National Institute for Health and Care Excellence

Final

Post-traumatic stress disorder

[E] Evidence reviews for pharmacological interventions for the prevention and treatment of PTSD in children

NICE guideline NG116

Evidence reviews

December 2018

Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Pharmacological interventions for the prevention of PTSD in children and young people

This evidence report contains information on 2 reviews relating to pharmacological interventions for the prevention of PTSD in children and young people:

- Review question 3.1 For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?
- Review question 3.2 For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?

Review question 3.1 For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?

Summary of the protocol (PICO table)

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Children and young people (under 18 years) at risk of PTSD (defined in accordance with DSM as exposure to actual or threatened death, serious injury or sexual violation). This population includes children and young people with a diagnosis of acute stress disorder/acute stress reaction (according to DSM, ICD or similar criteria), people with clinically important PTSD symptoms within a month of the traumatic event, and people with subthreshold symptoms
Intervention	Pharmacological interventions including: • Carbamazepine • Clonidine • Propranolol
Comparison	• Any other intervention • Placebo
Outcome	**Critical outcomes:** • Efficacy (PTSD symptoms/diagnosis) • Acceptability/tolerability of the intervention (discontinuation for any reason and discontinuation due to adverse events used as a proxy) **Important outcomes:** • Dissociative symptoms • Personal/social/educational functioning (including global functioning/functional impairment) • Sleeping difficulties • Quality of life Symptoms of a coexisting condition (including anxiety, depression and emotional and behavioural problems)

DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Disease; PTSD=Post-Traumatic Stress Disorder

For full details see review protocol in Appendix A.

Introduction

Ordinarily, pharmacological interventions are neither the first nor the main intervention for the prevention (or treatment) of PTSD in children and young people. There has been very little research examining the impact of such interventions with children and young people, and support for their use tends to be extrapolated from trials with adults.

No drugs are currently licenced in the UK for the prevention (or treatment) of PTSD in children and young people.

Evidence for carbamazepine and clonidine was searched for but none was found.

Methods and processes

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 and 2018 conflicts of interest policies.

Selective serotonin reuptake inhibitors (SSRIs) for prevention of PTSD: clinical evidence

Included studies

Two studies of SSRIs, for the prevention of PTSD in children and young people, were identified. Neither of these studies could be included.

Excluded studies

Two studies were reviewed at full-text and excluded from this review due to small sample size (N<10 per arm), or because outcomes measures were not validated.

Propranolol for prevention of PTSD: clinical evidence

Included studies

Two studies of propranolol for the prevention of PTSD in children and young people were identified for full-text review. Of these 2 studies, 1 RCT (N=29) was included in a single comparison of propranolol compared with placebo for the early prevention (within the first month) of PTSD in children and young people (Nugent 2010).

Excluded studies

One study was reviewed at full-text and excluded from this review because the outcome measures were not validated.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profile below (Table 3).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 2: Summary of included studies: Propranolol for early prevention (<1 month)

Comparison	Propranolol versus placebo
Total no. of studies (N randomised)	1 (29)
Study ID	Nugent 2010
Country	US
Diagnostic status	Unclear
Mean age (range)	15 (10-18)
Sex (% female)	48
Ethnicity (% BME)	7
Coexisting conditions	31% chronic psychiatric diagnosis
Mean months since traumatic event	0.016 (within 12 hours)
Type of traumatic event	Motor Vehicle Collision: Motor vehicle accident (55%); Bicycle accident (10%); Pedestrian versus automobile (10%); Fall (7%); Other (17%)
Single or multiple incident index trauma	Single
Lifetime experience of trauma	28% prior trauma (including motor vehicle accidents, burglary, assault, sexual abuse/assault, and parent partner violence)
Intervention details	Propranolol (hydrochloric acid 20 mg/5 mL) twice daily for 10 days followed by 5-day taper. Therapeutic dose was 2.5 mg/kg per day with a maximum dose of 40mg twice daily
Intervention format	Oral
Actual intervention intensity	64% showed adequate adherence (< one missed dose or < four incidents of poor time adherence, according to medication log)
Comparator	Placebo
Intervention length (weeks)	2

BME=Black and Minority Ethnic

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review (propranolol for the prevention of PTSD in children and young people) is presented in Table 3.

Table 3: Summary clinical evidence profile: Propranolol versus placebo for the early prevention (<1 month) of PTSD in children and young people

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Propranolol			
Diagnosis of PTSD at 1-month follow-up CAPS-CA Follow-up: mean 1 months	267 per 1000	357 per 1000 (120 to 1000)	RR 1.34 (0.45 to 4)	29 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Propranolol			
Discontinuation due to any reason Number of participants lost to follow-up for any reason, including adverse events Follow-up: mean 2 weeks	-	-	Not estimable	29 (1 study)	moderate[2]

CAPS-CA=Clinician-Administered PTSD Scale-Child/Adolescent version; CI=confidence interval; PTSD=post-traumatic stress disorder; RR=risk ratio
[1] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm
[2] OIS not met (events<300)

See Appendix F for full GRADE tables.

Economic evidence

Included studies

No economic studies assessing the cost effectiveness of pharmacological interventions for the prevention of PTSD in children and young people were identified. The search strategy for economic studies is provided in Appendix B.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was conducted for this question because other topics were agreed as higher priorities for economic evaluation.

Resource impact

The recommendation made by the committee based on this review is in line with previously recommended practice and therefore it is not expected to have an impact on resources.

Clinical evidence statements

- Low quality single-RCT (N=29) evidence suggests a non-significant effect of propranolol relative to placebo on diagnosis of PTSD at 1-month follow-up for children and young people exposed to trauma within the last month. No participants dropped out of this study.

Economic evidence statements

No economic evidence on pharmacological interventions for the prevention of PTSD in children and young people was identified and no economic modelling was undertaken.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Critical outcomes were measures of PTSD symptom improvement on validated scales and prevention of PTSD (as measured by the number of people with a diagnosis or scoring above clinical threshold on a validated scale at endpoint or follow-up). Attrition from treatment (for any reason) was also considered an important outcome as a proxy for the acceptability of treatment, and discontinuation due to adverse events was considered as particularly important as an indicator of potential harm in terms of tolerability. The committee considered dissociative symptoms, personal/social/occupational functioning (including global functioning/functional impairment, sleeping or relationship difficulties, and quality of life), and symptoms of a coexisting condition (including anxiety and depression symptoms) as important but not critical outcomes. This distinction was based on the primacy of targeting the core PTSD symptoms, whilst acknowledging that broader symptom measures may be indicators of a general pattern of effect. Change scores were favoured over final scores as although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for self-rated PTSD symptomatology, particularly for pharmacological interventions where the participant is likely to be blinded and may be less susceptible to bias than the study investigator(s). However, the committee discussed potential threats to blinding of the participant, for example in the context of side effects, and therefore triangulation with blinded clinician-rated outcome measures was also regarded as important.

The quality of the evidence

The evidence for this review was of moderate to low quality, and of very limited volume with a single small study in a single comparison for a single intervention. The considerable gaps in the evidence, included no data for effects on PTSD symptomatology, short-term follow-up period, and no information about effects on associated symptoms.

Consideration of clinical benefits and harms

The committee considered that providing a treatment that had no clinical effect over placebo was harmful, as this prevents someone from accessing a treatment that could improve their condition. Such harms were evident in patients treated with propranolol, and based on the consensus opinion of the committee the findings were judged to be generalizable to other drug treatments. The committee agreed that the potential harms outweighed the benefits for drug treatments in order to prevent PTSD.

Cost effectiveness and resource use

No evidence on the cost effectiveness of pharmacological interventions for the prevention of PTSD in children and young people was identified and no economic modelling was undertaken in this area. As there was no evidence of clinical benefit

associated with pharmacological interventions, a negative recommendation ('do not offer') for pharmacological interventions was made. This recommendation is in line with the previous guideline, which recommended that pharmacotherapy should not be prescribed for children and young people with PTSD. Therefore no impact on resources is expected.

References for the included studies

SSRI

Nugent 2010

Nugent NR, Christopher NC, Crow JP (2010) The efficacy of early propranolol administration at reducing PTSD symptoms in paediatric injury patients: a pilot study. Journal of traumatic stress 23(2), 282-7

Review question 3.2 For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?

Summary of the protocol (PICO table)

Please see Table 4 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 4: Summary of the protocol (PICO table)

Population	Children and young people (18 years and under) with clinically important post-traumatic stress symptoms (more than one month after a traumatic event), defined by a diagnosis of PTSD according to DSM, ICD or similar criteria (including PTSD preschool subtype) or clinically-significant PTSD symptoms as indicated by baseline scores above threshold on a validated scale
Intervention	Pharmacological interventions including: • Carbamazepine • Clonidine • Propranolol
Comparison	• Any other intervention • Placebo
Outcome	**Critical outcomes:** • Efficacy (PTSD symptoms/diagnosis/response/remission/relapse) • Acceptability/tolerability of the intervention (discontinuation for any reason and discontinuation due to adverse events used as a proxy) **Important outcomes:** • Dissociative symptoms • Personal/social/educational functioning (including global functioning/functional impairment) • Sleeping difficulties • Quality of life • Symptoms of a coexisting condition (including anxiety, depression and emotional and behavioural problems)

DSM= Diagnostic and Statistical Manual; ICD= International Classification of Diseases; PTSD=Post-Traumatic Stress Disorder

For full details see review protocol in Appendix A.

Introduction

Pharmacological management strategies are commonly used in mental health problems. This review is important to establish whether pharmacological interventions are of use in the treatment of children and young people with clinically important post-traumatic stress symptoms, and what the benefits and harms of these are.

No drugs are currently licenced in the UK for the treatment of PTSD in children and young people.

Evidence for carbamazepine, clonidine and propranolol was searched for but none was found. Evidence was identified for selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other drugs and these drug classes form the subsections below.

Selective serotonin reuptake inhibitors (SSRIs) for treatment of PTSD: clinical evidence

Included studies

Five studies of SSRIs for the treatment of PTSD in children and young people were identified for full-text review. Of these 5 studies, 2 RCTs (N=155) were included in 2 comparisons for SSRIs.

There were no studies for early treatment (intervention initiated 1-3 months post-trauma) of PTSD symptoms.

For delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms: 1 RCT (N=131) compared SSRIs with placebo (Robb 2010); 1 RCT (N=24) compared sertraline in addition to cognitive processing therapy with placebo in addition to cognitive processing therapy (Cohen 2007).

Excluded studies

Three studies were reviewed at full text and excluded from this review due to non-randomised group assignment, or because the paper was a conference abstract, or a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 5 provides brief summaries of the included studies and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 6 and Table 7).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 5: Summary of included studies: SSRIs for delayed treatment (>3 months)

Comparison	Sertraline versus placebo	Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy)
Total no. of studies (N randomised)	1 (131)	1 (24)
Study ID	Robb 2010	Cohen 2007
Country	US	US

Comparison	Sertraline versus placebo	Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy)
Diagnostic status	PTSD diagnosis according to ICD/DSM criteria	PTSD diagnosis according to ICD/DSM criteria
Mean months since onset of PTSD	29.4	NR
Mean age (range)	11 (6-17)	Mean NR (10-17)
Sex (% female)	60	100
Ethnicity (% BME)	42	22
Coexisting conditions	NR	68% met criteria for diagnosis other than PTSD: 64% met criteria for major depressive disorder (MDD). Other diagnoses included general anxiety disorder, substance abuse not otherwise specified, oppositional defiant disorder, panic disorder, and anorexia nervosa
Mean months since traumatic event	NR	22.9
Type of traumatic event	Mixed: Sexual abuse (41%); Confronted with traumatic news (33%); Victim of physical abuse/violence (32%); In car or other accident (24%); Witness to violence (48%); In a fire or natural disaster (16%); Other (22%)	Childhood sexual abuse: Contact sexual abuse
Single or multiple incident index trauma	Multiple	Multiple
Lifetime experience of trauma	Most participants reported more than one type of trauma	Mean of 3.0 different types of previous traumas in addition to sexual abuse, including the following: serious accidents (45%), disasters (9%), violent crime (27%), traumatic death or life-threatening illness (77%), domestic violence (18%), physical abuse (9%), and other PTSD-level traumas (18%)
Intervention details	Sertraline (50–200 mg/day)	Sertraline 50-200mg/day + cognitive processing therapy (based on protocol of Cohen 2006)
Intervention format	Oral	Oral
Actual intervention intensity	Mean final dose 106.9mg (SD=51.4)	NR

Comparison	Sertraline versus placebo	Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy)
Comparator	Placebo	Placebo + cognitive processing therapy
Intervention length (weeks)	10	12

BME=Black and Minority Ethnic; NR=not reported; PTSD=post-traumatic stress disorder; SD=standard deviation

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review (SSRIs for the treatment of PTSD in children and young people) are presented in Table 6 and Table 7.

Table 6: Summary clinical evidence profile: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Sertraline			
PTSD symptomatology clinician-rated UCLA PTSD-I change score Follow-up: mean 10 weeks		The mean PTSD symptomatology clinician-rated in the intervention groups was 0.19 standard deviations higher (0.15 lower to 0.54 higher)		128 (1 study)	low[1,2]
Remission Number of people no longer meeting diagnostic criteria for PTSD Follow-up: mean 10 weeks	459 per 1000	390 per 1000 (257 to 583)	RR 0.85 (0.56 to 1.27)	128 (1 study)	very low[2,3]
Response Number of people rated 'much' or 'very much' improved on CGI-I Follow-up: mean 10 weeks	574 per 1000	505 per 1000 (367 to 700)	RR 0.88 (0.64 to 1.22)	128 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo	Corresponding risk Sertraline			
Depression symptoms CDRS-R change score Follow-up: mean 10 weeks		The mean depression symptoms in the intervention groups was 0.18 standard deviations higher (0.16 lower to 0.53 higher)		128 (1 study)	low[1,2]
Quality of life PQ-LES-Q change score Follow-up: mean 10 weeks Better indicated by higher values		The mean quality of life in the intervention groups was 0.31 standard deviations lower (0.66 lower to 0.04 higher)		128 (1 study)	low[1,2]
Discontinuation due to any reason Number of participants lost to follow-up for any reason, including adverse events Follow-up: mean 10 weeks	177 per 1000	298 per 1000 (156 to 571)	RR 1.68 (0.88 to 3.22)	129 (1 study)	moderate[1]
Discontinuation due to adverse events Number of participants who dropped out due to adverse events Follow-up: mean 10 weeks	32 per 1000	75 per 1000 (15 to 371)	RR 2.31 (0.47 to 11.49)	129 (1 study)	low[3]

CI=confidence interval; CDRS-R=Children's Depression Rating Scale-Revised; CGI-I=Clinical Global Impression Scale-Improvement; PQ-LEB-Q=; Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire; PTSD=post-traumatic stress disorder; RR=risk ratio; SMD=standard mean difference; UCLA PTSD-I=UCLA PTSD-Index

[1] 95% CI crosses both line of no effect and threshold for clinically important harm

[2] Funding from pharmaceutical company

[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Table 7: Summary clinical evidence profile: Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy) for the

delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ cognitive processing therapy)	Corresponding risk Sertraline (+ cognitive processing therapy)			
Global functioning CGAS change score Follow-up: mean 12 weeks Better indicated by higher values		The mean global functioning in the intervention groups was 1.2 standard deviations higher (0.27 to 2.12 higher)		22 (1 study)	moderate[1]
Discontinuation due to any reason Number of participants lost to follow-up for any reason, including adverse events Follow-up: mean 12 weeks	83 per 1000	83 per 1000 (6 to 1000)	RR 1 (0.07 to 14.21)	24 (1 study)	low[2]

CGAS=Clinical Global Assessment Scale; CI=confidence interval; PTSD=post-traumatic stress disorder; RR=risk ratio; SMD=standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

See Appendix F for full GRADE tables.

Tricyclic antidepressants (TCAs) for treatment of PTSD: clinical evidence

Included studies

Two studies of TCAs for the treatment of PTSD in children and young people were identified for full-text review. Neither of these studies could be included.

Excluded studies

Two studies were reviewed at full text and excluded from this review because the outcome measures were not validated, or the paper was a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Other drugs for treatment of PTSD: clinical evidence

Included studies

Sixteen studies of other drugs for the treatment of PTSD in children and young people were identified for full-text review. Of these 16 studies, 1 RCT (N=57) was included in a single comparison comparing d-cycloserine in addition to exposure therapy with placebo in addition to exposure therapy for the delayed treatment (intervention initiated more than 3 months post-trauma) of PTSD symptoms (Scheeringa & Weems 2014).

Excluded studies

Fifteen studies were reviewed at full text and excluded from this review. The most common reasons for exclusion were non-randomised group assignment, or the paper was a non-systematic review, or a systematic review with no new useable data and any meta-analysis results not appropriate to extract.

Studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 8 provides a brief summary of the included study and evidence from this study is summarised in the clinical GRADE evidence profile below (Table 9).

See also the study selection flow chart in Appendix C, forest plots in Appendix E and study evidence tables in Appendix D.

Table 8: Summary of included studies: Other drugs for delayed treatment (>3 months)

Comparison	d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy)
Total no. of studies (N randomised)	1 (57)
Study ID	Scheeringa 2014
Country	US
Diagnostic status	Clinically important PTSD symptoms (scoring above a threshold on validated scale)
Mean months since onset of PTSD	NR
Mean age (range)	12.5 (range NR)
Sex (% female)	56
Ethnicity (% BME)	60
Coexisting conditions	NR
Mean months since traumatic event	NR
Type of traumatic event	Mixed: Disaster (14%); Domestic violence (26%); Assaulted (7%); Sexual (32%); Accident (2%); Seen/heard someone killed/hurt badly (5%); Seen unexpected dead body (14%). Mean number of occurrences of traumas: 157
Single or multiple incident index trauma	Multiple

Comparison	d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy)
Lifetime experience of trauma	Mean number of types of trauma: 2.9
Intervention details	d-cycloserine (50mg) prior to sessions 5-11 of exposure therapy, 1 hour before the session started
Intervention format	Oral
Actual intervention intensity	NR
Comparator	Placebo (+ exposure therapy)
Intervention length (weeks)	12

BME=Black and Minority Ethnic; NR=not reported; PTSD=post-traumatic stress disorder

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review (other drugs for the treatment of PTSD in children and young people) is presented in Table 9.

Table 9: Summary clinical evidence profile: d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk d-cycloserine (+ exposure therapy)			
PTSD symptomatology self/parent-rated at endpoint CPSS change score Follow-up: mean 12 weeks		The mean PTSD symptomatology self/parent-rated at endpoint in the intervention groups was 0.07 standard deviations higher (0.45 lower to 0.59 higher)		57 (1 study)	low[1,2]
PTSD symptomatology self/parent-rated at 3-month follow-up CPSS change score Follow-up: mean 3 months		The mean PTSD symptomatology self/parent-rated at 3-month follow-up in the intervention groups was 0.09 standard deviations lower (0.61 lower to 0.43 higher)		57 (1 study)	low[1,3]
Response Number of people	643 per 1000	411 per 1000 (251 to 694)	RR 0.64	57 (1 study)	low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk d-cycloserine (+ exposure therapy)			
showing ≥50% improvement on CPSS Follow-up: mean 12 weeks			(0.39 to 1.08)		
Depression symptoms at endpoint CDI change score Follow-up: mean 12 weeks		The mean depression symptoms at endpoint in the intervention groups was 0.09 standard deviations higher (0.43 lower to 0.61 higher)		57 (1 study)	low[1,2]
Depression symptoms at 3-month follow-up CDI change score Follow-up: mean 3 months		The mean depression symptoms at 3-month follow-up in the intervention groups was 0.17 standard deviations lower (0.69 lower to 0.35 higher)		57 (1 study)	low[1,3]
Anxiety symptoms at endpoint SCARED change score Follow-up: mean 12 weeks		The mean anxiety symptoms at endpoint in the intervention groups was 0.31 standard deviations higher (0.21 lower to 0.83 higher)		57 (1 study)	low[1,2]
Anxiety symptoms at 3-month follow-up SCARED change score Follow-up: mean 3 months		The mean anxiety symptoms at 3-month follow-up in the intervention groups was 0.05 standard deviations higher (0.47 lower to 0.57 higher)		57 (1 study)	low[1,2]
Discontinuation due to any reason Number of participants lost to follow-up for any	143 per 1000	207 per 1000 (66 to 656)	RR 1.45 (0.46 to 4.59)	57 (1 study)	very low[1,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo (+ exposure therapy)	Corresponding risk d-cycloserine (+ exposure therapy)			
reason, including adverse events Follow-up: mean 12 weeks					

CDI=Children's Depression Inventory; CI=confidence interval; CPSS=Child PTSD Symptom Scale; PTSD=post-traumatic stress disorder; RR=risk ratio; SCARED=Screen for Child Anxiety Related Disorders; SMD=standard mean difference

[1] Risk of bias associated with randomisation method suggested by statistically significant difference at baseline

[2] 95% CI crosses both line of no effect and threshold for clinically important harm

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

See Appendix F for full GRADE tables.

Economic evidence

Included studies

No economic studies assessing the cost effectiveness of pharmacological interventions for the treatment of PTSD in children and young people were identified. The search strategy for economic studies is provided in Appendix B.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was conducted for this question because other topics were agreed as higher priorities for economic evaluation.

Resource impact

The recommendation made by the committee based on this review is in line with previously recommended practice and therefore it is not expected to have an impact on resources

Clinical evidence statements

- Very low to low quality single-RCT (N=128) evidence suggests non-significant effects of sertraline relative to placebo on PTSD symptomatology, remission, response, depression symptoms, and quality of life in children and young with PTSD over 3 months after trauma. Low to moderate quality evidence from this same RCT (N=129) suggests a higher rate of discontinuation due to any reason and due to adverse events associated with sertraline, although these effects are not statistically significant.

- Moderate quality single-RCT (N=22) evidence suggests a large and statistically significant benefit of combined sertraline and cognitive processing therapy, relative to combined placebo and cognitive processing therapy, on improving global functioning in children and young with PTSD over 3 months after trauma. No difference in discontinuation due to any reason observed in this study. No PTSD outcomes were available.
- Low to very low quality single-RCT (N=57) evidence suggests non-significant effects of combined d-cycloserine and exposure therapy, relative to combined placebo and exposure therapy at endpoint or 3-month follow-up, on PTSD symptomatology, response (only endpoint available), depression and anxiety symptoms, and discontinuation due to any reason for children and young with PTSD over 3 months after trauma.

Economic evidence statements

No economic evidence on pharmacological interventions for the treatment of PTSD in children and young people was identified and no economic modelling was undertaken.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Critical outcomes were measures of PTSD symptom improvement on validated scales, remission (as defined as a loss of diagnosis or scoring below threshold on a validated scale), and response (as measured by an agreed percentage improvement in symptoms and/or by a dichotomous rating of much or very much improved). Attrition from treatment (for any reason) was also considered an important outcome as a proxy for the acceptability of treatment, and discontinuation due to adverse events was considered as particularly important as an indicator of potential harm in terms of tolerability. The committee considered dissociative symptoms, personal/social/occupational functioning (including global functioning/functional impairment, sleeping or relationship difficulties, and quality of life), and symptoms of a coexisting condition (including anxiety and depression symptoms) as important but not critical outcomes. This distinction was based on the primacy of targeting the core PTSD symptoms, whilst acknowledging that broader symptom measures may be indicators of a general pattern of effect. Change scores were favoured over final scores as although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for self-rated PTSD symptomatology, particularly for pharmacological interventions where the participant is likely to be blinded and may be less susceptible to bias than the study investigator(s). However, the committee discussed potential threats to blinding of the participant, for example in the context of side effects, and therefore triangulation with blinded clinician-rated outcome measures was also regarded as important.

The quality of the evidence

The evidence for this review was of moderate to very low quality, and of limited volume with all comparisons consisting of single studies with relatively few participants. There were also considerable gaps in the evidence, including very limited data reported for discontinuation due to adverse events (only reported by a single study), most

comparisons including either self-rated or clinician-rated PTSD symptomatology measures but not both so triangulation not possible, relatively short-term follow-up periods, and limited evidence in terms of effects on associated symptoms.

Consideration of clinical benefits and harms

No reliable evidence of benefit was found within this review. Based on the clinical experience of the committee, SSRI medication is known to increase suicide risk in people under 18 years of age. Additionally, the greater discontinuation rates in those treated with SSRIs were interpreted as evidence of potential harm.

There are also potential harms associated with the prescription of d-cycloserine (an antibiotic) for PTSD not just for treated patients, but society more widely. Prescription for this indication in the absence of compelling evidence of efficacy could cause harm by contributing to antibiotic resistance.

Taken together, the committee agreed that the potential harms outweighed the benefits for drug treatments in order to treat PTSD in children and young people.

Cost effectiveness and resource use

No evidence on the cost effectiveness of pharmacological interventions for the treatment of PTSD in children and young people was identified and no economic modelling was undertaken in this area. As there was no evidence of clinical benefit, a negative recommendation ('do not offer') for pharmacological interventions was made. This recommendation is in line with the previous guideline, which recommended that pharmacotherapy should not be prescribed for children and young people with PTSD. Therefore no impact on resources is expected.

Other factors the committee took into account

The committee noted that the largest trial considered (comparing sertraline alone with placebo), was terminated prematurely due to lack of efficacy.

References for included studies

SSRI

Cohen 2007

Cohen JA, Mannarino AP, Perel JM and Staron V (2007) A pilot randomized controlled trial of combined trauma-focused CBT and sertraline for childhood PTSD symptoms. Journal of the American Academy of Child and Adolescent Psychiatry 46(7), 811–9

Robb 2010

Robb A, Cueva J, Sporn J, et al. (2010) Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. Journal of Child and Adolescent Psychopharmacology 20, 463-471

Other drugs

Scheeringa 2014

Scheeringa MS and Weems CF (2014) Randomized placebo-controlled D-cycloserine with cognitive behaviour therapy for paediatric posttraumatic stress. Journal of Child and Adolescent Psychopharmacology 24(2), 69-77

Appendices

Appendix A – Review protocols

Review protocols for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Review protocols for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Both evidence review questions are covered by the same protocol.

Review protocol for pharmacological interventions for the prevention and treatment of PTSD in children and young people

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
Review question(s)	Review question 3.1 For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions? Review question 3.2 For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?
Sub-question(s)	Where evidence exists, consideration will be given to the specific needs of: • women who have been exposed to sexual abuse or assault, or domestic violence • lesbian, gay, bisexual, transsexual or transgender people • people from black and minority ethnic groups • people who are homeless or in insecure accommodation • asylum seekers or refugees or other immigrants who are entitled to NHS treatment • people who have been trafficked • people who are socially isolated (and who are not captured by any other subgroup listed) • people with complex PTSD • people with neurodevelopmental disorders (including autism)

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	• people with coexisting conditions (drug and alcohol misuse, common mental health disorders, eating • disorders, personality disorders, acquired brain injury, physical disabilities and sensory impairments) • people who are critically ill or injured (for instance after a vehicle crash)
Objectives	To identify the most effective pharmacological interventions for the prevention or treatment of PTSD in children and young people
Population	Review question3.1: Children and young people (under 18 years) at risk of PTSD At risk of PTSD is defined (in accordance with DSM) as: Exposure to actual or threatened death, serious injury or sexual violation. The exposure must result from one or more of the following scenarios, in which the individual: directly experiences the traumatic event; witnesses the traumatic event in person; learns that the traumatic event occurred to a close family member or close friend (with the actual or threatened death being either violent or accidental); or experiences first-hand repeated or extreme exposure to aversive details of the traumatic event (not through media, pictures, television or movies unless work-related) This population includes people with a diagnosis of acute stress disorder/acute stress reaction (according to DSM, ICD or similar criteria), people with clinically important PTSD symptoms within a month of the traumatic event, and people with sub-threshold symptoms. The at-risk population for this review will also include the following groups that may not be captured by the DSM criteria: • family members of people with PTSD • family members or carers of people with a life-threatening illness or injury

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	Children and young people (under 18 years) with clinically important post-traumatic stress symptoms more than one month after the traumatic event will be excluded from RQ 3.1 as this question addresses prevention, this group are included in RQ 3.2. Review question 3.2: Children and young people (under 18 years) with clinically important post-traumatic stress symptoms (more than one month after a traumatic event), defined by a diagnosis of PTSD according to DSM, ICD or similar criteria (including PTSD preschool subtype) or clinically-significant PTSD symptoms as indicated by baseline scores above threshold on a validated scale (see PTSD scales listed under outcomes). For mixed adult and children populations, where possible disaggregated data will be obtained. If this is not possible then the study will be categorised according to the mean age of the population (<18 years as children and young people and ≥18 years as adult). If some, but not all, of a study's participants are eligible for the review, where possible disaggregated data will be obtained. If this is not possible then the study will be included if at least 80% of its participants are eligible for this review.
Exclude	Trials of people with adjustment disorders Trials of people with traumatic grief Trials of people with psychosis as a coexisting condition Trials of people with learning disabilities Trials of young women with PTSD during pregnancy or in the first year following childbirth
Intervention	Pharmacological interventions (pharmacological interventions listed below are examples of interventions which may be included either alone or in combination, for any duration at a dose at or above the minimum effective dose): carbamazepine clonidine propranolol

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	Combination interventions, such as combined pharmacological plus psychological versus psychological alone, will also be considered here. A distinction will be made between early interventions (delivered within 3 months of the traumatic event) and delayed interventions (delivered more than 3 months after the traumatic event). Exclude: Inoculation interventions for people who may be at risk of experiencing but have not experienced, a traumatic event Interventions that are not targeted at PTSD symptoms
Comparison	Any other intervention Placebo
Critical outcomes	Efficacy PTSD symptomology (mean endpoint score or change in PTSD score from baseline) Diagnosis of PTSD (number of people meeting diagnostic criteria for PTSD according to DSM, ICD or similar criteria) Recovery from PTSD/Remission (number of people no longer meeting diagnostic criteria for PTSD according to DSM, ICD or similar criteria at endpoint, or endpoint scores below threshold on a validated scale) Response (as measured by an agreed percentage improvement in symptoms and/or by a dichotomous rating of much or very much improved on Clinical Global Impressions [CGI] scale) Relapse (number of people who remitted at endpoint but at follow-up either met diagnostic criteria for PTSD according to DSM, ICD or similar criteria, or whose follow-up scores were above threshold on a validated scale) The following PTSD scales will be included: Assessor-rated PTSD symptom scales: Clinician-Administered PTSD Scale for Children and Adolescents for DSM–IV (CAPS–CA) or DSM-V (CAPS-CA-5) Anxiety Disorders Interview Schedule for Children for DSM–IV (ADIS–C) Schedule for Affective Disorders and Schizophrenia for School Age Children (K–SADS)

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	Children's PTSD Inventory (CPTSDI) Self-report (parent-report) instruments of PTSD symptoms: Children's Impact of Event Scale/Children's Revised Impact of Event Scale (CRIES) Child Post Traumatic Stress Reaction Index (CPTS–RI)/UCLA PTSD Index for DSM-IV (UPID)/CPTS-RI Revision 2 (also referred to as the PTSD Index for DSM-IV) Child PTSD Symptom Scale (CPSS) Trauma Screening Checklist for Children (TSCC) Children's Reaction to Traumatic Events Scale (CRTES) Angie/ Andy Cartoon Trauma Scales (ACTS)/Angie/Andy Parent Rating Scales Pediatric Emotional Distress Scale (PEDS) Acceptability/tolerability Acceptability of the intervention Discontinuation due to adverse effects Discontinuation due to any reason (including adverse effects)
Important, but not critical outcomes	Dissociative symptoms as assessed by: Assessor-rated scales: Dissociation symptom cluster score on CAPS-CA Self-report (parent-report) scales: Adolescent Dissociative Experiences Scale (ADES) Child Dissociative Checklist (CDC) Personal, social, educational and occupational functioning Emotional and behavioural problems (as assessed with a validated scale including Strengths and Difficulties Questionnaire [SDQ]) Sleeping difficulties (as assessed with a validated scale including Children's Sleep Habits Questionnaire [CSHQ], Sleep Disturbance Scale for Children (SDSC)) School attendance

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	Employment (for instance, number in paid employment) Housing (for instance, number homeless or in insecure accommodation) Quality of life (as assessed with a validated scale including Pediatric Quality of Life Inventory [PedsQL] and Warwick-Edinburgh Mental Well-being Scale [WEMWBS]) Coexisting conditions (note that target of intervention should be PTSD symptoms): Symptoms of and recovery from a coexisting condition Self-harm Suicide
Study design	Systematic reviews of RCTs RCTs
Include unpublished data?	Clinical trial registries (ISRCTN and ClinicalTrials.gov) will be searched to identify any relevant unpublished trials and authors will be contacted to request study reports (where these are not available online). Unpublished data will only be included where a full study report is available with sufficient detail to properly assess the risk of bias. Authors of unpublished evidence will be asked for permission to use such data, and will be informed that summary data from the study and the study's characteristics will be published in the full guideline. Conference abstracts and dissertations will not be included.
Restriction by date?	All relevant studies from existing reviews from the 2005 guideline will be carried forward. No restriction on date for the updated search.
Minimum sample size	N = 10 in each arm
Study setting	Primary, secondary, tertiary, social care and community settings. Treatment provided to troops on operational deployment or exercise will not be covered.
The review strategy	Reviews

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	If existing systematic reviews are found, the committee will assess their quality, completeness, and applicability to the NHS and to the scope of the guideline. If the committee agrees that a systematic review appropriately addresses a review question, a search for studies published since the review will be conducted. Data Extraction (selection and coding) Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90% or Kappa statistics, K>0.60). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer. All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. Non-English-language papers will be excluded (unless data can be obtained from an existing review). Data Analysis Where data is available, meta-analysis using a fixed-effects model will be used to combine results from similar studies. Heterogeneity will be considered and if a random-effects model is considered more appropriate it will be conducted. For risk of bias, outcomes will be downgraded if the randomisation and/or allocation concealment methods are unclear or inadequate. Outcomes will also be downgraded if no attempts are made to blind the assessors or participants in some way, i.e. by either not knowing the aim of the study or the result from other tests. Outcomes will also be downgraded if there is considerable missing data (see below). Handling missing data: Where possible an intention to treat approach will be used. Outcomes will be downgraded if there is a dropout of more than 20%, or if there was a difference of >20% between the groups.

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	For heterogeneity: outcomes will be downgraded once if I2>50%, twice if I2 >80% For imprecision: outcomes will be downgraded if: Step 1: If the 95% CI is imprecise i.e. crosses 0.8 or 1.25 (dichotomous) or -0.5 or 0.5 (for continuous). Outcomes will be downgraded one or two levels depending on how many lines it crosses. Step 2: If the clinical decision threshold is not crossed, we will consider whether the criterion for Optimal Information Size is met, if not we will downgrade one level for the following. for dichotomous outcomes: <300 events for continuous outcomes: <400 participants For clinical effectiveness, if studies report outcomes using the same scale mean differences will be considered, if not standardized mean differences (SMDs) will be considered and the following criteria will be used: SMD <0.2 too small to likely show an effect SMD 0.2 small effect SMD 0.5 moderate effect SMD 0.8 large effect RR <0.8 or >1.25 clinical benefit Anything less (RR >0.8 and <1.25), the absolute numbers will be looked at to make a decision on whether there may be a clinical effect.
Heterogeneity (sensitivity analysis and subgroups)	Where substantial heterogeneity exists, sensitivity analyses will be considered, for instance: Studies with <50% completion data (drop out of >50%) will be excluded. Where possible, the influence of subgroups will be considered, including subgroup analyses giving specific consideration to the groups outlined in the sub-question section and to the following groups: Trauma type (including single incident relative to chronic exposure) Duration of intervention (for instance, short-term [≤12 weeks] relative to long-term [>12 weeks]) Intensity of intervention (for instance, low dose relative to high dose) First-line treatment relative to second-line treatment and treatment-resistant PTSD (≥2 inadequate treatments)

Topic	Pharmacological interventions for the prevention and treatment of PTSD in children and young people
	Acute PTSD symptoms (clinically important PTSD symptoms for less than 3 months) relative to chronic PTSD symptoms (clinically important PTSD symptoms for 3 months or more)
Notes	None

Appendix B – Literature search strategies

Literature search strategies for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Literature search strategies for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

One literature search covers both evidence review questions.

Clinical evidence

Database: Medline

Last searched on: **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase, PsycINFO**

Date of last search: 29 January 2018

#	Searches
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
2	1 use emez
3	stress disorders, traumatic/ or combat disorders/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or stress, psychological/
4	3 use mesz
5	exp posttraumatic stress disorder/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or traumatic neurosis/ or trauma/ or stress reactions/ or psychological stress/ or chronic stress/
6	5 use psyh
7	(railway spine or (rape adj2 trauma*) or reexperienc* or re experienc* or torture syndrome or traumatic neuros* or traumatic stress).ti,ab.
8	(trauma* and (avoidance or grief or horror or death* or nightmare* or night mare* or emotion*)).ti,ab.
9	(posttraumatic* or post traumatic* or stress disorder* or acute stress or ptsd or asd or desnos or (combat neuros* or combat syndrome or concentration camp syndrome or extreme stress or flashback* or flash back* or hypervigilan* or hypervigilen* or psych* stress or psych* trauma* or psycho?trauma* or psychotrauma*)).ti,ab.
10	or/2,4,6-9
11	exp *antidepressant agent/
12	11 use emez

#	Searches
13	antidepressive agents/ or serotonin uptake inhibitors/ or monoamine oxidase inhibitors/
14	13 use mesz
15	antidepressant drugs/ or serotonin reuptake inhibitors/ or serotonin reuptake inhibitors/ or monoamine oxidase inhibitors/
16	15 use psyh
17	(tricyclic* or tca*1).tw.
18	(ssri* or ((serotonin or 5 ht or 5 hydroxytryptamine) adj (uptake or reuptake or re uptake) adj inhibit*)).tw.
19	(antidepress* or anti depress* or maoi* or ((adrenaline or amine or mao or mono amin* or monoamin* or tyramin*) adj2 inhibit*)).tw.
20	(snri* or ssnri* or ((noradrenalin or norepinephrine) adj serotonin adj (uptake or reuptake or re uptake) adj inhibitor*) or (serotonin adj (noradrenalin or norepinephrine) adj (uptake or reuptake or re uptake) adj inhibitor*)).tw.
21	or/12,14,16,17-20
22	fluoxetine/ use emez,mesz,psyh
23	paroxetine/ use emez,mesz,psyh
24	sertaline/ use emez,mesz,psyh
25	(fluoxetin* or fluctin*1 or flunirin* or fluoxifar or lovan or prosac or prozac or prozamin* or sarafem or symbyax).tw.
26	(paroxetin* or aropax or deroxat or motivan or paxil* or pexeva or seroxat or tagonis).tw.
27	(sertralin* or altrulin* or aremis or besitran* or gladem or lustral* or naphthylamin* or sealdin* or serad or serlain* or tresleen or zoloft).tw.
28	or/22-27
29	*amitriptyline/ use emez or amitriptyline/ use mesz,psyh
30	(amitriptyl* or amitryptil* or amitryptin* or amitryptylin* or amytriptil* or amytriptyl* or amytryptil* or adepress or adepril* or ambivalon* or amineurin* or amitid* or amitril* or amitrip or amitrol* or anapsique or anp 3548 or antitriptylin* or apoamitriptylin* or damilen* or damylen* or domical* or elatrol* or elavil* or endep or enovil* or etafon* or etafron* or euplit* or lantron* or laroxal* or laroxyl* or lentizol* or novoprotect or proheptadien* or redomex or sarboten retard 75 or saroten* or sarotex or stelminal* or sylvemid* or syneudon* or teperin* or terepin* or triptafen* or triptanol* or triptizol* or triptyl or triptylin* or tryptanol* or tryptin* or tryptizol*).tw.
31	*imipramine/ use emez or imipramine/ use mesz,psyh
32	(imipramin* or antideprin* or berkomin* or chrytemin* or deprinol* or ia pram or imavate or imidobenzyl* or imidol* or imipramid* or imiprex or imiprin* or imizin* or janimin* or melipramin* or norchlorimipramin* or norpramin* tablets or novopramin* or presamin* or pryleugan* or psychoforin* or psychoforin* or servipramin* or sk pramin* or tofranil* or trofanil*).tw.
33	or/29-32
34	brofaromin*.sh.
35	(brofaremin* or brofaromin* or brofarominum or consonar).ti,ab.
36	phenelzin*.sh.

#	Searches
37	(phenelzin* or 2 phenethylhydrazin* or 2 phenylethylhydrazin* or benzylmethylhydrazin* or beta phenethylhydrazin* or beta phenylethylhydrazine or fenelzin or fenizin* or mao rem or nardelzin* or nardil* or phenalzin* or phenethylhydrazin* or phenylethylhydrazin* or stinerval*).tw.
38	or/34-37
39	*venlafaxine/ use emez
40	venlafaxine hydrochloride/ use mesz or venlafaxine/ use psyh
41	(venlafaxin* or efexor or effexor or trevilor).tw.
42	or/39-41
43	*mirtazapine/ use emez or mirtazapine/ use mesz,psyh or (mirtazapin* or 6 azamianserin* or lerivon* or remergil* or remergon* or remeron* or tolvon* or zispin).tw.
44	neuroleptic agent/ use emez or antipsychotic agents/ use mesz or neuroleptic drugs/ use psyh
45	(antipsychotic* or anti psychotic* or (major adj2 (butyrophenon* or phenothiazin* or tranquil*)) or neuroleptic*).tw.
46	45
47	*olanzapine/ use emez or olanzapine/ use mesz,psyh
48	(olanzapin* or lanzac or ly 170053 or ly170053 or midax or olansek or zydis or zyprex*).tw.
49	*risperidone/ use emez or risperidone/ use mesz,psyh
50	(risperidon* or belivon* or risolept or risperdal*).tw.
51	or/47-50
52	or/43,44,46-51
53	carbamazepin*.sh. or (amizepin or amizepine or atretol or biston or calepsin or camapine or carbadac or carbamazepin or carbategral or carbatol or carbatrol or carbazene or carbazep or carbazin* or carmaz or carpaz or carzepin or carzepine or clostedal or convuline or epileptol or epimax or epitol or eposal retard or equetro or espa-lepsin or finlepsin or foxalepsin or hermolepsin or karbamazepin or kodapan or lexin or mazepine or mazetol or neugeron or neurotol or neurotop or nordotol or panitol or servimazepin or sirtal or tardotol or taver or tegol or tegral or tegretal or tegretol or tegrital or telesmin or temporal or temporol or teril or timonil).ti,ab.
54	clonidine/ use emez,mesz or (adesipress or arkamin or atensina or caprysin or catapres or catapresan or catapressant or catasan or chlofazolin or chlophazolin or chlophelin or chlophazolin or clinidine or clofelin or clofeline or clomidine or clondine or clonicel or clonidin* or clonipresan or clonistada or clonnirit or clophelin* or daipres or dixarit or duraclon or gemiton or haemiton or hemiton or hypodine or isoglaucon or jenloga or kapvay or klofelin or klofenil or melzin or normopresan or normopresin or paracefan or sulmidine or taitecin or tenso timelets).ti,ab.
55	propranolol/ use emez,mesz or (acifol or adrexan or alperol or anaprilin * or anaprilinium or anaprylin* or angilol or apsolol or arcablock or artensol or authus or avlocardyl or becardin or bedranol or beprane or bercolol or berkolol or beta neg or beta tablinen or beta timelets or betabloc or betadipresan or betaneg or betaprol or betares or betraden or betaryl or blocard or blocaryl or cardinol or ciplar or corbeta or deralin or dexpropranolol or dibudinate or dideral or dociton * or durabeton or duranol or efektolol or elbrol or emforal or farmadral or farprolol or frekven or frina or

#	Searches
	hemangeol or hemangiol or hopranolol or ikopal or impral or inderal or inderalici or inderex or indicardin or indobloc or innopran or inpanol or ipran or lederpronol or levopropranolol or napriline or noloten or obsidan or obsin or obzidan or oposim or phanerol or prandol or prano puren or pranopuren or prestoral or prolol or pronovan or propabloc or propal or propalong or propanolol or propayerst or propercuten or prophylux or propra ratiopharm or propral or propranur or proprasylyt* or reducor or rexigen or sagittol or slow deralin or stapranolol or sumial or tenomal or tensiflex or waucoton).ti,ab.
56	or/53-55
57	*carbamazepine/ use emez or carbamazepine/ use mesz,psyh or (amizepin * or carbamazepin* or atretol or biston or carbamazepin or carbategral or carbatol or carbatrol or carzepin or carzepine or epimax or epitol or equetro or finlepsin or lexin or neurotop or sirtal or tegral or tegretal or tegretol or tegrital or timonil).ti,ab.
58	*valproate semisodium/ use emez or valproic acid/ use mesz,psyh or (delepsine or depakote or divalproex or epilim chrono or valproate or valproic acid).ti,ab.
59	*lamotrigine/ use emez or lamotrigine/ use mesz,psyh or (labileno or lamotrigin* or lamepil or lamictal or lamictin or lamodex).ti,ab.
60	*tiagabine/ use emez or tiagabine/ use mesz,psyh or (gabitril or tiabex or tiagabin*).ti,ab.
61	*topiramate/ use emez or topiramate/ use mesz,psyh or (epitomax or qudexy or topamax or topimax or topiramat* or trokendi).ti,ab.
62	*nefazodone/ use emez or nefazodone/ use mesz,psyh or (nefazodon* or nefadar or nefazadone or reseril or serzone).ti,ab.
63	*buspirone/ use emez or buspirone/ use mesz,psyh or (axoren or bespar or buspar or buspin or buspiron*).ti,ab.
64	*lorazepam/ use emez or lorazepam/ use mesz,psyh or (almazine or alzapam or ativan or bonatranquan or kendol or laubeel or lorabenz or loram or loranase or loranaze or lorans or lorax or lorazepam or lorazin or loridem or lorivan or mesmerin or nervistop or orifadal or pro dorm or quait or securit or tavor or temesta or tolid or upan or wypax).ti,ab.
65	*diazepam/ use emez or diazepam/ use mesz,psyh or (antenex or assival or calmpose or cercin or cercine or diapam or diastat or diazemuls or diazepam or diazidem or ducene or eurosan or fanstan or faustan or neocalme or novazam or paceum or pacitran or plidan or psychopax or relanium or seduxen or serendin or sonacon or stesolid or valaxona or valiquid or valium or valpam or valrelease or vatran or zetran).ti,ab.
66	*clonazepam/ use emez or clonazepam/ use mesz,psyh or (aklonil or antelepsin or clonazepam or clonex or clonopin or clonotril or iktorivil or klonopin or rivatril or rivotril).ti,ab.
67	*alprazolam/ use emez or alprazolam/ use mesz,psyh or (aceprax or alprazolam or anax or constan or frontal or helex or neupax or niravam or solanax or tafil or trankimazin or valeans or xanax or xanor).ti,ab.
68	*cycloserine/ use emez or cycloserine/ use mesz,psyh or (cycloserin* or seromicina or seromycin or terizidon or 4-amino-3-isoxazolidinone).ti,ab.
69	*ketamine/ use emez or ketamine/ use mesz,psyh or (ketamin* or ketalar or calipsol or calypsol or imalgene or kalipsol or ketaject or ketalar or ketaminol or ketanest or ketased or ketaset or ketaved or ketavet or ketoject or ketolar or narkamon or narketan or velonarcon or vetalar).ti,ab.

#	Searches
70	*3,4 methylenedioxymethamphetamine/ use emez or n-methyl-3,4-methylenedioxyamphetamine/ use mesz or methylenedioxymethamphetamine/ use psyh or (ecstasy or mdma or methylenedioxy-methamphetamine or methylenedioxymethamphetamine).ti,ab.
71	*neuropeptide y/ use emez or neuropeptide/ use mesz,psyh or (neuropeptide y or neuropeptide tyrosine).ti,ab.
72	*oxytocin/ use emez or oxytocin/ use mesz,psyh or (atonin or di sipidin or disipidin or endopituitrin or mipareton or orasthin or orastina or oxystin or oxytan or pareton or partacon or partocon or partolact or partoxin or physormon or pitocin or piton or pituilobine or pitupartin or synpitan or syntocinon or utedrin or uteracon or uterason).ti,ab.
73	prazosin.sh. or (prazosin or adversuten or alpress or deprazolin or hypovase or lentopres or minipress or peripress or pratsiol or prazac or prazosin diffutab or vasoflex).ti,ab.
74	*propranolol/ use emez or propranolol/ use mesz,psyh or (propranolol or anaprilin or anapriline or arcablock or authus or avlocardyl or avlocardyl retard or bedranol or beprane or beta timelets or betadipresan or cardinol or ciplar or corbeta or deralin or dociton or duranol or efektolol or elbrol or frekven or hemangeol or hemangiol or inderal or inderalici or inderex or innopran or ipran or obsidan or prandol or prolol plus or propabloc or propal or propercuten or prophylux or propra ratiopharm or propral or propranur or sagittol or sumial).ti,ab.
75	*hydrocortisone/ use emez or hydrocortisone/ use mesz,psyh or (alfacort or cort dome or cortef or cortenema or cortisol* or dioderm or ef cortelan or efcortelan or egocort or eksalb or epicort or ficortril or hycor or hycort or hydracort or hydrocort or hydrocortison* or hydrocortone or hydrokortison or hydrotopic or hysone or hytisone or hytone or mildison or munitren or novohydrocort or plenadren or proctocort or proctosone or rectocort or schericur or scherosone or synacort or texacort).ti,ab.
76	or/57-75
77	anticonvulsant agent/ use emez or benzodiazepine derivative/ use emez or tranquilizer/ use emez or anticonvulsants/ use mesz or anti anxiety agents/ use mesz or benzodiazepines/ use mesz or anticonvulsant drugs/ use psyh or benzodiazepines/ use psyh or tranquilizing drugs/ use psyh or (anticonvuls* or anti convuls*).ti,ab.
78	(anxiolytic* or antianxiety or anti anxiety).ti,ab.
79	benzodiaz*.ti,ab.
80	or/77-79
81	or/21,28,33,38,42,52,56,76,80
82	meta analysis/ or "meta analysis (topic)"/ or systematic review/
83	82 use emez
84	meta analysis.sh,pt. or "meta-analysis as topic"/ or "review literature as topic"/
85	84 use mesz
86	(literature review or meta analysis).sh,id,md. or systematic review.id,md.
87	86 use psyh
88	(exp bibliographic database/ or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit

#	Searches
	or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,sh,pt. or systematic*.ti,ab.)
89	88 use emez
90	(exp databases, bibliographic/ or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,sh,pt. or systematic*.ti,ab.)
91	90 use mesz
92	(computer searching.sh,id. or (((electronic or computer* or online) adj database*) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review*.ti,ab,pt. or systematic*.ti,ab.)
93	92 use psyh
94	((analy* or assessment* or evidence* or methodol* or quantativ* or systematic*) adj2 (overview* or review*)).tw. or ((analy* or assessment* or evidence* or methodol* or quantativ* or systematic*).ti. and review*.ti,pt.) or (systematic* adj2 search*).ti,ab.
95	(metaanal* or meta anal*).ti,ab.
96	(research adj (review* or integration)).ti,ab.
97	reference list*.ab.
98	bibliograph*.ab.
99	published studies.ab.
100	relevant journals.ab.
101	selection criteria.ab.
102	(data adj (extraction or synthesis)).ab.
103	(handsearch* or ((hand or manual) adj search*)).ti,ab.
104	(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
105	(fixed effect* or random effect*).ti,ab.
106	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
107	or/83,85,87,89,91,93-106
108	exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/
109	108 use emez
110	exp clinical trial/ or exp "clinical trials as topic"/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/
111	110 use mesz
112	(clinical trials or placebo or random sampling).sh,id.
113	112 use psyh
114	(clinical adj2 trial*).ti,ab.
115	(crossover or cross over).ti,ab.
116	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.
117	(placebo* or random*).ti,ab.

#	Searches
118	treatment outcome*.md. use psyh
119	animals/ not human*.mp. use emez
120	animal*/ not human*/ use mesz
121	(animal not human).po. use psyh
122	or/109,111,113-118
123	122 not (or/119-121)
124	or/107,123
125	10 and 81 and 124

Database: CDSR, DARE, HTA, CENTRAL

Date of last search: 29 January 2018

#	Searches
#1	MeSH descriptor: Stress Disorders, Traumatic this term only
#2	MeSH descriptor: Combat Disorders this term only
#3	MeSH descriptor: Psychological Trauma this term only
#4	MeSH descriptor: Stress Disorders, Post-Traumatic this term only
#5	MeSH descriptor: Stress Disorders, Traumatic, Acute this term only
#6	MeSH descriptor: Stress, Psychological this term only
#7	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ti (Word variations have been searched)
#8	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ab (Word variations have been searched)
#9	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ti (Word variations have been searched)
#10	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ab (Word variations have been searched)
#11	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ti (Word variations have been searched)
#12	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ab (Word variations have been searched)
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

Database: CINAHL PLUS

Date of last search: 29 January 2018

#	Searches
s52	s6 and s51
s51	s40 or s50
s50	s48 not s49
s49	(mh "animals") not (mh "human")
s48	s41 or s42 or s43 or s44 or s45 or s46 or s47
s47	ti (placebo* or random*) or ab (placebo* or random*)
s46	ti (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* or tripleblind*) or ab (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* or tripleblind*)
s45	ti (crossover or cross over) or ab (crossover or cross over)
s44	ti clinical n2 trial* or ab clinical n2 trial*
s43	(mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")
s42	mw double blind* or single blind* or triple blind*
s41	(mh "clinical trials+")
s40	s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s29 or s30 or s31 or s34 or s35 or s36 or s37 or s38 or s39
s39	ti (analy* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*) or ab (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or qualitativ* n5 review* or quantativ* n5 review* or systematic* n5 review*)
s38	ti (pool* n2 results or combined n2 results or combining n2 results) or ab (pool* n2 results or combined n2 results or combining n2 results)
s37	ti (pool* n2 studies or combined n2 studies or combining n2 studies) or ab (pool* n2 studies or combined n2 studies or combining n2 studies)
s36	ti (pool* n2 trials or combined n2 trials or combining n2 trials) or ab (pool* n2 trials or combined n2 trials or combining n2 trials)
s35	ti (pool* n2 data or combined n2 data or combining n2 data) or ab (pool* n2 data or combined n2 data or combining n2 data)
s34	s32 and s33
s33	ti review* or pt review*
s32	ti analy* or assessment* or evidence* or methodol* or quantativ* or qualitativ* or systematic*
s31	ti “systematic* n5 search*” or ab “systematic* n5 search*”
s30	ti “systematic* n5 review*” or ab “systematic* n5 review*”
s29	(s24 or s25 or s26) and (s27 or s28)
s28	ti systematic* or ab systematic*

#	Searches
s27	tx review* or mw review* or pt review*
s26	(mh "cochrane library")
s25	ti (bids or cochrane or embase or “index medicus” or “isi citation” or medline or psyclit or psychlit or scisearch or “science citation” or web n2 science) or ab (bids or cochrane or “index medicus” or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science)
s24	ti (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”) or ab (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”)
s23	(mh "literature review")
s22	pt systematic* or pt meta*
s21	ti (“fixed effect*” or “random effect*”) or ab (“fixed effect*” or “random effect*”)
s20	ti (“mantel haenszel” or peto or dersimonian or “der simonian”) or ab (“mantel haenszel” or peto or dersimonian or “der simonian”)
s19	ti (handsearch* or "hand search*" or "manual search*") or ab (handsearch* or "hand search*" or "manual search*")
s18	ab "data extraction" or "data synthesis"
s17	ab "selection criteria"
s16	ab "relevant journals"
s15	ab "published studies"
s14	ab bibliograph*
s13	ti "reference list*"
s12	ab "reference list*"
s11	ti (“research review*” or “research integration”) or ab (“research review*” or “research integration”)
s10	ti (metaanal* or “meta anal*” or metasynthes* or “meta synethes*”) or ab (metaanal* or “meta anal*” or metasynthes* or “meta synethes*”)
s9	(mh "meta analysis")
s8	(mh "systematic review")
s7	(mh "literature searching+")
s6	s1 or s2 or s3 or s4 or s5
s5	ti ((posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*"))) or ab ((posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")))
s4	ti ((trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*))) or ab ((trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)))

#	Searches
s3	ti (("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress")) or ab (("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"))
s2	(mh "stress, psychological")
s1	(mh "stress disorders, post-traumatic")

Health economic evidence

Note: evidence resulting from the health economic search update was screened to reflect the final dates of the searches that were undertaken for the clinical reviews (see review protocols).

Database: Medline

Last searched on: **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase, PsycINFO**

Date of last search: 1 March 2018

#	Searches
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
1	*acute stress/ or *behavioural stress/ or *emotional stress/ or *critical incident stress/ or *mental stress/ or *posttraumatic stress disorder/ or *psychotrauma/
2	1 use emez
3	stress disorders, traumatic/ or combat disorders/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or stress, psychological/
4	3 use mesz, prem
5	exp posttraumatic stress disorder/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or traumatic neurosis/ or "trauma"/ or stress reactions/ or psychological stress/ or chronic stress/
6	5 use psyh
7	(railway spine or (rape adj2 trauma*) or reexperienc* or re experienc* or torture syndrome or traumatic neuros* or traumatic stress).ti,ab.
8	(trauma* and (avoidance or grief or horror or death* or nightmare* or night mare* or emotion*)).ti,ab.
9	(posttraumatic* or post traumatic* or stress disorder* or acute stress or ptsd or asd or desnos or (combat neuros* or combat syndrome or concentration camp syndrome or extreme stress or flashback* or flash back* or hypervigilan* or hypervigilen* or psych* stress or psych* trauma* or psycho?trauma* or psychotrauma*)).ti,ab.
10	or/2,4,6-9
11	budget/ or exp economic evaluation/ or exp fee/ or funding/ or exp health care cost/ or health economics/ or exp pharmacoeconomics/ or resource allocation/

#	Searches
12	151 use emez
13	exp budgets/ or exp "costs and cost analysis"/ or economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp "fees and charges"/ or value of life/
14	153 use mesz, prem
15	exp "costs and cost analysis"/ or cost containment/ or economics/ or finance/ or funding/ or "health care economics"/ or pharmacoeconomics/ or exp professional fees/ or resource allocation/
16	155 use psyh
17	(cost* or economic* or pharmacoeconomic* or pharmaco economic*).ti. or (cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab. or (budget* or fee or fees or financ* or price or prices or pricing or resource* allocat* or (value adj2 (monetary or money))).ti,ab.
18	or/12,14,16-17
19	decision theory/ or decision tree/ or monte carlo method/ or nonbiological model/ or (statistical model/ and exp economic aspect/) or stochastic model/ or theoretical model/
20	159 use emez
21	exp decision theory/ or markov chains/ or exp models, economic/ or models, organizational/ or models, theoretical/ or monte carlo method/
22	161 use mesz, prem
23	exp decision theory/ or exp stochastic modeling/
24	163 use psyh
25	((decision adj (analy* or model* or tree*)) or economic model* or markov).ti,ab.
26	or/20,22,24-25
27	quality adjusted life year/ or "quality of life index"/ or short form 12/ or short form 20/ or short form 36/ or short form 8/ or sickness impact profile/
28	167 use emez
29	quality-adjusted life years/ or sickness impact profile/
30	169 use mesz, prem
31	(((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab.
32	(disutili* or dis utili* or (utilit* adj1 (health or score* or value* or weigh*))).ti,ab.
33	(health year equivalent* or hye or hyes).ti,ab.
34	(daly or qal or qald or qale or qaly or qtime* or qwb*).ti,ab.
35	discrete choice.ti,ab.
36	(euroqol* or euro qol* or eq5d* or eq 5d*).ti,ab.
37	(hui or hui1 or hui2 or hui3).ti,ab.
38	(((general or quality) adj2 (wellbeing or well being)) or quality adjusted life or qwb or (value adj2 (money or monetary))).ti,ab.
39	(qol or hql* or hqol* or hrqol or hr ql or hrql).ti,ab.
40	rosser.ti,ab.
41	sickness impact profile.ti,ab.

#	Searches
42	(standard gamble or time trade* or tto or willingness to pay or wtp).ti,ab.
43	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
44	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
45	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
46	(sf16 or sf 16 or short form 16 or shortform 16 or shortform16).ti,ab.
47	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
48	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
49	or/28,30-48
50	or/18,26,49

Database: HTA, NHS EED

Date of last search: 1 March 2018

#	Searches
#1	MeSH descriptor: Stress Disorders, Traumatic this term only
#2	MeSH descriptor: Combat Disorders this term only
#3	MeSH descriptor: Psychological Trauma this term only
#4	MeSH descriptor: Stress Disorders, Post-Traumatic this term only
#5	MeSH descriptor: Stress Disorders, Traumatic, Acute this term only
#6	MeSH descriptor: Stress, Psychological this term only
#7	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ti (Word variations have been searched)
#8	("railway spine" or (rape near/2 trauma*) or reexperienc* or "re experienc*" or "torture syndrome" or "traumatic neuros*" or "traumatic stress"):ab (Word variations have been searched)
#9	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ti (Word variations have been searched)
#10	(trauma* and (avoidance or grief or horror or death* or nightmare* or "night mare*" or emotion*)):ab (Word variations have been searched)
#11	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ti (Word variations have been searched)
#12	(posttraumatic* or "post traumatic*" or "stress disorder*" or "acute stress" or ptsd or asd or desnos or ("combat neuros*" or "combat syndrome" or "concentration camp syndrome" or "extreme stress" or flashback* or "flash back*" or hypervigilan* or hypervigilen* or "psych* stress" or "psych* trauma*" or psychotrauma* or psychotrauma*) or (posttrauma* or traumagenic* or "traumatic stress*")):ab (Word variations have been searched)
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

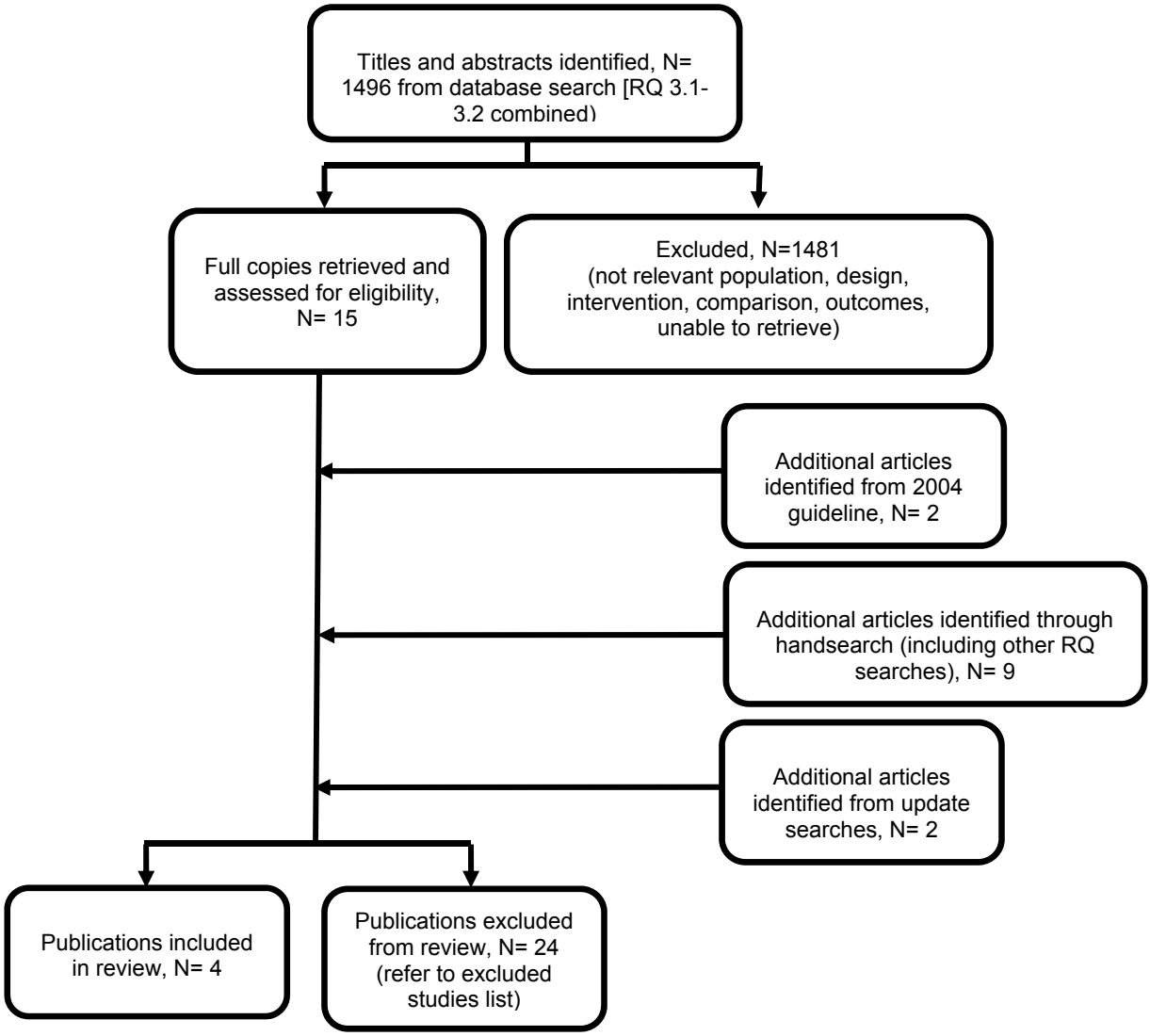
Appendix C – Clinical evidence study selection

Clinical evidence study selection for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Clinical evidence study selection for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

One flow diagram covers both evidence review questions.

Figure 1: Flow diagram of clinical article selection for pharmacological interventions for PTSD in children and young people review



Appendix D – Clinical evidence tables

Clinical evidence tables for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Clinical evidence tables for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Pharmacological prevention of PTSD in children and young people

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Nugent 2010	Unclear symptom severity at baseline	Motor Vehicle Collision: Motor vehicle accident (55%); Bicycle accident (10%); Pedestrian versus automobile (10%); Fall (7%); Other (17%) Mean months since trauma: 0.016 (within 12 hours)	29	Age: 15 (10-18) Gender (% female): 48 BME (% non-white): 7 Country: US Coexisting conditions: 31% chronic psychiatric diagnosis	Inclusion criteria: paediatric trauma emergency department patients; aged 10-18 years; Glasgow Coma Scale score ≥ 14; an "at risk" score (4 or more positive responses) on Screening Tool for Early Predictors of PTSD (STEPP). Exclusion criteria: children admitted for injuries secondary to physical or sexual abuse; hypersensitivity to beta-blockers; bradycardia; cardiogenic or hypovolemic shock; diabetes; pre-existing heart condition; treatment for asthma; injuries or medical treatment procedures contraindicated propranolol

BME=Black and Minority Ethnic N=number being randomised; PTSD=post-traumatic stress disorder

Pharmacological treatment of PTSD in children and young people

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
Cohen 2007	PTSD diagnosis according to ICD/DSM criteria Mean months since onset of PTSD: NR	Childhood sexual abuse: Contact sexual abuse Mean months since traumatic event: 22.9	24	Age: Mean NR (10-17) Gender (% female): 100 BME (% non-white): 22 Country: US Coexisting conditions: 68% met criteria for diagnosis other than PTSD: 64% met criteria for major depressive disorder (MDD). Other diagnoses included general anxiety disorder, substance abuse not otherwise specified, oppositional defiant disorder, panic disorder, and anorexia nervosa	Inclusion criteria: children aged 10-17 years who had experienced contact sexual abuse that was confirmed by Child Protective Services (CPS), law enforcement, or a professional independent forensic evaluator; having sexual abuse-related PTSD symptoms (defined as at least five PTSD symptoms on the Schedule for Affective Disorders and Schizophrenia for School- Age Children-Present and Lifetime version [K-SADS-PL] with at least one symptom in each of the three PTSD clusters and clinically significant impairment); having a parent or caregiver who was available to give consent and participate. Exclusion criteria: non-English speaking; schizophrenia or other active psychotic disorder; mental retardation or pervasive developmental disorder; taking current psychotropic medications
Robb 2010	PTSD diagnosis according to ICD/DSM criteria	Mixed: Sexual abuse (41%); Confronted with traumatic news (33%); Victim of physical abuse/violence (32%); In	131	Age: 11 (6-17) Gender (% female): 60 BME (% non-white): 42	Inclusion criteria: children and adolescents aged 6–17 years; met DSM-IV criteria for PTSD as determined by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
	Mean months since onset of PTSD: 29.4	car or other accident (24%); Witness to violence (48%); In a fire or natural disaster (16%); Other (22%) Mean months since traumatic event: NR		Country: US Coexisting conditions: NR	Version (K-SADS-PL); scored ≥ 30 on the UCLA PTSD-I at baseline; a Clinical Global Impressions–Severity (CGI-S) score ≥ 4 at both the screen and baseline visit; the patient and their parent/legal guardian must be judged to be sufficiently reliable to cooperate with study procedures; if female of childbearing potential, must be nonpregnant, nonlactating, have a negative serum pregnancy test prior to entry into the study, and, if sexually active, must agree to use a medically acceptable form of contraception; written informed consent provided by a parent and/or legal guardian, and verbal or written assent provided by the patient. Exclusion criteria: trauma was ongoing or likely to recur, or who were living in the same home as their abuser, or who were expected to participate in litigation related to their trauma during the course of the study; patients with a past history of meeting DSM-IV criteria for bipolar disorder, schizophrenia or any other psychotic disorder, bulimia or anorexia nervosa, or autistic spectrum disorder; patients with a suicide attempt history, or who, in the clinical judgment of the investigator, are currently a suicide risk; meeting DSM-IV criteria for substance abuse or dependence in the previous 6 months; receiving any therapy specifically for PTSD

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
					(ongoing supportive psychotherapy and/or family therapy were permitted); a history of seizure disorder or with cognitive or neurological deficits that would significantly limit their ability to perform the rating scales; any clinically significant abnormalities on physical examination, medical history, electrocardiogram (ECG) or laboratory tests; concomitant psychotropic medication, other than diphenhydramine or chloral hydrate for sleep or stimulants for attention-deficit/hyperactivity disorder (ADHD), or who have taken any psychotropic medication in the 2 weeks prior to the baseline visit (or four weeks in the case of fluoxetine); a history of intolerance or hypersensitivity to selective SSRIs or sertraline, or who have previously failed to respond to a clinically adequate dose of SSRIs
Scheeringa 2014	Clinically important PTSD symptoms (scoring above a threshold on validated scale) Mean months since onset of PTSD: NR	Mixed: Disaster (14%); Domestic violence (26%); Assaulted (7%); Sexual (32%); Accident (2%); Seen/heard someone killed/hurt badly (5%); Seen unexpected dead body (14%). Mean number of occurrences of traumas: 157	57	Age: 12.5 (range NR) Gender (% female): 56 BME (% non-white): 60 Country: US Coexisting conditions: NR	Inclusion criteria: children aged 7–18 years; who have experienced or witnessed at least one life-threatening event; five or more PTSD symptoms plus functional impairment; had been offered 12 sessions of CBT and remained in treatment at the fifth session. Exclusion criteria: Glasgow Coma Scale score of ≤5 in the emergency room; moderate mental retardation (standard scores <50 on the Peabody Picture Vocabulary Test), autistic disorder (from clinical observations by the first author), blindness, deafness, or

Study ID	PTSD details	Trauma type	N	Demographics	Inclusion/Exclusion criteria
		Mean months since traumatic event: NR			coming from foreign language speaking families; being suicidal, homicidal, or severely disabled; concurrent counselling outside of the study; any kidney or liver ailment; epilepsy or history of seizures; bipolar disorder or schizophrenia; concurrent psychoactive medications unless the dose had been stable for at least 4 weeks prior to treatment and remained stable

BME=Black and Minority Ethnic; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases; N=Number being randomised; NR=not reported; PTSD=post-traumatic stress disorder

Appendix E – Forest plots

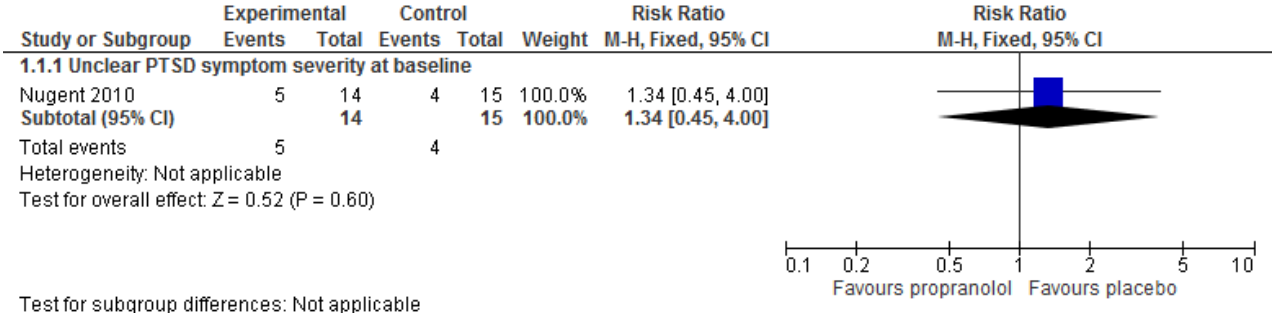
Forest plots for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Forest plots for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Pharmacological prevention of PTSD in children and young people

Propranolol versus placebo for the early prevention (<1 month) of PTSD in children and young people

Figure 2: Propranolol versus placebo for the early prevention (<1 month) of PTSD in children and young people: Diagnosis of PTSD at 1-month follow-up



Pharmacological treatment of PTSD in children and young people

Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Figure 3: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: PTSD symptomatology clinician-rated (UCLA PTSD-I change score)

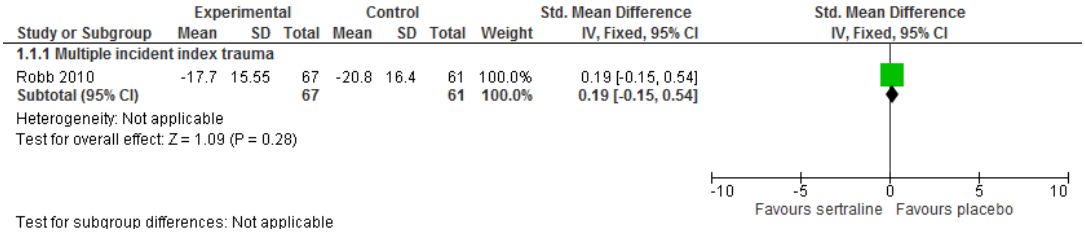


Figure 4: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Remission (number of people no longer meeting diagnostic criteria for PTSD)

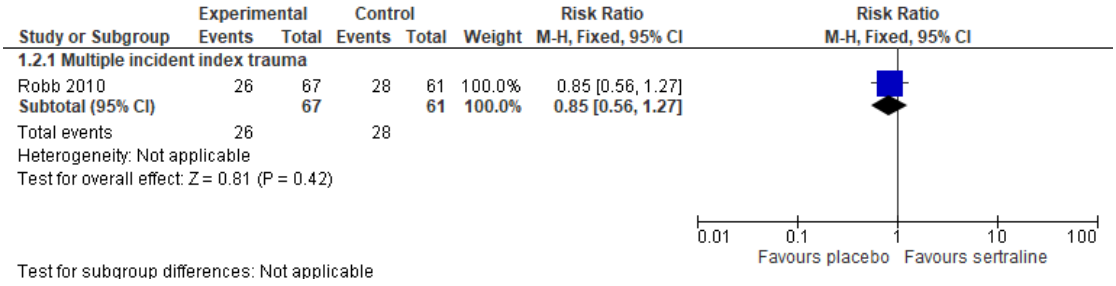


Figure 5: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Response (number of people rated 'much' or 'very much' improved on CGI-I)

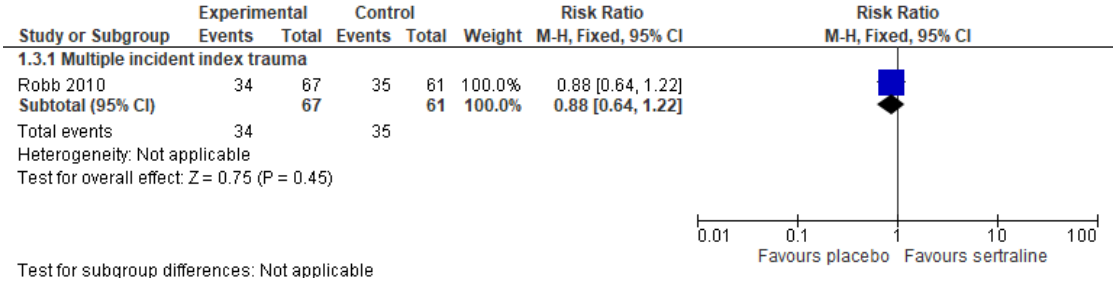


Figure 6: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Depression symptoms (CDRS-R change score)

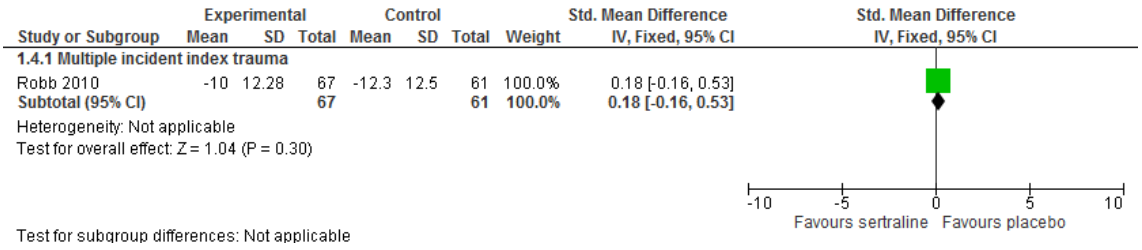


Figure 7: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Quality of life (PQ-LES-Q change score)

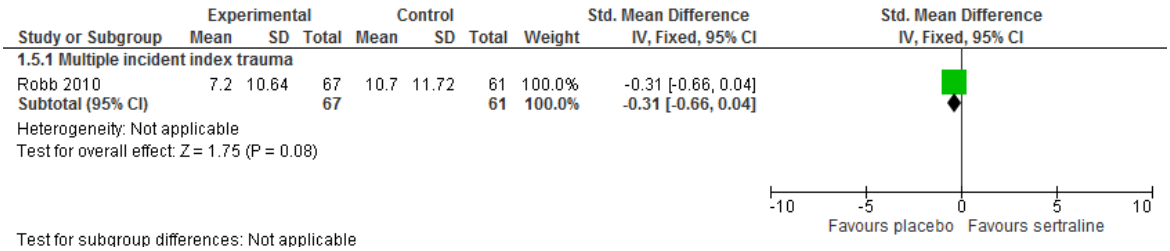


Figure 8: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Discontinuation due to any reason (including adverse events)

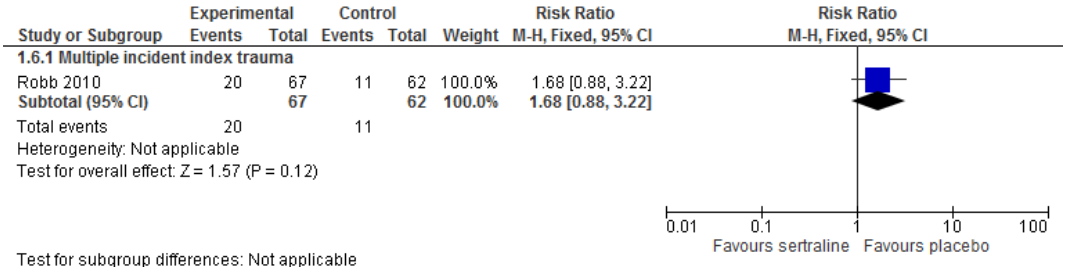
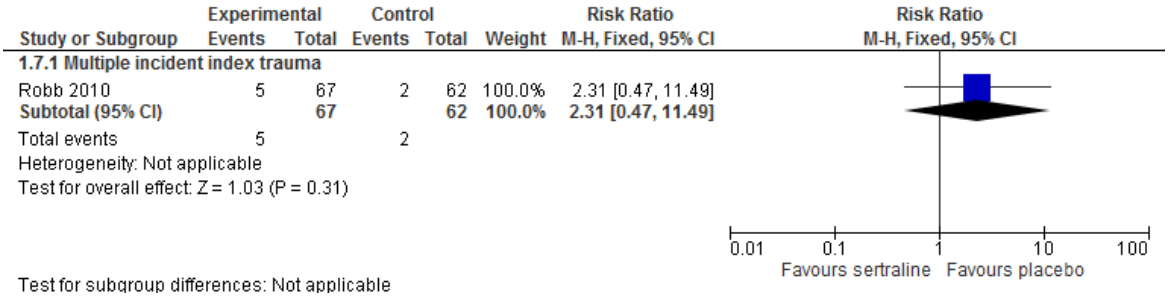


Figure 9: Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Discontinuation due to adverse events



Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Figure 10: Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Global functioning (CGAS change score)

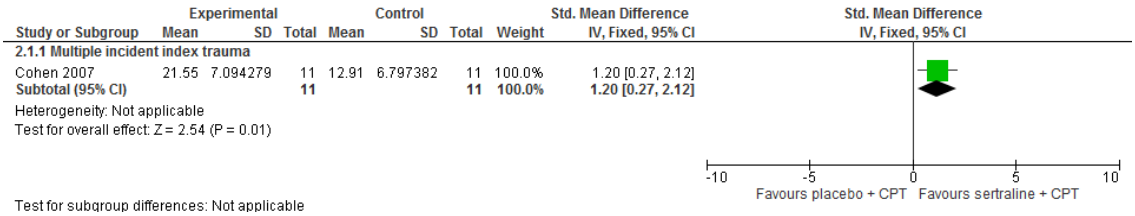
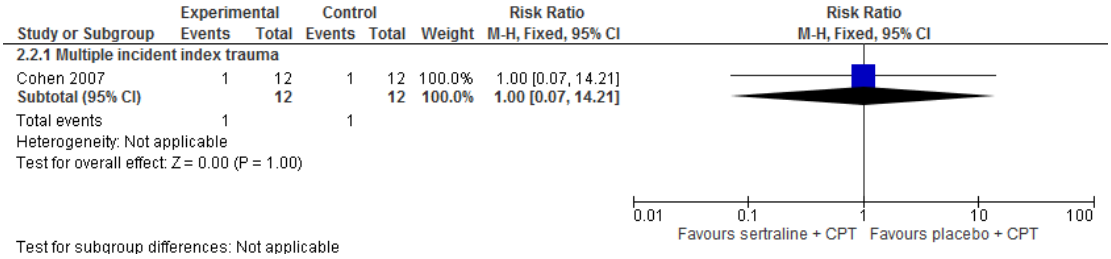


Figure 11: Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people: Discontinuation due to any reason (including adverse effects)



D-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Figure 12: *d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people:* PTSD symptomatology self/parent-rated (CPSS change score); Multiple incident index trauma

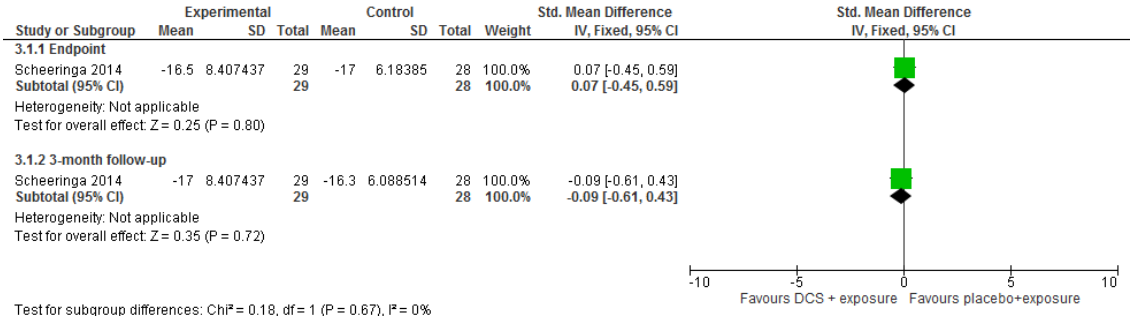


Figure 13: *d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people:* Response (number of people showing ≥50% improvement on CPSS)

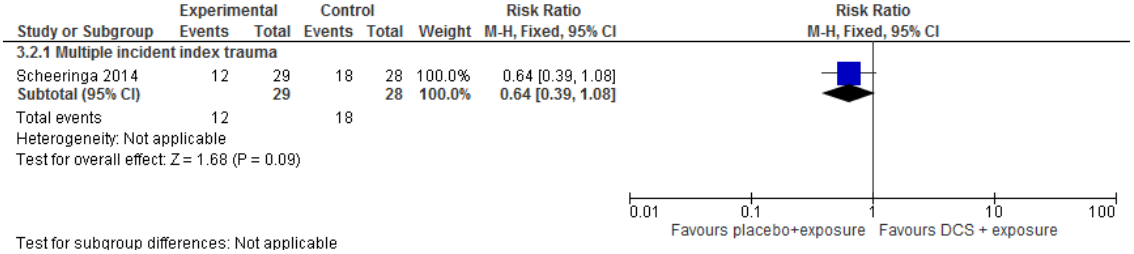


Figure 14: ***d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people:*** **Depression symptoms (CDI change score); Multiple incident index trauma**

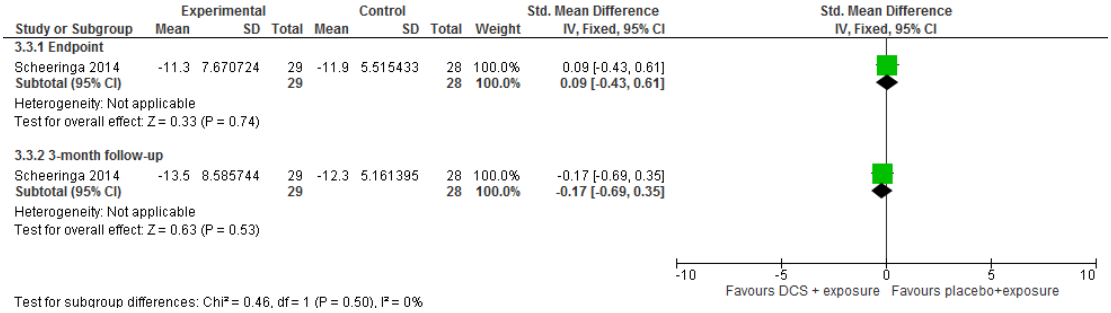


Figure 15: ***d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people:*** **Anxiety symptoms (SCARED change score); Multiple incident index trauma**

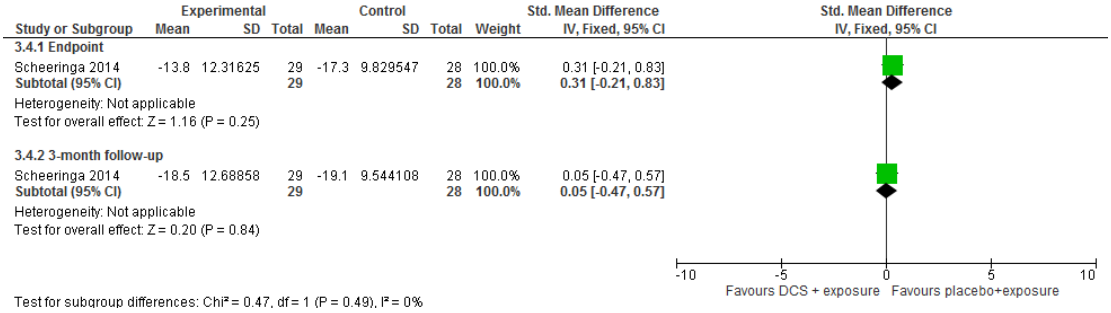
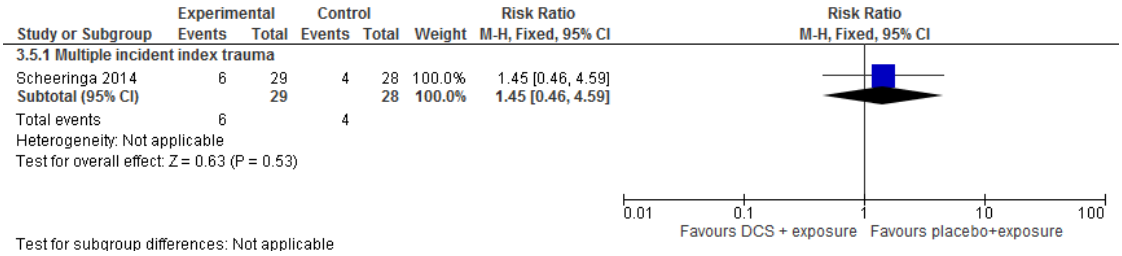


Figure 16: ***d-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people:*** **Discontinuation due to any reason (including adverse events)**



Appendix F – GRADE tables

GRADE tables for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

GRADE tables for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Pharmacological prevention of PTSD in children and young people

Propranolol versus placebo for the early prevention (<1 month) of PTSD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute		
Diagnosis of PTSD at 1-month follow-up (follow-up mean 1 months; assessed with: CAPS-CA)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/14 (35.7%)	4/15 (26.7 %)	RR 1.34 (0.45 to 4)	91 more per 1000 (from 147 fewer to 800 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 2 weeks; assessed with: Number of participants lost to follow-up for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/14 (0%)	0/15 (0%)	not pooled	not pooled	MODERATE	CRITICAL

CAPS-CA=Clinician-Administered PTSD Scale-Child/Adolescent version; CI=confidence interval; PTSD=post-traumatic stress disorder; RR=risk ratio

[1] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

[2] OIS not met (events<300)

Pharmacological treatment of PTSD in children and young people

Sertraline versus placebo for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Placebo	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology clinician-rated (follow-up mean 10 weeks; measured with: UCLA PTSD-I change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	67	61	-	SMD 0.19 higher (0.15 lower to 0.54 higher)	LOW	CRITICAL
Remission (follow-up mean 10 weeks; assessed with: Number of people no longer meeting diagnostic criteria for PTSD)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	26/67 (38.8 %)	28/61 (45.9%)	RR 0.85 (0.56 to 1.27)	69 fewer per 1000 (from 202 fewer to 124 more)	VERY LOW	CRITICAL
Response (follow-up mean 10 weeks; assessed with: Number of people rated 'much' or 'very much' improved on CGI-I)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	34/67 (50.7 %)	35/61 (57.4%)	RR 0.88 (0.64 to 1.22)	69 fewer per 1000 (from 207 fewer to 126 more)	LOW	CRITICAL
Depression symptoms (follow-up mean 10 weeks; measured with: CDRS-R change score; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	67	61	-	SMD 0.18 higher (0.16 lower to 0.53 higher)	LOW	IMPORTANT
Quality of life (follow-up mean 10 weeks; measured with: PQ-LES-Q change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	67	61	-	SMD 0.31 lower (0.66 lower to 0.04 higher)	LOW	IMPORTANT
Discontinuation due to any reason (follow-up mean 10 weeks; assessed with: Number of participants lost to follow-up for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/67 (29.9 %)	11/62 (17.7%)	RR 1.68 (0.88 to 3.22)	121 more per 1000 (from 21 fewer to 394 more)	MODERATE	CRITICAL
Discontinuation due to adverse events (follow-up mean 10 weeks; assessed with: Number of participants who dropped out due to adverse events)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/67 (7.5%)	2/62 (3.2%)	RR 2.31 (0.47 to 11.49)	42 more per 1000 (from 17 fewer to 338 more)	LOW	CRITICAL

CI=confidence interval; CDRS-R=Children's Depression Rating Scale-Revised; CGI-I=Clinical Global Impression Scale-Improvement; PQ-LEB-Q=; Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire; PTSD=post-traumatic stress disorder; RR=risk ratio; SMD=standard mean difference; UCLA PTSD-I=UCLA PTSD-Index
[1] 95% CI crosses both line of no effect and threshold for clinically important harm
[2] Funding from pharmaceutical company
[3] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Sertraline (+ cognitive processing therapy) versus placebo (+ cognitive processing therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline (+ cognitive processing therapy)	Placebo (+ cognitive processing therapy)	Relative (95% CI)	Absolute		
Global functioning (follow-up mean 12 weeks; measured with: CGAS change score; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11	11	-	SMD 1.2 higher (0.27 to 2.12 higher)	MODERATE	IMPORTANT
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants lost to follow-up for any reason, including adverse events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/12 (8.3%)	1/12 (8.3%)	RR 1 (0.07 to 14.21)	0 fewer per 1000 (from 77 fewer to 1000 more)	LOW	CRITICAL

CGAS=Clinical Global Assessment Scale; CI=confidence interval; PTSD=post-traumatic stress disorder; RR=risk ratio; SMD=standard mean difference
[1] OIS not met (N<400)
[2] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

D-cycloserine (+ exposure therapy) versus placebo (+ exposure therapy) for the delayed treatment (>3 months) of clinically important PTSD symptoms/PTSD in children and young people

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-cycloserine (+ exposure therapy)	Placebo (+ exposure therapy)	Relative (95% CI)	Absolute	Quality	Importance
PTSD symptomatology self/parent-rated at endpoint (follow-up mean 12 weeks; measured with: CPSS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	SMD 0.07 higher (0.45 lower to 0.59 higher)	LOW	CRITICAL
PTSD symptomatology self/parent-rated at 3-month follow-up (follow-up mean 3 months; measured with: CPSS change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	29	28	-	SMD 0.09 lower (0.61 lower to 0.43 higher)	LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of people showing ≥50% improvement on CPSS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/29 (41.4%)	18/28 (64.3%)	RR 0.64 (0.39 to 1.08)	231 fewer per 1000 (from 392 fewer to 51 more)	LOW	CRITICAL
Depression symptoms at endpoint (follow-up mean 12 weeks; measured with: CDI change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	SMD 0.09 higher (0.43 lower to 0.61 higher)	LOW	IMPORTANT
Depression symptoms at 3-month follow-up (follow-up mean 3 months; measured with: CDI change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	29	28	-	SMD 0.17 lower (0.69 lower to 0.35 higher)	LOW	IMPORTANT
Anxiety symptoms at endpoint (follow-up mean 12 weeks; measured with: SCARED change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	SMD 0.31 higher (0.21 lower to 0.83 higher)	LOW	IMPORTANT
Anxiety symptoms at 3-month follow-up (follow-up mean 3 months; measured with: SCARED change score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	SMD 0.05 higher (0.47 lower to 0.57 higher)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-cycloserine (+ exposure therapy)	Placebo (+ exposure therapy)	Relative (95% CI)	Absolute	Quality	Importance
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants lost to follow-up for any reason, including adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/29 (20.7%)	4/28 (14.3%)	RR 1.45 (0.46 to 4.59)	64 more per 1000 (from 77 fewer to 513 more)	VERY LOW	CRITICAL

CDI=Children's Depression Inventory; CI=confidence interval; CPSS=Child PTSD Symptom Scale; PTSD=post-traumatic stress disorder; RR=risk ratio; SCARED=Screen for Child Anxiety Related Disorders; SMD=standard mean difference

[1] Risk of bias associated with randomisation method suggested by statistically significant difference at baseline

[2] 95% CI crosses both line of no effect and threshold for clinically important harm

[3] 95% CI crosses both line of no effect and threshold for clinically important benefit

[4] 95% CI crosses line of no effect and thresholds for both clinically important benefit and harm

Appendix G – Economic evidence study selection

Economic evidence study selection for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Economic evidence study selection for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

A global health economics search was undertaken for all areas covered in the guideline. The flow diagram of economic article selection across all reviews is provided in Appendix A of Supplement 1 – Methods Chapter'.

Appendix H – Economic evidence tables

Economic evidence tables for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Economic evidence tables for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

No economic evidence on pharmacological interventions for the prevention or treatment of PTSD in children and young people was identified.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Health economic evidence profiles for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

No economic evidence on pharmacological interventions for the prevention or treatment of PTSD in children and young people was identified and no primary economic modelling was undertaken in this area.

Appendix J – Health economic analysis

Health economic analysis for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Health economic analysis for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

No economic analysis of pharmacological interventions for the prevention or treatment of PTSD in children and young people was undertaken.

Appendix K – Excluded studies

Clinical studies

Excluded studies for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Pharmacological prevention of PTSD in children and young people

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Robert 2008	Handsearch	Outcome measures are not validated	Robert, R., Blakeney, P., Villareal, C. (2008) Treating thermally injured children suffering symptoms of acute stress with imipramine and fluoxetine: a randomized, double blind study, Burns, 34, 919-928	
Sharp 2010	RQ 3.1-3.2 (maximizing sensitivity)	Outcome measures are not validated	Sharp S, Thomas C, Rosenberg L, Rosenberg M, Meyer III W. Propranolol does not reduce risk for acute stress disorder in pediatric burn trauma. Journal of Trauma and Acute Care Surgery. 2010 Jan 1;68(1):193-7.	
Stoddard 2011	Handsearch	Sample size (N<10/arm)	Stoddard F Jr, Luthra R, Sorrentino E, Saxe G, Drake J, Chang Y, Levine J, Chedekel D, Sheridan R. (2011) A randomized controlled trial of sertraline to prevent posttraumatic stress disorder in burned children, Journal of Child	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			and Adolescent Psychopharmacology, 21, 469-77	

Excluded studies for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

Pharmacological treatment of PTSD in children and young people

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Akinsanya 2017	RQ 3.1-3.2,4.1-4.2 update	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Akinsanya A, Marwaha R, Tampi RR. Prazosin in Children and Adolescents With Posttraumatic Stress Disorder Who Have Nightmares: A Systematic Review. Journal of clinical psychopharmacology. 2017 Feb 1;37(1):84-8.	
Birmaher 1998	RQ 3.1-3.2 (maximizing sensitivity)	Paper unavailable	Birmaher, B., Yelovich, A. & Renaud, J. (1998) Pharmacologic treatment for children and adolescents with anxiety disorders, Pediatric Clinics of North America, 45, 1187-1204	
Brown 2005	RQ 3.1-3.2 (maximizing sensitivity)	Non-systematic review	Brown, E. (2005) Clinical characteristics and efficacious treatment of posttraumatic stress disorder in children and adolescents, Pediatric Annals, 34, 138-146	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
Cohen 2003	RQ 3.1-3.2 (maximizing sensitivity)	Non-systematic review	Cohen, J., Berliner, L. & Mannarino, A. (1998) Psychosocial and pharmacological interventions for child crime victims, Journal of Traumatic Stress, 16, 175-186	
Famularo 1988	Handsearch	Non-randomised group assignment	Famularo, R., Kinscherff, R., Fenton, T. (1988) Propanalol treatment for childhood posttraumatic stress disorder, acute type, American Journal of Diseases in Childhood, 142, 1244-1247	Stamatakos, M. & Campo, J. (2010) Psychopharmacologic treatment of traumatized youth, Current Opinion in Pediatrics, 22, 599-605
Harmon 1996	RQ 3.1-3.2 (maximizing sensitivity)	Non-randomised group assignment	Harmon, R. & Riggs, P. (1996) Clonidine for posttraumatic stress disorder in preschool children, Journal of the American Academy of Child and Adolescent Psychiatry, 35, 1247-1249	
Huemer 2010	RQ 1.1-1.2 & 2.1-2.2 (searches combined)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Huemer, J., Erhart, F., Steiner, H. (2010) Posttraumatic stress disorder in children and adolescents: a review of psychopharmacological treatment, Child psychiatry and human development, 41, 624-640	
Kinzie 1994	RQ 3.1-3.2 (maximizing sensitivity)	Non-randomised group assignment	Kinzie, J., Sack, R. & Riley, C. (1994) The polysomnographic effects of clonidine on sleep disorders in posttraumatic stress	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			disorder: A pilot study with Cambodian patients, Journal of Nervous and Mental Disease, 182, 585-587	
Locher 2017	RQ 3.1-3.2,4.1-4.2 update	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I, Kessler RC, Kossowsky J. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. JAMA psychiatry. 2017 Oct 1;74(10):1011-20.	
Lustig 2002	RQ 3.1-3.2 (maximizing sensitivity)	Efficacy or safety data cannot be extracted	Lustig, S., Botelho, C., Lynch, L., Nelson, S., Eichelberger, W., Vaughan, B. (2002) Implementing a randomized clinical trial on a pediatric psychiatric inpatient unit at a children's hospital: the case of clonidine for post-traumatic stress, General Hospital Psychiatry, 24, 422-429	
Najjar 2008	RQ 3.1-3.2 (maximizing sensitivity)	Non-systematic review	Najjar, F., Weller, R., Weisbrot, J. & Weller, E. (2008) Post-traumatic stress disorder and its treatment in children and	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			adolescents, Current Psychiatry Reports, 10, 104-108	
NCT01157429	Handsearch	Unpublished (registered on clinical trials.gov and author contacted for full trial report but not provided)	NCT01157429. D-cycloserine Adjunctive Treatment for Posttraumatic Stress Disorder (PTSD) in Adolescents. Available from: https://clinicaltrials.gov/show/NCT01157429 [accessed 05.01.17]	
Peters 2012	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Peters, T. & Connolly, S. (2012) Psychopharmacologic Treatment for Pediatric Anxiety Disorders, Child and Adolescent Psychiatric Clinics of North America, 21, 789-806	
Reinblatt 2005	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Reinblatt, S. & Walkup, J. (2007) Psychopharmacologic treatment of pediatric anxiety disorders, Child and Adolescent Psychiatric Clinics of North America, 14, 877-908	
Reinblatt 2007	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Reinblatt, S. & Riddle, M. (2007) The pharmacological management of childhood anxiety disorders: A review, Psychopharmacology, 191, 67-86	
Robb 2008	Handsearch	Conference abstract	Robb, A., Cueva, J., Sporn, J. (2008) Efficacy of sertraline in childhoodPTSD. Presented at the 55th annual meeting of the American Academy of Child and	Strawn, J., Keeshin, B., Del Bello, M., Geracioti Jr, T. & Putnam, F. (2010) Psychopharmacologic treatment of posttraumatic

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			Adolescent Psychiatry; October 28-November 2, 2008; Chicago, Illinois	stress disorder in children and adolescents: A review, Journal of Clinical Psychiatry, 71, 932-941
Robert 1999	2004 GL (excluded)	Outcome measures are not validated	Robert, R., Blakeney, P. E., Villarreal, C., Rosenberg, L., & Meyer, W. J., III (1999). Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study.[comment]. Journal of the American Academy of Child & Adolescent Psychiatry, 38, 873-882.	
Rynn 2011	RQ 3.1-3.2 (maximizing sensitivity)	Non-systematic review	Rynn, M., Puliafico, A., Heleniak, C., Rikhi, P., Ghalib, K. & Vidair, H. (2011) Advances in pharmacotherapy for pediatric anxiety disorders, Depression and Anxiety, 28, 76-87	
Seedat 2001	2004 GL (excluded)	Non-randomised group assignment	Seedat, S.; Lockhat, R.; Kaminer, D.; Zungu-Dirwayi, N. & Stein, D.J. (2001) An open trial of citalopram in adolescents with post-traumatic stress disorder. International Clinical Psychopharmacology. 16, 21-25	
Stamatkos 2010	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Stamatakos, M. & Campo, J. (2010) Psychopharmacologic treatment of traumatized youth,	

Study ID	Search	Reason for exclusion	Ref 1	Ref 2
			Current Opinion in Pediatrics, 22, 599-604	
Strawn 2010	RQ 3.1-3.2 (maximizing sensitivity)	Systematic review with no new useable data and any meta-analysis results not appropriate to extract	Strawn, J., Keeshin, B., Del Bello, M., Geracioti Jr, T. & Putnam, F. (2010) Psychopharmacologic treatment of posttraumatic stress disorder in children and adolescents: A review, Journal of Clinical Psychiatry, 71, 932-941	

Economic studies

No economic studies of pharmacological interventions for the prevention or treatment of PTSD in children and young people were reviewed at full text and excluded.

Appendix L – Research recommendations

Research recommendations for "For children and young people at risk of PTSD, what are the relative benefits and harms of specific pharmacological interventions?"

Research recommendations for "For children and young people with clinically important post-traumatic stress symptoms, what are the relative benefits and harms of specific pharmacological interventions?"

No research recommendations were made for these review questions.