. 8. EMBASE; (Carbazepine OR Caroxazone OR cck-4 OR Chlorimipramine OR Chlorphenamidine OR Chlorpoxiten OR Cilosamine OR Cimoxatone OR Citalopram OR Clomipramine OR clonidine OR Clorgyline OR Clovoxamine OR Cyproheptadine OR d-Cycloserine).ti,ab; 27850 results. 9. EMBASE; (Deanol OR Demexiptiline OR Deprenyl OR Desipramine OR Desvenlafaxine OR Dibenzipin OR Diclofensine OR divalproex OR dopamin* OR Dosulepin OR Dothiepin OR Doxazosin OR Doxepin OR Duloxetine).ti,ab; 151727 results. 10. EMBASE; (Escitalopramor AND Etoperidone OR Femoxetine OR Fenfluramine OR flumazenil OR Fluotracen OR fluoxetine OR Fluparoxan OR fluphenazine OR Fluvoxamine OR Furazolidone OR Guanfacine).ti,ab; 23908 results. 11. EMBASE; (haloperidol OR Harmaline OR Harmine OR hydrocortisone OR Idazoxan OR Imipramine OR inositol OR Iprindole OR Iproniazid OR Isocarboxazid OR lamotrigine).ti,ab; 83916 results. 12. EMBASE; (Lithium AND carbonate OR Lithium AND compounds OR Litoxetine OR Lofepramine).ti,ab; 1784 results. 13. EMBASE; (MAOI* OR Maprotiline OR medicat* OR Medifoxamine OR Melitracen OR Metapramine OR Metyrapone OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Monoamine AND Oxidase AND Inhibitor*).ti,ab; 7338 results. 14. EMBASE; (Naloxone OR Naltrexone OR Nefazodone OR Nialamide OR Nomifensine OR noradrenerg* OR Norfenfluramine OR Nortriptyline OR Noxiptiline OR Olanzapine OR Opipramol OR Oxaflozane OR Oxaprotiline OR Oxcarbazepine).ti,ab; 58920 results. 15. EMBASE; N-Methyl-3,4-methylenedioxyamphetamine.ti,ab; 19 results. 16. EMBASE; (Pargyline OR Paroxetine OR pharmacother* OR Phenelzine OR Pheniprazine OR Piribedil OR Pirlindole OR Pivagabine OR Pizotyline OR Prazosin OR Pregabalin OR Procaine OR Propranolol OR Prosulpride OR Protriptyline OR psychotropic*).ti,ab; 106521 results. 17. EMBASE; (Quetiapine OR Quinupramine OR Quipazine OR Reboxetine OR Risperidone OR Ritanserin		

	OR Rolipram).ti,ab; 18444 results. 18. EMBASE; (Selegiline OR seroto* OR Sertraline OR Setiptiline OR SNRI* OR SSRI* OR Sulpiride).ti,ab; 110001 results. 19. EMBASE; (Teniloxine OR Tetrindole OR Thiazesim OR Thozalinone OR Tiagabine OR Tianeptine OR Toloxatone OR Tomoxetine OR Topiramate OR Tranylcypromine OR Trazodone OR tricyclic* OR Trimipramine OR Tryptophan).ti,ab; 65244 results. 20. EMBASE; (Venlafaxine OR Viloxazine OR Viqualine OR Yohimbine OR Zimeldine).ti,ab; 12133 results. 22. EMBASE; 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 620818 results. 31. EMBASE; CLINICAL TRIAL/; 837236 results. 32. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 355354 results. 33. EMBASE; RANDOMIZATION/; 64127 results. 34. EMBASE; SINGLE BLIND PROCEDURE/; 19202 results. 35. EMBASE; DOUBLE BLIND PROCEDURE/; 116683 results. 36. EMBASE; CROSSOVER PROCEDURE/; 40890 results. 37. EMBASE; "Randomi?ed controlled trial$".ti,ab; 106713 results. 38. EMBASE; rct.ti,ab; 15444 results. 39. EMBASE; "Random allocation".ti,ab; 1351 results. 40. EMBASE; "Randomly allocated".ti,ab; 21214 results. 41. EMBASE; ((allocated adj2 random)).ti,ab; 719 results. 42. EMBASE; "Single blind$".ti,ab; 14987 results. 43. EMBASE; "Double blind$".ti,ab; 145543 results. 44. EMBASE; (treble ADJ blind$).ti,ab; 0 results. 45. EMBASE; (triple ADJ blind$).ti,ab; 409 results. 46. EMBASE; Placebo$.ti,ab; 205530 results. 47. EMBASE; PROSPECTIVE STUDY/; 269427 results. 48. EMBASE; 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 47 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47; 1404594 results. 49. EMBASE; "case report".ti,ab; 270399 results. 50. EMBASE; ABSTRACT REPORT/; 71430 results. 51. EMBASE; LETTER/; 837890 results. 52. EMBASE; 60 OR 49 OR 50 OR 51; 1203133 results.		

	53. EMBASE; 48 not 52; 1366224 results. 54. EMBASE; POSTTRAUMATIC STRESS DISORDER/ [Limit to: Publication Year 1998-2015]; 31938 results. 55. EMBASE; (ptsd OR post-trauma* OR (post adj1 trauma*)).ti,ab [Limit to: Publication Year 1998-2015]; 28318 results. 56. EMBASE; 54 OR 55 [Limit to: Publication Year 1998-2015]; 42604 results. 57. EMBASE; 22 AND 56 [Limit to: Publication Year 1998-2015]; 3274 results. 58. EMBASE; 53 AND 57 [Limit to: Publication Year 1998-2015]; 979 results.		
Medline	58. MEDLINE; ((serotonin OR norepinephrine OR noradrenaline OR dopamine OR neurotransmitter) adj1 (uptake OR reuptake OR re-uptake)).ti,ab; 17866 results. 59. MEDLINE; ((antiadrenergic OR anti-adrenergic)).ti,ab; 604 results. 60. MEDLINE; (5-hydroxytrypotophan OR Acetylcarnitine OR Alaproclate OR alprazolam OR Amersergide OR Amiflamine OR Amineptine OR Amitriptyline).ti,ab; 8854 results. 61. MEDLINE; (Amoxapine OR anticonvulsant* OR Antidepress* OR antipsychotic* OR anxiolytic* OR Aripiprazole).ti,ab; 102980 results. 62. MEDLINE; (Befloxatone OR Benactyzine OR Benzodiazepine* OR Brofaromine OR Bupropion OR Butriptyline).ti,ab; 33418 results. 63. MEDLINE; (Carbazepine OR Caroxazone OR cck-4 OR Chlorimipramine OR Chlorphenamidine OR Chlorpoxiten OR Cilosamine OR Cimoxatone OR Citalopram OR Clomipramine OR clonidine OR Clorgyline OR Clovoxamine OR Cyproheptadine OR d-Cycloserine).ti,ab; 25390 results. 64. MEDLINE; (Deanol OR Demexiptiline OR Deprenyl OR Desipramine OR Desvenlafaxine OR Dibenzipin OR Diclofensine OR divalproex OR dopamin* OR Dosulepin OR Dothiepin OR Doxazosin OR Doxepin OR Duloxetine).ti,ab; 141706 results. 65. MEDLINE; (Escitalopramor AND Etoperidone OR Femoxetine OR Fenfluramine OR flumazenil OR Fluotracen OR fluoxetine OR Fluparoxan OR fluphenazine OR Fluvoxamine OR Furazolidone OR Guanfacine).ti,ab; 21079 results. 66. MEDLINE; (haloperidol OR Harmaline OR Harmine OR hydrocortisone OR Idazoxan OR Imipramine OR inositol OR Iprindole OR Iproniazid OR Isocarboxazid OR lamotrigine).ti,ab; 80505 results. 67. MEDLINE; (Lithium AND carbonate OR Lithium AND compounds OR Litoxetine OR Lofepramine).ti,ab; 1485 results. 68. MEDLINE; (MAOI* OR Maprotiline OR medicat* OR Medifoxamine OR Melitracen OR Metapramine OR Metyrapone OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Monoamine AND Oxidase AND Inhibitor*).ti,ab; 7225 results.	460	0

	69. MEDLINE; (Naloxone OR Naltrexone OR Nefazodone OR Nialamide OR Nomifensine OR noradrenerg* OR Norfenfluramine OR Nortriptyline OR Noxiptiline OR Olanzapine OR Opipramol OR Oxaflozane OR Oxaprotiline OR Oxcarbazepine).ti,ab; 53830 results. 70. MEDLINE; N-Methyl-3,4-methylenedioxyamphetamine.ti,ab; 17 results. 71. MEDLINE; (Pargyline OR Paroxetine OR pharmacother* OR Phenelzine OR Pheniprazine OR Piribedil OR Pirlindole OR Pivagabine OR Pizotyline OR Prazosin OR Pregabalin OR Procaine OR Propranolol OR Prosulpride OR Protriptyline OR psychotropic*).ti,ab; 92255 results. 72. MEDLINE; (Quetiapine OR Quinupramine OR Quipazine OR Reboxetine OR Risperidone OR Ritanserin OR Rolipram).ti,ab; 13673 results. 73. MEDLINE; (Selegiline OR seroto* OR Sertraline OR Setiptiline OR SNRI* OR SSRI* OR Sulpiride).ti,ab; 98945 results. 74. MEDLINE; (Teniloxine OR Tetrindole OR Thiazesim OR Thozalinone OR Tiagabine OR Tianeptine OR Toloxatone OR Tomoxetine OR Topiramate OR Tranylcypromine OR Trazodone OR tricyclic* OR Trimipramine OR Tryptophan).ti,ab; 60712 results. 75. MEDLINE; (Venlafaxine OR Viloxazine OR Viqualine OR Yohimbine OR Zimeldine).ti,ab; 10515 results. 76. MEDLINE; 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75; 556645 results. 77. MEDLINE; POSTTRAUMATIC STRESS DISORDER/ [Limit to: Publication Year 1998-2015]; 19224 results. 78. MEDLINE; (ptsd OR post-trauma* OR (post adj1 trauma*)).ti,ab [Limit to: Publication Year 1998-2015]; 22853 results. 79. MEDLINE; 77 OR 78 [Limit to: Publication Year 1998-2015]; 30474 results. 80. MEDLINE; 76 AND 79 [Limit to: Publication Year 1998-2015]; 1844 results. 81. MEDLINE; RANDOMIZED CONTROLLED TRIALS AS TOPIC/; 101212 results. 82. MEDLINE; RANDOMIZED CONTROLLED TRIAL/; 405342 results. 83. MEDLINE; RANDOM ALLOCATION/; 84631 results. 84. MEDLINE; DOUBLE-BLIND METHOD/; 133525 results. 85. MEDLINE; SINGLE-BLIND METHOD/; 20871 results. 86. MEDLINE; CLINICAL TRIAL/; 503192 results. 87. MEDLINE; "clinical trial, phase i".pt; 15599 results. 88. MEDLINE; "clinical trial, phase ii".pt; 24983 results. 89. MEDLINE; "clinical trial, phase iii".pt; 10262 results. 90. MEDLINE; "clinical trial, phase iv".pt; 1058 results.		

	91. MEDLINE; "controlled clinical trial".pt; 91125 results. 92. MEDLINE; "randomized controlled trial".pt; 405342 results. 93. MEDLINE; "clinical trial".pt; 503192 results. 94. MEDLINE; exp CLINICAL TRIALS AS TOPIC/; 297601 results. 95. MEDLINE; (single$ ADJ blind$).ti,ab; 12546 results. 96. MEDLINE; (doubl$ ADJ blind$).ti,ab; 123745 results. 97. MEDLINE; (treb$ ADJ blind$).ti,ab; 0 results. 98. MEDLINE; (trip$ ADJ blind$).ti,ab; 373 results. 99. MEDLINE; (single$ ADJ mask$).ti,ab; 338 results. 100. MEDLINE; (doub$ ADJ mask$).ti,ab; 2828 results. 101. MEDLINE; (treb$ ADJ mask$).ti,ab; 0 results. 102. MEDLINE; (trip$ ADJ mask$).ti,ab; 44 results. 103. MEDLINE; PLACEBOS/; 34188 results. 104. MEDLINE; placebo$.ti,ab; 171163 results. 105. MEDLINE; "randomly allocated".ti,ab; 18532 results. 106. MEDLINE; (allocated adj2 random$).ti,ab; 21226 results. 107. MEDLINE; 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94; 1006550 results. 108. MEDLINE; 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106; 252711 results. 109. MEDLINE; 107 OR 108; 1056137 results. 110. MEDLINE; "case report".ti,ab; 218135 results. 111. MEDLINE; LETTER/; 891840 results. 112. MEDLINE; HISTORICAL ARTICLE/; 314109 results. 113. MEDLINE; 110 OR 111 OR 112; 1411791 results. 114. MEDLINE; 109 not 113; 1027266 results. 115. MEDLINE; 80 AND 114 [Limit to: Publication Year 1998-2015]; 460 results.		
Summary	**NA**	**NA**	

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