PROBLEMS AND DISORDERS SPECIFICALLY RELATED TO STRESS (SPE-STRESS)

Interventions recommended by WHO

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WHO mhGAP Guidelines

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Contents

Glossary

Acute traumatic stress symptoms: Symptoms of intrusion, avoidance and hyperarousal in the first month after exposure to potentially traumatic events**.**

Cognitive behavioural therapy (CBT) with a trauma focus: Cognitive-behavioural interventions that involve a focus on the traumatic event. Cognitive behavioural therapy (CBT) is based on the idea that people with posttraumatic stress disorder (PTSD) and acute traumatic stress symptoms have maladaptive cognitions (thoughts and beliefs) related to a traumatic event and its sequelae. These appraisals provoke unhelpful avoidance and maintain a sense of current threat. Cognitive-behavioural interventions with a trauma focus tends to include imaginal or in vivo exposure treatment and direct challenging of maladaptive cognitions.

The term cognitive behavioural therapy (CBT) with a trauma focus is synonymous to the term Trauma-Focused CBT (TF-CBT) as used in the National Institute for Clinical Evidence (NCCMH, 2005) Guidelines and in Cochrane Reviews (e.g. Bisson & Andrew 2005). It is noted that in the traumatic stress literature the latter term also has a more narrow definition for a very specific and widely disseminated multi-component CBT protocol for children and adolescents developed by Cohen and colleagues (2000).

Early psychological interventions: Psychological intervention delivered in the first month after exposure to a potentially traumatic event.

Eye movement desensitization and reprocessing (EMDR): This therapy is based on the idea that negative thoughts, feelings and behaviours are the result of unprocessed memories. The treatment entails standardized procedures that include focusing simultaneously on (a) spontaneous associations of traumatic images, thoughts, emotions and bodily sensations and (b) bilateral stimulation most commonly in the form of repetitive eye movements.

Like CBT with a trauma focus, EMDR therapy aims to reduce subjective distress and strengthen adaptive cognitions related to the traumatic event. Unlike CBT with a trauma focus, EMDR therapy involves treatment that is conducted without detailed descriptions of the event, without direct challenging of beliefs, and without extended exposure.

Problems and disorders specifically related to stress (SPE-STRESS): These problems include posttraumatic stress disorder, acute stress reaction, and bereavement reactions.

There are numerous other stress-related disorders and problems (e.g. depression, behavioural disorders, alcohol/substance use problems, self-harm/suicide, medically unexplained somatic complaints) but these are not specifically *related to stress (i.e., they also occur in the absence of identifiable stressful life events), and these have been covered previously in WHO mhGAP Guidelines.*

It is anticipated that acute stress reaction will no longer be classified as a mental disorder in ICD-11 and, accordingly, the current guidelines make recommendations for symptoms of acute (traumatic) stress rather than for acute stress reaction.

Psycho-education: The provision of information about the nature of a mental disorder and its symptoms, and what to do about them (Wessely et al, 2008).

Psychological first aid (PFA): Humane, supportive response to a fellow human being who is suffering and who may need support. It entails basic, non-intrusive pragmatic care with a focus on listening but not forcing talk, assessing needs and concerns, ensuring that basic needs are met, encouraging social support from significant others and protecting from further harm (WHO, 2010).

Psychological debriefing: The promotion of ventilation by encouraging the person to briefly but systematically recount perceptions, thoughts and emotional reactions experienced during a recent, stressful event (WHO, 2010).

Stress management: Psychological treatments that use cognitive or behavioral techniques (e.g. relaxation, stress inoculation training) that do not focus on the traumatic event (Bisson & Andrew, 2007).

Structured psychological interventions: Psychological interventions that go beyond general application of psychological principles of care that are part of health and social care. Examples of such principles of care are good communication and mobilizing and providing social support (cf. the mhGAP Intervention Guide, p.6, WHO, 2010).

Symptoms of acute stress: Psychological symptoms in the first month after exposure to potentially traumatic events.

Examples of such symptoms include:

- *Acute traumatic stress symptoms (defined above)*
- *Dissociative symptoms, including somatoform conversion*
- *Enuresis (bedwetting)*
- *Hyperventilation*
- *Insomnia*

Universally applied bereavement interventions: Interventions that are offered to all people who have experienced bereavement, regardless of whether bereaved people are experiencing symptoms of mental disorder

Executive Summary

Why these guidelines were developed

There are currently no suitable, evidence-based guidelines for managing problems and disorders related to stress in primary health care and other non-specialised health care settings. Agencies working in post-conflict and natural disaster settings are increasingly interested in mental health care. This requires the development and testing of a module on the management of problems and disorders specifically related to stress (SPE-STRESS).

Objectives and scope of the document

This document was developed to provide recommended management strategies for problems and disorders that are specifically related to the occurrence of a major stressful event. The recommended strategies will form the basis of a new module to be added to the WHO (2010) mhGAP Intervention Guide for use in non-specialized healthcare settings.

The scope of the problems covered by these guidelines is:

- symptoms of acute stress in the first month after a potentially traumatic event, with the following subtypes:
    - symptoms of acute traumatic stress (intrusion, avoidance and hyperarousal) in the first month after a potentially traumatic event;
    - symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event;
    - nonorganic (secondary) enuresis in the first month after a potentially traumatic event (in children);
    - hyperventilation in the first month after a potentially traumatic event;
    - insomnia in the first month after a potentially traumatic event;
- post-traumatic stress disorder (PTSD);
- bereavement in the absence of a mental disorder.

Who should use this guideline

The primary audience is non-specialized healthcare providers working at first and second level health care facilities. They include general physicians, family physicians, nurses and clinical officers. They also include those specialist medical doctors who work in areas other than mental health and substance abuse, such as pediatricians, emergency medicine physicians, obstetricians, gynaecologists and internists. A secondary audience is those tasked with the organization of healthcare at the district or sub-district level, including programme managers responsible for primary or non-mental health secondary care services.

How these guidelines were developed

Guideline groups: A WHO steering group comprising members from relevant WHO departments (see annex 1) was set up in May 2011. This group established the provisional scope and selected members of the Guideline Development Group (GDG) to reflect all regions and appropriate expertise and achieve a gender balance (see annex 2). A larger group of external reviewers (see annex 3) commented on the evidence profiles, draft recommendations and final documents. Their comments were considered by GDG.

Evidence search and retrieval: The WHO Secretariat initially proposed scoping questions that were modified and agreed upon during three rounds of electronic consultation with the Guideline Development Group (GDG). Further consultations with the GDG involved review of scoping questions phrased using the PICO (Population, Intervention, Comparator, Outcomes) format. Outcomes of interest were listed and the GDG voted to rank them according to importance.

By the end of July 2011 a set of scoping questions had been finalized. These were then used to guide searches for relevant systematic reviews that had been performed within the last two years and met inclusion criteria (see evidence profiles 1-21 in annex 5 for specific inclusion and exclusion criteria criteria). Where relevant systematic reviews (a) did not exist, (b) were not recent (had not been done within the last 2 years), or (c) were not of suitable quality or applicability, new systematic reviews were commissioned. For the new commissioned systematic review on medicines for PTSD, specific additional searches were carried out to identify studies in Japanese, Chinese, French, Portuguese, Russian, and Spanish.

Evidence to recommendations: *The WHO Handbook for Guideline Development* was followed and the GRADE system for assessing quality of evidence and using evidence to inform decisions was applied to inform drafting of recommendations. For each question, an evidence profile was developed summarizing the evidence retrieved, including discussion of values, preferences, benefits, harms and feasibility. Wherever possible, the evidence retrieved was graded and GRADE tables provided. A decision table was used by the GDG during a recommendation drafting meeting in Amman, Jordan (July 2012) to agree on the quality of evidence and certainty about harms and benefits, values and preferences, feasibility and resource implications (see annex for details of each decision). The strength of the recommendation was set as either:

> 'Strong': meaning that the GDG agreed that the quality of the evidence combined with certainty about the values, preferences, benefits and feasibility of this recommendation meant it should be done in all or almost all circumstances;
>
> or
>
> 'Standard': meaning there was less certainty about the combined quality of evidence and values, preferences, benefits and feasibility of this recommendation, thus there may be circumstances in which it will not apply. The word 'standard' (rather than 'weak' or 'conditional') was chosen to be in line with earlier WHO mhGAP guidelines and to avoid the negative connotations of the word 'weak', which could have risked biasing GDG members towards strong recommendations.

Recommendations

The guidelines have separate recommendations for children, adolescents and adults. For the purpose of these guidelines, adolescents are 12 to 17 years old while children are younger than 12 years old.

All recommendations come with remarks (see main body of this report). For example, the remarks note that even in instances where there is no recommendation for treatment, all individuals presenting with a potential mental health problem should be fully assessed to exclude physical causes of the problem. Similarly, the remarks refer to previous WHO mhGAP Guidelines (2010) recommendations, such as the recommendation to make available psychological first aid to people who have been recently exposed to a potentially traumatic event. Also, the remarks emphasize applying mhGAP general principles of care, such as good communication and mobilizing social support**.**

Overall, these remarks help communicate that people who suffer mental health problems should not be ignored and that certain practical steps can be taken, even in cases when there are no (new) recommendations for the management of problems and disorders specifically related to stress.

Acute traumatic stress symptoms (re-experiencing, avoidance, hyperarousal) after a potentially traumatic recent event (Recommendations 1-4)

Recommendation 1

(i) Cognitive-behavioural therapy with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: standard
Quality of evidence: moderate

(ii) On the basis of available evidence, no specific recommendations can be made about stand-alone problem-solving counselling, eye movement desensitization and reprocessing (EMDR), relaxation, or psycho-education for adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Recommendation 2

On the basis of available evidence, no specific recommendation can be made on early psychological interventions (covering problem-solving counseling; relaxation; psycho-education; eye movement desensitization and reprocessing (EMDR), and cognitive behavioural therapy (CBT)) for children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: not applicable
Quality of evidence: very low

Recommendation 3

Benzodiazepines and antidepressants should not be offered to adults to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event

Strength of recommendation:
For benzodiazepines: strong
For anti-depressants: standard
Quality of evidence: very low

Recommendation 4

Benzodiazepines and antidepressants should not be offered to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in children and adolescents.

Strength of recommendation: strong
Quality of evidence: very low

Insomnia after a potentially traumatic recent event (recommendations 5-8)

Recommendation 5

Relaxation techniques (e.g., progressive muscle relaxation or cultural equivalents) and advice about sleep hygiene (including advice about psychostimulants, such as coffee, nicotine, and alcohol) should be considered for adults with acute (secondary) insomnia in the first month after exposure to a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: very low

Recommendation 6

On the basis of available evidence, no specific recommendation can be made for early psychological interventions in children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: low

Recommendation 7

Benzodiazepines should not be offered to adults with insomnia within the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: moderate

Recommendation 8

Benzodiazepines should not be offered to children and adolescents with acute (secondary) insomnia within the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

Enuresis after a potentially traumatic recent event

Recommendation 9

(i) Psychoeducation about the negative effects of punitive responses should be given to caregivers of children with secondary nonorganic enuresis in the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

(ii) Parenting skills training and the use of simple behavioural interventions (i.e. star charts, toileting before sleep and rewarding having nights without wetting the bed) should be considered. Where resources permit, alarms should be considered.

Strength of recommendation: standard
Quality of evidence: moderate for alarms, low or very low for other behavioural interventions

Dissociative (conversion) disorders after a potentially traumatic recent event (recommendations 10-11)

Recommendation 10

***On the basis of available evidence no specific recommendation can be made on psychological interventions* for adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.**

Strength of recommendation: not applicable
Quality of evidence: very low

Recommendation 11

On the basis of available evidence, no specific recommendation can be made for children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Hyperventilation after a potentially traumatic, recent event (recommendations 12-13)

Recommendation 12

No specific recommendation can be made on the basis of available evidence on rebreathing into a paper bag for adolescents and adults with hyperventilation in the first month after exposure to a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Recommendation 13

Rebreathing into a paper bag should not be considered for children with hyperventilation in the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: very low

Posttraumatic Stress Disorder (recommendations 14-17)

Recommendation 14

Individual or group cognitive behavioural therapy (CBT) with a trauma focus, eye movement desensitization and reprocessing (EMDR), or stress management should be considered for adults with posttraumatic stress disorder (PTSD).

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, EMDR; low for group CBT, stress management

Recommendation 15

Individual or group cognitive behavioural therapy (CBT) with a trauma focus or eye movement desensitization and reprocessing (EMDR) should be considered for children and adolescents with posttraumatic stress disorder (PTSD).

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, low for EMDR, very low for group CBT

Recommendation 16

Selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) should not be offered as the first line of treatment for posttraumatic stress disorder (PTSD) in adults. SSRIs and TCAs should be considered if (a) stress management, cognitive-behavioural therapy (CBT) with a trauma focus and/or eye movement desensitization and reprocessing (EMDR) have failed or are not available or (b) if there is concurrent moderate-severe depression.

Strength of recommendation: standard
Quality of evidence: low

Recommendation 17

Anti-depressants should not be used to manage posttraumatic stress disorder (PTSD) in children and adolescents

Strength of recommendation: strong
Quality of evidence: very low

Bereavement in the absence of mental disorder (recommendations 18-21)

Recommendation 18

Structured psychological interventions should not be offered universally (to all) bereaved adults who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: moderate

Recommendation 19

Structured psychological interventions should not be offered universally (to all) bereaved children and adolescents who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Recommendation 20

Benzodiazepines should not be offered to bereaved adults who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Recommendation 21

Benzodiazepines should not be offered to bereaved children and adolescents who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Introduction

Traumatic events are common in people's lives. In a WHO study of 21 countries, more than 10% of respondents reported witnessing violence (21.8%) or experiencing interpersonal violence (18.8%), accidents (17.7%), exposure to war (16.2%), or trauma to a loved one (12.5%) (Stein et al, 2009). Stress-related problems and disorders are also common. A meta-analysis of post-conflict studies using representative samples and full diagnostic assessment found that 15.4% of people reported post-traumatic stress disorder (PTSD) and 17.3% reported depression (Steel et al, 2009).

The WHO (2010) mhGAP Intervention Guide (v. 1.0, http://www.who.int/mental_health/evidence/mhGAP_intervention_guide/en/index.html) provides clinical protocols for non-specialized health care for a range of mental, neurological and substance use disorders but does not currently provide clinical protocols for problems and disorders specifically related to stress (SPE-STRESS). The latter set of disorders and problems include post-traumatic stress disorder, acute stress reaction/acute symptoms of stress, and bereavement reactions.

In May 2011, WHO and the United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) signed an agreement to implement the WHO (2010) mhGAP Intervention Guide in UNRWA health services in Gaza, West Bank, Lebanon, Syria, and Jordan. Agencies working in post-conflict and natural disaster settings are increasingly interested in mental health care. This requires the development and testing of a new mhGAP module on the management of problems and disorders specifically related to stress (SPE-STRESS)

The term problems and disorders specifically related to stress (SPE-STRESS) refers here to problems such as PTSD, acute stress reaction, and bereavement reactions that require an exposure to a defined stressor as a precursor. There are numerous other stress-related disorders and problems (e.g. depression, behavioural disorders, alcohol/substance use problems, self-harm/suicide, medically unexplained somatic complaints) but these are not specifically related to stress (i.e., they may also occur in the absence of identifiable stressful life events) and these have already been covered through the mhGAP 2010 Guidelines and the mhGAP Intervention Guide (WHO, 2010).

Existing Guidelines on stress related problems and disorders

There are currently no suitable, evidence-based guidelines for managing, in non-specialised settings, problems and disorders related to stress. Existing guidelines do not meet these conditions because they:

- have been developed for high income country health systems (e.g. National Institute for Clinical Excellence, 2005);
- are for use in specialized care (e.g. American Psychiatric Association, 2004);
- are not based on a systematic review of evidence (e.g. Patel, 2003);
- focus mainly on policy and systems issues (e.g. Interagency Standing Committee, 2007)
- focus on primary health care *training* only (Eisenmann et al, 2006)

Recent WHO guidelines for mental, neurological and substance use conditions are available online on the mhGAP Resource Centre (www.who.int/entity/mental_health/mhgap/evidence/en), which conveys evidence profiles on a range of conditions (Barbui et al, 2010; Dua et al, 2011). The guidelines form the back-bone of the WHO (2010) mhGAP Intervention Guide (1.0), which contains modules with assessment and management algorithms for different conditions.

Objectives

The present project addresses the development of guidelines for the management strategies for problems and disorders that are specific to the occurrence of a major stressful event, such as posttraumatic stress disorder. These guidelines will form the back-bone of a corresponding module that will be added to the mhGAP Intervention Guide for use in non-specialized healthcare settings.

WHO guidelines on the health sector response to violence against women are also currently under development and will include recommendations on mental health. To avoid overlap and contradictions between these two guidelines, a colleague of the WHO Department of Reproductive Health and Research joined the SPE-Stress steering group.

Who should use this guideline

The primary audience is non-specialized healthcare providers working at first and second level facilities. They include general physicians, family physicians, nurses and clinical officers. They also include those specialist medical doctors who work in areas other than mental health and substance abuse such as paediatricians, emergency medicine physicians, obstetricians, gynaecologists and internists. A secondary audience is those tasked with the organization of healthcare at the district or sub-district level, including programme managers responsible for primary or non-mental health secondary care services.

Individuals and partners involved in development of the guideline

WHO steering group

An internal steering group drawn from the WHO Departments of Mental Health and Substance Abuse (MSD), Reproductive Health and Research (RHR), and Violence and Injury Prevention and Disability (VIP), and the Eastern Mediterranean Regional Office (EMRO) was set up in May 2011 to support development of these guidelines. The full list of names and affiliations is in annex 1.

Guideline Development Group (GDG)

The GDG was made up of people with content expertise (non-specialized health care, child and adult mental health, bereavement and traumatic stress, cultural psychiatry, and humanitarian response), relevant experience in low and middle income countries, and expertise in evidence-based guideline methodology. GDG member selection included concern for gender balance (6 of 12 members were female). Members were drawn from all WHO regions and included people from international organizations (International Committee for the Red Cross, International Medical Corps) as well as universities.

Consultants with high-level expertise in evidence review and GRADE methodology supported the GDG. The full list of GDG members and consultants along with their expertise, affiliations and geographical base is provided in annex 2 and their declaration of interest are summarized in annex 4.

External review group

External reviewers were drawn from end-users/partners working in the subject area of the guidelines such as Disaster Action (a charity run by people directly affected by disasters), Global Initiative on Psychiatry, Médicos del Mundo (Doctors of the World, Spain), United Nations High Commissioner for Refugees (UNHCR), War Trauma Foundation, and World Vision International), universities and national institutions (e.g. National Institute of Mental health (NIMH) Japan, National Health Services (NHS) United Kingdom). In total 78 people (from all 6 WHO regions) were contacted to review evidence profiles with draft recommendations, and 22 people responded within the time allotted (2 weeks). Their names, affiliations, and geographical base are given in annex 3 and their declarations of interest are summarized in annex 4. Unfortunately, there was no peer reviewer from the Eastern Mediterranean Region (EMRO).[1]

External reviewer response was compiled and comments used to inform the GDG meeting discussion of the evidence profiles and draft recommendations.

In November 2012, selected external reviewers were also asked to review an early version of this final guideline document. Their compiled and processed responses should help ensure that the document is understandable. A limitation of the process was that peer reviewers were not asked to comment early in the process on scoping questions and outcomes.

Management of conflicts of interest

All nominated GDG members, external reviewers and consultants completed WHO declaration of interest forms. Several GDG members declared interests at the time of their nomination. These were then reviewed by the WHO Secretariat for potential conflicts of interest (see summary in annex 4). It was decided that none of the nominated GDG members had a conflict of interest that would preclude their participation.

At the beginning of the recommendation drafting meeting (Amman, July, 2012), the nature of all types of conflict of interest-financial, academic/intellectual, non-academic - were explained by WHO consultants with substantial experience in WHO guideline development. Each participant then described in detail the areas where they had potentially real or perceived conflicts of interest, including intellectual conflicts of interest. The session took about one hour. At this time, all participants were asked to review and, if necessary, update their declaration of interest forms.

Upon review of the declaration of interest forms, the WHO Secretariat and one GDG member (Dr Seedat) agreed that Dr Seedat may have a perceived conflict on decisions related to pharmacological treatment of posttraumatic stress disorder (PTSD), because she had received financial support to attend conferences

[1] The lack of a peer reviewer from EMRO was compensated by the presence of 4 Jordanian colleagues (from Ministry of Health, International Medical Corps, and the Jordanian Nursing Council) who participated as special invitees in the Guidelines meeting in Amman. The 4 colleagues were 2 family physicians, a psychologist and a nurse. All 4 completed the declaration of interest form, and none expressed a conflict of interest.

(total limited to $5000 over nine years) from pharmaceutical companies. She recused herself from decision-making and drafting of recommendations involving pharmacological management of PTSD. Dr Cohen, a GDG member who according to her form may have a perceived conflict of interest related to psychological treatment of PTSD did not attend the meeting.

How the guidelines were developed

The Guidelines were developed according to the *WHO Handbook for Guideline Development*. For a detailed discussion on the merits and challenges of applying the WHO process of guideline development to the domain of mental, neurological and substance use disorders, please see Barbui et al (2010).

The scope

The WHO Secretariat initially proposed scoping questions. These questions included interventions for PTSD, bereavement, and a range of symptoms that can occur in the first month after a potentially traumatic event. The questions did not focus on the *acute stress reaction* concept, as it anticipated that it will no longer be classified as a mental disorder in ICD-11. Similarly, the questions did not focus on the *acute stress disorder* concept (which is not in the ICD), as this concept has poor predictive validity and its utility may depend on the need to have a diagnosis for making health insurance payment (Bryant et al 2011). After three rounds of electronic consultation with the Guideline Development Group (GDG), it was agreed that the guidelines should cover the management of the following problems in adults and children:

- symptoms of acute stress in the first month after a potentially traumatic event, with the following subtypes:
    - symptoms of acute traumatic stress (intrusion, avoidance and hyperarousal) in the first month after a potentially traumatic event;
    - symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event;
    - nonorganic (secondary) enuresis in the first month after a potentially traumatic event (in children);
    - hyperventilation in the first month after a potentially traumatic event;
    - insomnia in the first month after a potentially traumatic event;
- post-traumatic stress disorder (PTSD);
- bereavement in the absence of mental disorder

Further consultations with the GDG involved review of scoping questions phrased using the PICO (Population, Intervention, Comparator, Outcomes) format. Outcomes were listed, and the GDG voted to rank them according to importance using 3 levels (critical, important, not important). Individual scores were converted into a 9 point scale (critical = 8; important = 5; not important = 2), which were then

averaged, and rounded off to obtain average levels of importance on a 9 point scale consistent with GRADE methodology.[2]

The process of drafting, reviewing and revising PICO questions occurred during June- July 2011, while the priority ranking of outcomes occurred in November 2011. One hundred percent of GDG members rated the outcomes.

Evidence search and retrieval

By the end of July 2011 a set of scoping questions had been finalized. These were then used to guide searches for relevant systematic reviews that had been performed within the last two years and met inclusion criteria (see evidence profiles 1-21 in annex 5 for specific inclusion and exclusion criteria).

While only systematic reviews less than two years old at the time of the search were included, there were no age limitations on individual studies within those reviews. Although the same interventions were considered for adults and children, separate reviews were done. Evidence from the adult literature was not generalized to children.

Where relevant systematic reviews did not exist, were not recent (had not been done within the last 2 years) or were not of suitable quality or applicability, new systematic reviews were commissioned. Databases searched include Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. For the commissioned systematic review on medicines for PTSD, specific additional searches were carried out to identify international studies in Japanese, Chinese, French, Portuguese, Russian, and Spanish. (See evidence profiles in annex 5 for more detail on search terms, databases searched.)

Evidence to recommendations

While keeping in mind the strengths (transparency) and limitations of GRADE (low inter-rater reliability), the *WHO Handbook for Guideline Development* was followed. The GRADE system, created to enable explicit assessment of the quality of evidence and use of evidence for developing recommendations, was used. When assessing the evidence base, methodologists (consultants supporting the GDG) summarized the evidence extracted from systematic reviews and meta-analyses into ‘‘Summary of Findings tables’’ and graded the quality of evidence summarized in the tables (see annex 5).

In the GRADE system, the ‘quality of the evidence ‘is defined as the level of confidence that the estimate of the effect of an intervention is correct. The quality of evidence is rated as high, moderate, low, or very low quality, as detailed in the table below.

[2] The spreadsheet files to collect and analyze that data are available upon request and we believe these may be a slight improvement on the traditional GRADE way of asking people to rate the importance of scoping questions. A possible problem with the traditional way of rating is that many respondents who consider a question as important may have difficulties assigning it a 4, 5 or 6 rating if they have been conditioned (though their school grading system) that the values of 4, 5, or 6 are low and thus do not correspond to an “important” rating. The GRADE way of asking participants to rate outcomes on a 9 point scale may create a bias towards rating outcomes higher than intended. This problem may be overcome by asking people to rate using 3 levels (critical, important, not important) only and then convert these to a 9 point scale.

Quality level	Definition
High	High confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the true effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

During grading, evidence from randomized controlled trials begins as high quality, while that from observational study designs (e.g. non-randomized or quasi randomized intervention studies, cohort studies, case control studies and other correlational study designs) begins as low quality. The quality of the evidence is then further assessed. Five criteria can be used to downgrade the evidence. These are:

- **Risk of bias**: Limitations in the study design that may bias the overall estimates of the treatment effect.
- **Inconsistency**: Unexplained differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies.
- **Indirectness**: The question being addressed by the guideline panel is different from the available evidence regarding the population, intervention, comparator, or outcome.
- **Imprecision**: Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.
- **Publication bias**: Systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication (or reporting) of studies.

Three other criteria may be used to upgrade the quality of evidence rating: a strong association, a dose-response gradient, and plausible confounding.

During the guideline development meeting in Amman, Jordan, the GDG were provided with evidence profiles summarizing the evidence retrieved, including evidence on values, preferences, benefits, harms and feasibility for 21 questions on specific interventions. . Wherever possible, the evidence retrieved was graded and GRADE tables provided. A decision table was used by the GDG during their meeting in Amman to agree on the quality of evidence and certainty about harms and benefits, values and preferences, feasibility and resource implications (see annex 5 for details of each question, evidence search, inclusion and exclusion criteria, decision tables). In several instances the group decided that the lack of randomized evidence on the effect of proposed interventions, coupled with uncertainty about harms and benefits, values and preferences, feasibility and resource implications meant that no recommendation could be made at this time. This has been indicated in the list of recommendations.

The **strength of the recommendation** was set as either:

'Strong': meaning that the GDG members agreed that the quality of the evidence combined with certainty about the values, preferences, benefits and feasibility of this recommendation meant it should be done in all or almost all circumstances;

Or

'Standard': meaning there was less certainty about the combined quality of evidence and values, preferences, benefits and feasibility of this recommendation. Hence there may be circumstances in which it will not apply. The word 'standard' (rather than 'weak' or 'conditional') was chosen to be in line with earlier WHO mhGAP guidelines and also to avoid the negative connotations of the word 'weak', which could have risked biasing GDG members towards strong recommendations.

On the basis of summary text in the evidence profiles on quality of evidence, benefits versus harms, values and preferences (from an end user perspective), and resource consumption (from health services perspective), the following **decision table** was completed by the GDG to come to a decision on a strong versus a standard recommendation.

Factor	**Decision**
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes No
Are the expected values and preferences clearly in favour of the recommendation?	Yes No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes No

On a number of occasions, the GDG decided to give a strong recommendation despite a GRADE assessment of the available evidence on effect as being of 'very low quality' . This only occurred when the following conditions applied: (a) there was certainty about the balance of benefits versus harms and burdens, (b) the expected values and preferences were clearly in favour of the recommendation, and (c) there was certainty about the balance between benefits and resources being consumed.

Occasionally it was not necessary to complete the table entirely when a partially filled table already indicated that the recommendation would have to be standard (e.g., if GDG members agreed that the

answer was No to 2 questions, there was no need to ask the other 2 questions to decide on the strength of the recommendation as it would have to be standard). This saved sparsely-available time during the meeting, given that discussions on each of the decision tables' questions were often lengthy.

Group Process

During the GDG meeting in Amman, decisions were usually made by consensus but where there was disagreement a vote was taken and a two thirds majority required for a decision to be carried. After any vote, GDG members who were in the minority were asked if they would want to reconsider their position. In all cases, this led to at least two thirds majority.

Recommendations

The guidelines have separate recommendations for children, adolescents and adults. For the purpose of these guidelines, adolescents are 12 to 17 years old while children are younger than 12 years old.

It was noted by the Guideline Development Group that certain remarks apply to implementing all recommendations described below. These are:

Assessment: Even in instances where there is no recommendation for treatment, all individuals presenting with a potential mental health problem should be fully assessed to exclude physical causes of the problem

Children: Children's disorders and problems can involve complex interactions between child and parents/other carers of children. It is therefore essential that carers be assessed and educated to manage the child's problem in a positive way.

Context: Much of the evidence on which these recommendations are based comes from high income settings where different sociocultural forces apply. Understanding of context should be recognized as a source to identify people's specific sociocultural coping strategies and resources that can be relevant when implementing the recommendations.

Specific recommendations

The following text will provide the scoping questions used, the recommendation agreed after examination of the evidence, including evidence on harms, benefits, values, preferences, cost effectiveness and feasibility, and qualifying remarks. For full details of the evidence used and the decision-making process please consult the evidence profile for each numbered recommendation provided in annex 5.

Acute traumatic stress symptoms after a potentially traumatic recent event (recommendations 1-4)

Acute traumatic stress symptoms refer to symptoms of intrusion, avoidance and hyperarousal - associated with significant impairment in daily functioning - in the first month after a potentially traumatic event. Other symptoms of acute stress, including hyperventilation, conversion and dissociative symptoms, and secondary nonorganic nocturnal enuresis in children, are dealt with in other recommendations in these guidelines.

Psychological interventions and pharmacological treatments, especially benzodiazepines, have been used to manage people suffering symptoms of acute distress. There is currently no consensus on the effectiveness of such management. The GDG examined the evidence on use of early psychological and pharmacological interventions in adults and in children and adolescents with symptoms of acute traumatic stress syndrome and made the following recommendations.

1. Early psychological interventions in adults with acute traumatic stress symptoms in the first month after a potentially traumatic event

***Scoping Question 1*: For adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment, result in a reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 1

(i) Cognitive-behavioural therapy with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: standard
Quality of evidence: moderate

(ii) On the basis of available evidence, no specific recommendations can be made about stand-alone problem-solving counselling, eye movement desensitization and reprocessing (EMDR), relaxation, or psycho-education for adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

CBT with a trauma focus should only be offered in those contexts where individuals are competent (trained and supervised) to provide the therapy.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. When combined, these recommendations imply that psychological first aid should be considered in all adults with acute traumatic stress symptoms; and, where competent staff are available, CBT with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event. *In situations without sufficient resources to provide CBT with a trauma focus, other interventions such as stress management may be considered in addition to psychological first aid.*

2. Early psychological interventions in children and adolescents with acute traumatic stress symptoms in the first month after a potentially traumatic event

***Scoping question 2*: For children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment, result in a reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 2

On the basis of available evidence, no specific recommendation can be made on early psychological interventions (covering problem-solving counseling; relaxation; psycho-education; eye movement desensitization and reprocessing (EMDR), and cognitive behavioural therapy (CBT) for children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

3. Pharmacological interventions (benzodiazepines and anti-depressants) for adults with acute traumatic stress symptoms in the first month after a traumatic event

***Scoping question 3*: For adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do pharmacological interventions (benzodiazepines and anti-depressants) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 3

Benzodiazepines and antidepressants should not be offered to adults to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event

For benzodiazepines:
Strength of recommendation: strong
Quality of evidence: very low

For anti-depressants:
Strength of recommendation: standard
Quality of evidence: very low

Remarks

Clinicians should rule out concurrent disorders that may warrant treatment with benzodiazepines and antidepressants.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. In addition, question 1 (on psychological interventions for acute traumatic stress symptoms in adults) recommends that "cognitive-behavioural therapy (CBT) with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning." When combined, these recommendations imply that psychological first aid and (where resources exist) CBT should be considered in adults with acute traumatic stress symptoms associated with impairment in daily functioning in the first month after a potentially traumatic event.

4: Pharmacological interventions (benzodiazepines and anti-depressants) for children and adolescents with acute traumatic stress symptoms in the first month after a traumatic event

Scoping question 4: **For children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do pharmacological interventions (benzodiazepines and anti-depressants) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 4

Benzodiazepines and antidepressants should not be offered to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in children and adolescents.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

Insomnia after a potentially traumatic recent event (recommendations 5-8)

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. Insomnia is a commonly reported symptom of acute stress. The GDG considered the evidence and made the following recommendations on psychological and pharmacological interventions for children and adults with insomnia after a potentially traumatic recent event.

5. Psychological interventions for adults with insomnia in the first month after a traumatic event

***Scoping question 5*: For adults with acute (secondary) insomnia in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 5

Relaxation techniques (e.g., progressive muscle relaxation or cultural equivalents) and advice about sleep hygiene (including advice about psychostimulants, such as coffee, nicotine, and alcohol) should be considered for adults with acute (secondary) insomnia in the first month after exposure to a potentially traumatic event.

Strength of recommendation: Standard
Quality of evidence: very low

Remarks

In many settings,relaxation may be made available through existing cultural practices.

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depressive disorder, and, in adolescents, alcohol or drug use disorder.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. When combined, these recommendations imply that psychological first aid, relaxation techniques and advice about sleep hygiene should be considered in adults with acute (secondary) insomnia in the first month after a potentially traumatic event.

6. Psychological interventions for children with insomnia in the first month after a traumatic event

Scoping question 6: **For children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 6

On the basis of available evidence, no specific recommendation can be made for early psychological interventions in children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: low

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. This includes assessment of the child's perception as to why insomnia may be present. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

Relaxation techniques and advice about sleep hygiene (see question 5 on psychological interventions for insomnia in adults) may be safe, feasible and potentially effective strategies in adolescents (age 10-17 years).

Health care providers should explain that insomnia is common after exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessedfor other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depressive disorder, and, in adolescents, alcohol or drug use disorder.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

7. Use of benzodiazepines in adults with insomnia in the first month after a potentially traumatic event

Scoping question 7: ***For adults with acute (secondary) insomnia in the first month after a potentially traumatic event, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in a reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?***

Recommendation 7

Benzodiazepines should not be offered to adults with insomnia n the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: moderate

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

There are alternatives to pharmacological treatment (see (a) recommendation 5 on psychological interventions for insomnia in adults and (b) WHO (2010) mhGAP recommendations on psychological first aid).

In exceptional cases when psychologically oriented interventions are not feasible, short-term treatment (3-7 days) with benzodiazepines may be considered as a treatment option for insomnia that interferes severely with daily functioning. The following precautions should be considered (a) there are possible interactions with other drugs, (b) necessary precautions should be taken when prescribing to elderly populations and pregnant or breastfeeding women and (c) use of benzodiazepines can quickly lead to dependence in some people. Accordingly benzodiazepines should only be prescribed for insomnia in exceptional cases and for a very short time period. Benzodiazepines are often overprescribed.

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month, the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depression, and alcohol or drug use disorder.

8. Benzodiazepines in children and adolescents with insomnia in the first month after a potentially traumatic event

Scoping question 8: **For children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 8

Benzodiazepines should not be offered to children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

There are alternatives to pharmacological treatment (see question 6's remarks on psychological interventions for insomnia in children and adolescents).

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depression, and, in adolescents, alcohol or drug use disorder.

Enuresis after a potentially traumatic recent event (recommendation 9)

Enuresis is a common complaint in primary care for children recently exposed to potentially traumatic events and may have important harmful mental and social consequences, including decreased sense of self-worth, anxiety, and harsh punitive parental reactions. The ICD-10 describes nonorganic enuresis as "involuntary voiding of urine, by day and/or by night which is abnormal in relation to the individual's mental age and which is not a consequence of a lack of bladder control due to any neurological disorder, to epileptic attacks or to any structural abnormality of the urinary tract." The GDG considered the evidence on management of enuresis, and developed the following recommendation.

9. Early psychological interventions in children with secondary nonorganic enuresis in the first month after a potentially traumatic event

***Scoping question 9*: In children with secondary nonorganic enuresis after a potentially traumatic recent event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 9

(i) Psycho-education about the negative effects of punitive responses should be given to caregivers of children with secondary nonorganic enuresis in the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

(ii) Parenting skills training and the use of simple behavioural interventions (i.e. star charts, toileting before sleep and rewarding having nights without wetting the bed) should be considered. In addition, where resources permit, alarms should be considered.

Strength of recommendation: standard
Quality of evidence: moderate for alarms, low or very low for other behavioural interventions

Remarks

Medical causes of bedwetting should be assessed and managed to ensure that the bedwetting is indeed secondary to a potentially traumatic event.

Health care providers should explain that bedwetting is common after recent exposure to extreme stressors. If the bed-wetting persists for more than one month the child should be re-asssesed for other disorder that may need treatment.

Dissociative (conversion) disorders after a potentially traumatic recent event (recommendations 10-11)

Dissociative (conversion) disorders can be according to ICD-10 as " associated closely in time with traumatic events, insoluble and intolerable problems, or disturbed relationships." Dissociative symptoms have been observed in varying ways (e.g. expressed through different psychological or somatic idioms of distress) in various cultures. The evidence search covered both psychological and somatoform dissociation in adults in the first month after a potentially traumatic event. The GDG considered the evidence retrieved, and it made two recommendations.

10: Early psychological intervention in adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event

***Scoping question 10*: For adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 10

On the basis of available evidence no specific recommendation can be made on psychological interventions for adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

Possible physical causes for dissociation should be ruled out or managed.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made: psychological first aid should be considered in adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

For somatoform dissociation (i.e. conversion disorder), existing WHO guidance on the management of somatic medically unexplained symptoms may be considered (see Other Significant Emotional or Medically Unexplained Complaints module ofthe mhGAP Intervention Guide (WHO, 2010)).

Health care providers should explain that these symptoms can sometimes occur after recent exposure to extreme stressors. When interacting with people with conversion disorder, clinicians should acknowledge suffering and maintain a relationship of respect with the person. At the same time they should carefully avoid reinforcing any secondary gain that the person may get from somatoform dissociation (conversion). The use of culturally appropriate interventions that are not harmful may be considered.

11. Early psychological intervention in children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event

Scoping question 11: **For children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 11

On the basis of available evidence, no specific recommendation can be made for children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

Possible physical causes for dissociation should be ruled out or managed.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made psychological first aid should be considered in adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

For somatoform dissociation (i.e. conversion disorder), existing WHO guidance on the management of somatic medically unexplained symptoms may be considered (see Other Significant Emotional or Medically Unexplained Complaints module of the mhGAP Intervention Guide (WHO, 2010)).

Health care providers should explain that these symptoms can sometimes occur after recent exposure to extreme stressors. When interacting with people with conversion disorder, clinicians should acknowledge suffering and maintain a relationship of respect with the person. At the same time they should carefully avoid reinforcing any secondary gain that the person may get from somatoform dissociation (conversion). The use of culturally specific interventions that are not harmful may be considered.

Hyperventilation after a potentially traumatic recent event (recommendations 12-13)

Clinical experience suggests that in the immediate aftermath of potentially traumatic events, help-seeking for hyperventilation is common. Because symptoms are associated with hypocapnia, clinicians frequently encourage persons to increase their CO2 levels by re-breathing into a paper bag. The evidence search focused on whether rebreathing into a paper bag, compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects.

12: Hyperventilation in adults and adolescents in the first month after a potentially traumatic event

Scoping question 12: **For adolescents and adults with hyperventilation in the first month after a potentially traumatic event, does rebreathing into a paper bag when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 12

No specific recommendation can be made on the basis of available evidence on rebreathing into a paper bag for adolescents and adults with hyperventilation in the first month after exposure to a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

There are significant risks if this technique is used in specific populations (e.g. people with heart disease and asthma).

Health care providers should always rule out physical causes before considering psychological intervention for hyperventilation. They should maintain a calm approach, where possible remove sources of anxiety and coach respirations (i.e. encourage normal breathing, not deeper and quicker than usual).

Health care providers should explain that hyperventilation can sometimes occur after recent exposure to extreme stressors. Acute stress should be managed using psychological first aid as per WHO (2010) mhGAP guidelines. Moreover, as per question 1 (on psychological interventions for acute traumatic stress symptoms in adults), cognitive-behavioural therapy with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning.

13: Hyperventilation in children in the first month after a potentially traumatic event

Scoping question 13: **For children with hyperventilation in the first month after a potentially traumatic event, does rebreathing into a bag when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 13

Rebreathing into a paper bag should not be considered for children with hyperventilation in the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: very low

Remarks

Health care providers should always rule out physical causes before considering psychological intervention. They should maintain a calm approach, where possible remove sources of anxiety and coach respirations (i.e., encourage normal breathing, not deeper and quicker than usual).

Health care providers should explain that hyperventilation can sometimes occur after recent exposure to extreme stressors. Acute stress in children should be managed using psychological first aid as per WHO (2010) mhGAP guidelines.

Posttraumatic Stress Disorder (recommendations 14-17)

Posttraumatic stress disorder (PTSD) is the most studied disorder occurring after exposure to potentially traumatic events. Psychological interventions for PTSD include individual and group cognitive behavioural therapy (CBT), eye movement desensitization and reprocessing (EMDR), stress management, and psycho-education for adult PTSD in non-specialized health care settings. There is currently no consensus on the effectiveness of EMDR and pharmacological treatments between different clinical practice guidelines. For pharmacological interventions, the evidence search was limited to treatments most likely to be available now or in the next 5 years in non-specialized health care in low and middle income countries (tricyclic antidepressants (TCAs and selective serotonin re-uptake inhibitors (SSRIs)) (cf. van Ommeren et al, 2005). The GDG considered the evidence for psychological and pharmacological interventions for PTSD and developed the following four recommendations.

14. Psychological interventions for adults with posttraumatic stress disorder

Scoping question 14: **For adults with posttraumatic stress disorder (PTSD), do psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 14

Individual or group cogntive-behavioural therapy (CBT) with a trauma focus, eye movement desensitization and reprocessing (EMDR), or stress management should be considered for adults with PTSD

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, EMDR; low for group CBT, stress management

Remarks

Individual and group CBT with a trauma focus and EMDR should only be offered in those contexts where individuals are competent (i.e. trained and supervised) to provide the therapies. Although studies show that individual CBT with a trauma focus is more effective than stress management, in resource constrained settings stress management may be the most feasible treatment option.

15: Psychological interventions for children and adolescents with posttraumatic stress disorder

Scoping question 15: **For children and adolescents with posttraumatic stress disorder (PTSD), do psychological interventions when compared to treatment as usual, waiting list or no treatment, result in a reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 15

Individual or group cogntive-behavioural therapy (CBT) with a trauma focus or eye movement desensitization and reprocessing (EMDR) should be considered for children and adolescents with PTSD.

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, low for EMDR, very low for group CBT

Remarks

Individual and group CBT with a trauma focus and EMDR should only be offered in those contexts where individuals are competent (i.e. trained and supervised) to provide the therapies. Stress management may also be beneficial for children and adolescents with PTSD.

16. Pharmacological interventions for adults with posttraumatic stress disorder

Scoping question 16: **For adults with posttraumatic stress disorder (PTSD), do tricyclic antidepressants (TCAs) or selective serotonin re-uptake inhibitors (SSRIs) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 16:

Selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) should not be offered as the first line of treatment for posttraumatic stress disorder in adults.

SSRIs and TCAs should be considered if:

(a) stress management, CBT with a trauma focus, and EMDR have failed or are not available

or

(b) if there is comorbid moderate-severe depression.

Strength of recommendation: standard
Quality of evidence: low

Remarks

Interactions with other drugs need to be considered and necessary precautions should be taken when prescribing to elderly populations and pregnant or breastfeeding women (see WHO (2010) mhGAP Intervention Guide module on moderate-severe depression).

17. Pharmacological interventions for children with posttraumatic stress disorder

Scoping question 17: **For children and adolescents with posttraumatic stress disorder (PTSD), do antidepressants when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 17

Anti-depressants should not be used to manage PTSD in children and adolescents

Strength of recommendation: strong
Quality of evidence: very low

Remarks

If there is concurrent moderate-severe depression, also use guidance for helping depressed children and adolescents as included in the WHO (2010) mhGAP Intervention Guide module on depression. There are alternatives to pharmacological treatment (see recommendation 15 on psychological interventions for PTSD in children and adolescents).

Bereavement in the absence of mental disorder (recommendations 18-21)

Bereavement is referred to here as the event of a loss of a loved one, a common occurrence in life, which for most people will not lead to mental disorder. For a small minority, bereavement and grief may be associated with prolonged symptomatology and impairment in functioning amounting to mental disorder. The evidence considered concerned adults, children and adolescents who do *not* meet criteria for a mental disorder

18. Structured psychological interventions in bereaved adults without a mental disorder

Scoping question 18: **For bereaved adults *without* a mental disorder, do universally applied structured psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 18:

Structured psychological interventions should *not* be offered universally (to all) bereaved adults who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: moderate

Remarks

General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and the principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

19: Children: Structured psychological interventions in bereaved children without a mental disorder

***Scoping question 19*: For bereaved children and adolescents *without* a mental disorder, do universally applied structured psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 19

Structured psychological interventions should not be offered universally (to all) bereaved children and adolescents who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

In cases where the child has lost a primary caregiver, the issue of protection and continued supportive caregiving, socio-emotional support, should be addressed.

20: Use of benzodiazepines in bereaved adults who do not have a mental disorder

Scoping question 20: **For bereaved adults without a mental disorder, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 20

Benzodiazepines should not be offered to bereaved adults who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

As mentioned in the remarks for recommendation 18 on psychological interventions for bereaved adults: General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and the principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

21. Use of benzodiazepines in bereaved children and adolescents who do not have a mental disorder

Scoping question 21: **For bereaved children and adolescents without a mental disorder, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?**

Recommendation 21

Benzodiazepines should not be offered to bereaved children and adolescents who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Q*uality of evidence: very low*

Remarks

As mentioned in the remarks for recommendation 19 on psychological interventions for bereaved children and adolescents: general principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

In cases where the child has lost a primary caregiver, the issue of protection and continued supportive caregiving, including socio-emotional support, should be addressed.

Plans for disseminating, adapting and implementing these recommendations

As described above, these recommendations will be used to develop a mhGAP clinical module on management of adults, adolescents and children for disorders and problems specifically associated with stress (SPE-STRESS). This will be widely disseminated through the WHO mhGAP programme using regional and country WHO offices, collaborating centres, professional organizations and partner agencies. It The module will be promoted as a WHO-UNHCR tool for humanitarian work.

The evidence profiles will be uploaded on the WHO website's mhGAP Evidence Resource Centre.

An article will be drafted and submitted to a public health journal to disseminate these guidelines and the process of developing them.

These recommendations will be adapted for the field by developing suitable training materials in consultation with regional, national and local stakeholders. Adaptation will include translation into appropriate languages and checking that the interventions are acceptable in local sociocultural contexts and are suitable for local health systems.

Impact of the guideline

Process measures will also be used to monitor the uptake of these guidelines (eg frequency of downloading of guidelines and its derivative products from the internet; frequency of citations of an article based on the Guidelines).

With respect to routine monitoring and evaluation of implementation of the guidelines, WHO is developing a monitoring and evaluation tool – with input, process, output and outcome measures) to assess implementation of the mhGAP Intervention Guide. That tool will also be able to assess implementation of the mhGAP module on Problems and Disorders Specifically Related to Stress (SPE-STRESS). Moreover, WHO mhGAP partners (such as the International Medical Corps) are developing their own tool to evaluate mhGAP implementation.

With respect to rigorous research, the mhGAP programme has helped attract a substantial amount of funds to global mental health research partners. Major donors (e.g., Department for International Development (DFID), National Institute of Mental Health (NIMH), European Commission (EC), and Grand Challenges Canada) have made funds available to mainly university partners to study the impact of applying mhGAP guidelines, including conduct of randomized trials to strengthen relevant implementation science.

Research

In several instances, GDG decided that there was not enough evidence to make recommendations. In such instances, the quality of the evidence has been summarized as very low. New research is needed on all scoping questions with low or very low quality evidence.

Review by date

The recommendations and evidence base should be reviewed within five years (before 2018)

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Annex 1: WHO Steering Group

Tarun Dua	Medical Officer	Department of Mental Health and Substance Abuse
Claudia Garcia-Moreno	Team Leader	Department of Reproductive Health and Research
Berit Kiesbelbach	Technical Officer	Department of Violence and Injury Prevention and Disability
Khalid Saeed	Regional Advisor	Regional Office for the Eastern Mediterranean
Shekhar Saxena	Director	Department of Mental Health and Substance Abuse
Yuta Setoya	Technical Officer	Department of Mental Health and Substance Abuse
Chiara Servili	Medical Officer	Department of Mental Health and Substance Abuse
Mark van Ommeren	Scientist	Department of Mental Health and Substance Abuse
Taghi Yasamy	Medical Officer	Department of Mental Health and Substance Abuse

Annex 2: Guideline Development Group (GDG)

2.1 GDG Membership

1. Jonathan Bisson, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, United Kingdom.
2. Judith Cohen, Department of Psychiatry, Drexel University College of Medicine, Philadelphia, United States.
3. Zeinab Hijasi, International Medical Corps, International Medical Corps, Beirut, Lebanon.
4. Joop de Jong, Department of Psychiatry, Vrije Universiteit, Amsterdam, the Netherlands.
5. Olayinka Omigbodun, Department of Psychiatry, University College Hospital, Ibadan, Nigeria.
6. Soraya Seedat, Stellenbosch University, Department of Psychiatry, Tygerberg, South Africa
7. Derrick Silove, Psychiatry Research and Teaching Unit, Liverpool Hospital's Mental Health Centre, University of New South Wales, Sydney, Australia.
8. Renato Souza, International Committee of the Red Cross, Geneva, Switzerland (until July 2012); Institute of Psychiatry - Hospital das Clínicas - University of Sao Paulo Medical School, Sao Paulo, Brazil (from July 2012).
9. Athula Sumathipala, Department of Mental Health and Population Research, Institute of Psychiatry, Kings College, London, United Kingdom & Institute for Research and Development, Colombo, Sri Lanka.
10. Lakshmi Vijayakumar, Sneha, Voluntary Health Services, Department of Psychiatry, Chennai, India.
11. Inka Weissbecker, International Medical Corps, Washington DC, United States.
12. Doug Zatzick, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, United States.

2.2 Background of Guideline Development Group Members

NAME		ORIGIN (WHO REGION)		EXPERIENCE/KNOWLEDGE BASIS					
		Country of Origin	WHO Region	Has extensive work experience as non-specialist healthcare staff	Has extensive work experience in non-specialist health care in emergency settings	Has extensive low and middle income country experience	Methodologist (systematic reviews)	Expert on children	Holds an academic position
Joop de Jong (chair)	M	Netherlands	EURO	x	x	x			x
Jonathan Bisson	M	UK	EURO				X		x
Judith Cohen	F	USA	AMRO					x	x
Zeinab Hijasi	F	Lebanon	EMRO		x	x			
Olayinka Omigbodun	F	Nigeria	AFRO			x		x	x
Derrick Silove	M	Australia	WPRO		x	X			x
Soraya Seedat	F	South Africa	AFRO			x			x
Renato Souza	M	Brazil	AMRO		x	x			
Athula Sumathipala	M	Sri Lanka	SEARO	x	x	x			x
Laskhmi Vijaykumar	F	India	SEARO		x	x			
Inka Weissbecker	F	Germany	EURO		x	x			
Doug Zatzick	M	USA	AMRO		x	x			x

2.3 Consultants supporting the Guideline Development Group:

Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health, University of Verona, Italy)

Margaret Harris (non-affiliated consultant, Hong Kong, People's Republic of China)

Lynne Jones (FXB Center for Health and Human Rights, Harvard School of Public Health
Boston, United States)

Nicola Magrini (WHO Collaborating Centre for Evidence-based Research Synthesis and Guideline Development, Bologna, Italy)

Wietse A Tol (Johns Hopkins Bloomberg School of Public health, Baltimore, United States)

Annex 3 External Reviewers

Name	Affiliation	Country of residence	WHO Region
1. Alain Brunet & Daniel Saumier	McGill University	Canada	AMRO
2. Andreas Maercker	University of Zürich	Switzerland	EURO
3. Andrew Rasmussen	Fordham University	United States of America	AMRO
4. Alison Schafer	World Vision International	Australia	WPRO
5. Boris Budosan	In non-affiliated capacity	Croatia	EURO
6. Bhava Poudyal	In non-affiliated capacity	Nepal	SEARO
7. Carolina Echeverri	United Nations High Commissioner of Refugees	Senegal	AFRO
8. Cécile Rousseau	McGill University	France	EURO
9. Laura Murray	Johns Hopkins University School of Public Health	United States of America	AMRO
10. Leslie Snider	War Trauma Foundation	The Netherlands	EURO
11. Miranda Olff	University of Amsterdam	The Netherlands	EURO
12. Nino Makhashvili	Global Initiative on Psychiatry & Tbilisi Ilia University	Georgia	EURO
13. Pam Dix	Disaster Action	United Kingdom	EURO
14. Peter Hughes	National Health Service – United Kingdom	United Kingdom	EURO
15. Patti Levin	In non-affiliated capacity	United States of America	AMRO
16. Pau Pérez-Sales	Médicos del Mundo & Hospital La Paz, Madrid	Spain	EURO
17. Robert Pynoos	University of California, Los Angeles	United States of America	AMRO
18. Sarah Meyer	Johns Hopkins University School of Public Health	United States of America	AMRO
19. Sonali Sharma	In non-affiliated capacity	United States of America	AMRO
20. Thomas Barrett	University of Denver	United States of America	AMRO
21. William Yule	Institute of Psychiatry - King's College London	United Kingdom	EURO
22. Yuriko Suzuki	National Institute of Mental Health (NIMH) Japan	Japan	WPRO

Annex 4: Declarations of Interest

4.1 Consultants

Potential perceived conflict of interest (as expressed in declaration of interest form): none.

4.2 Guideline Development Group

	Name	Current Affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
1	Joop de Jong (chair)	Vrije Universiteit	None	
2	Jonathan Bisson	University of Wales	Yes: 1b (consulting)	Was paid by WHO USD 5000 in 2009 for performing systematic review of efficacy of Psychological First AID; was paid by WHO USD 5000 in 2011 for performing systematic review of efficacy of pharmacological interventions for PTSD
3	Judith Cohen	Drexel University College of Medicine	Yes: 1b (consulting) 2a: (research support for salary) 4a: (copyright)	1b: Consultant for training in TF-CBT treatment model in 3 US states-US$ 10,000 per year-ongoing; 2a: Salary paid to Allegheny Singer Research Institute by National Institute for Mental health (US)-ongoing; 4a:copyright for book: 'treating traumatic grief in children and adolescents'-approximately US$ 5000 per year-ongoing Judith Cohen did not participate in recommendation development meeting in Amman, Jordan
4	Zeinab Hijasi	International Medical Corps	None	
5	Olayinka Omigbodun	University of Ibadan	Yes: 5b: (held relevant office)	President of International Association for Child and Adolescent Psychiatry and Allied Professions - current
6	Derrick Silove	University of New South Wales	None	
7	Soraya Seedat	Stellenbosch University	Yes: 1a (research grants) 2b (travel sponsorship)	1a: National Research Foundation and National Institutes of Health (NIH) provided research grants of US$ 700,000 in 2002-2011-past. 2b:Travel to congresses and educational meetings sponsored by Astra Zeneca, Eli Lily, Glaxo Smith Kline, Lundbeck and Servier, Dr Reddy's. Total value estimated at $5000 between 2002-2011 5a co-author of Cochrane review on pharmacological interventions for PTSD (past); involvement in making guidelines for PTSD for the South African Society for Psychiatrists (current); involvement in the International Psychopharmacological Algorithm Project 's guidelines for PTSD (past). Dr Seedat did not participate in decision-making on any recommendations involving pharmacological interventions for PTSD.

	Name	Current Affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
8	Renato Souza	International Committee for the Red Cross (until July 2012); University of Sao Paulo (from July 2012)	None	
9	Athula Sumathipala	Institute for Research & Development	None	
10	Laskhmi Vijaykumar	Sneha	None	
11	Inka Weissbecker	International Medical Corps	None)	
12	Doug Zatzick	University of Washington	5b (holds relevant office)	Chairs a study section of the US National Institute of Mental Health (NIMH) and is on the Institute of Medicine (IOM) Committee for the study of PTSD (2011-2014)

4.3 External reviewers

Name	Potential perceived conflict of interest (as expressed in declaration of interest form)
1. Alain Brunet & Daniel Saumier	No No
2. Andreas Maercker	Yes – consulting and positions, appointed chair to the WHO ICD-10 revision working group on disorders associated with stress (2011-2013)
3. Andrew Rasmussen	No
4. Alison Schafer	No
5. Boris Budosan	No
6. Bhava Poudyal	No
7. Carolina Echeverri	No
8. Cécile Rousseau	No
9. Laura K. Murray	Yes – consulting, research, public speaking
10. Leslie Snider	No
11. Miranda Olff	No
12. Nino Makhashvili	No
13. Pam Dix	No
14. Peter Hughes	Yes- consulting for WHO and International Medical Corps
15. Patti Levin	No
16. Pau Pérez-Sales	No
17. Robert S. Pynoos	Yes – research, intellectual property rights (Copyright UCLA PTSD-RI for Children and Adolescents, PFA Field Operations Guide)
18. Sarah Meyer	No
19. Sonali Sharma	Yes- consulting, public statement and positions
20. Thomas Barrett	No
21. William Yule	No
22. Yukiro Suzuki	No

Annex 5: Evidence Profiles

1. Acute Traumatic Stress Symptoms (first month): Early Psychological Interventions --Adults

Q1. For adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Acute traumatic stress symptoms in the current scoping question refer to symptoms of intrusion, avoidance and hyperarousal - when these are associated with significant impairment in daily functioning - in the first month after a potentially traumatic event. In terms of nosology, these symptoms can be part of

(a) DSM-IV Acute Stress Disorder (not included in ICD) , which in DSM is limited to one month of the event and

(b) ICD-10 Posttraumatic Stress Disorder, which in ICD can be diagnosed within one month of the event.

Other symptoms of acute stress, including hyperventilation, conversion and dissociative symptoms, and secondary nonorganic nocturnal enuresis in children, are the focus of other evidence profiles of these guidelines.

There has been no demonstrated benefit in preventing Posttraumatic Stress Disorder, from either psychological debriefing or multiple-session psychological interventions, when applied universally (regardless of symptom levels) in the immediate aftermath of

potentially traumatic events.[3] Access to psychological first aid – which despite its name involves largely social intervention - has been recommended by a WHO Guidelines Development Group in 2009 as an alternative to psychological debriefing.

An important question remains as to which other early psychological interventions may be effective in those with acute traumatic stress symptoms during the first month after the event.

In this scoping question, *early psychological interventions* may include problem-solving counseling; relaxation; psycho-education; eye movement desensitization and reprocessing (EMDR); and cognitive behavioral therapy (CBT) applied during the first month after the event. Psycho-education refers to "the provision of information about the nature of stress, posttraumatic and other symptoms, and what to do about them".[4]

The term trauma-focused CBT (TF-CBT) has been used in different manners in the literature. For example, in the widely used NICE Guidelines, this term is used for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing of thoughts related to the event), while the same term is widely used for a very specific multi-component CBT protocol for children and adolescents developed by Cohen and colleagues. To avoid confusion, this guideline avoids the term TF-CBT and uses the term *CBT with a trauma focus* for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing).

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with acute traumatic stress symptoms[5], within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Early psychological interventions[6]
- **Comparison:** Treatment as usual or no treatment/ waitlist

[3] Roberts et al (2010b). Multiple session early psychological interventions for the prevention of posttraumatic stress disorder. Cochrane Database of Systematic Reviews, Issue 4.

[4] Wessely et al (2008). Does psychoeducation help prevent post traumatic psychological distress? *Psychiatry*, 71(4), 287-302

[5] *Acute traumatic stress symptoms* in this scoping question refer to symptoms of intrusion, avoidance and hyperarousal associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

[6] *Early psychological interventions* may include problem-solving counseling; relaxation; psycho-education; and CBT applied during the first month after the event.

- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("acute stress") AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "acute stress". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Roberts, N.P., Kitchiner, N.J., Kenardy, J., Bisson, J.I. (2010a). Early psychological interventions to treat acute traumatic stress symptoms. Cochrane Database of Systematic Reviews, Issue 3.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

American Psychiatric Association (2004). Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder. Washington, DC: APA & Benedek, D.M., Friedman, M.J., Zatzick, D., Ursano, R.J. (2009). Guideline Watch (March 2009): Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder. Washington, DC: American Psychiatric Association
COMMENT: Benedek et al (2009) describe studies that have come out since the APA (2004) publication, but this is not a formal update of the guidelines. No update of ASD related studies is provided.
REASON FOR EXCLUSION: No formal meta-analysis reported. Only Medline and PILOTS searched.

Australian Centre for Posttraumatic Mental Health (2007). Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder. Melbourne, Australia: ACPMH
COMMENT: aimed to update both the NICE and VA/DoD guidelines. P.103-114 focuses on adults without ASD symptoms, p.115-124 focus on people with ASD symptoms
REASON FOR EXCLUSION: More than 2 years old

Department of Veterans Affairs/ Department of Defense (2010). Clinical Practice Guideline for Management of Posttraumatic Stress. Washington, DC: VA/ DoD
REASON FOR EXCLUSION: No formal meta-analysis reported

Hofmann, S.G., Smits, J.A.J. (2008). Cognitive-Behavioral Therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *Journal of Clinical Psychiatry*, 69, 621-632
COMMENT: includes four studies by Bryant et al focused on ASD
REASON FOR EXCLUSION: More than 2 years old

Kornør, H., Winje, D. Ekeberg, Ø., Weisæth, L., Kirkehei1, I., Johansen, K., Steiro, A. (2008). Early trauma-focused cognitive-behavioural therapy to prevent chronic post-traumatic stress disorder and related symptoms: A systematic review and meta-analysis. *BMC Psychiatry*, 8(81), doi:10.1186/1471-244X-8-81
REASON FOR EXCLUSION: More than 2 years old. NOTE: findings are consistent with the selected Roberts et al (2010a) review.

Litz, B.T. & Bryant, R.A. (2009). Early cognitive behavioral interventions for adults. In E.B. Foa, T.M. Keane, M.J. Friedman, J.A. Cohen (Eds). Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies 2nd Edition. New York: the Guilford Press
REASON FOR EXCLUSION: No formal meta-analysis reported

National Collaborating Centre for Mental Health (2005). The Management of PTSD in Adults and Children in Primary and Secondary Care. London, UK: Royal College of Psychiatrists & British Psychological Society
REASON FOR EXCLUSION: More than 2 years old

Ponniah, K., Hollon, S.D. (2009). Empirically supported psychological treatments for adult acute stress disorder and posttraumatic stress disorder: a review. *Depression and Anxiety*, 26, 1086-1109
REASON FOR EXCLUSION: No formal meta-analysis reported

Roberts, N.P., Kitchiner, N.J. Kenardy, J., Bisson, J.I. (2009). Systematic review and meta-analysis of multiple-session early interventions following traumatic events. *American Journal of Psychiatry*, 166, 293-301
REASON FOR EXCLUSION: Same author team published a more detailed report as a Cochrane review

Roberts, N.P., Kitchiner, N.J. Kenardy, J., Bisson, J.I. (2010b). Multiple session early psychological interventions for the prevention of posttraumatic stress disorder. *Cochrane Database of Systematic Reviews*, Issue 4.

REASON FOR EXCLUSION: focuses on psychological interventions for people without symptoms of acute stress

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Psychological interventions vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Roberts et al, 2010a No data Roberts et al, 2010a (proxy follow-up effects) Roberts et al, 2010a (proxy drop-out)	Roberts et al, 2010a presents the only recent systematic review with a formal meta-analysis. Limitation: Roberts et al included studies up to 3 months after the event

Narrative description of the studies that went into analysis

Roberts and colleagues performed a systematic review and meta-analysis of studies following the Cochrane Handbook, focused on people presenting with DSMIV-defined Acute Stress Disorder and acute Posttraumatic Stress Disorder (both sub-threshold and meeting diagnostic criteria) in the first three months after a traumatic event. Their search identified 15 studies, ranging in sample size from 8 to 152 participants and all conducted with civilian populations exposed to single traumas in high-income countries (Australia, USA, UK, the Netherlands, Sweden, and Spain). Most studies focused on Cognitive Behavioral Therapy (CBT) with a trauma focus, but also evaluated were general CBT, supportive counseling, stepped collaborative care, structured writing therapy, relaxation, CBT plus anxiety management and CBT plus hypnosis.

GRADE Table

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-24
Question: Should early psychological interventions vs treatment as usual or no treatment/waitlist be used for adults with acute traumatic stress symptoms?
Settings:
Bibliography: Roberts 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early psychological interventions	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
symptom severity (clinician): after intervention (Better indicated by lower values)												
6[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	243	226	-	SMD 0.64 lower (1.06 to 0.23 lower)	□□□□ MODERATE	IMPORTANT
symptom severity (clinician): 3-5 month follow-up (Better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	110	94	-	SMD 0.17 lower (0.45 lower to 0.11	□□□□ LOW	IMPORTANT

										higher)		
symptom severity (clinician): 9-11 month follow-up (Better indicated by lower values)												
2[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	37	36	-	SMD 0.33 lower (0.8 lower to 0.15 higher)	□□□□ LOW	IMPORTANT
symptom severity (self report): after intervention (Better indicated by lower values)												
6[9]	randomised trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecision	none	185	185	-	SMD 0.83 lower (1.43 to 0.23 lower)	□□□□ MODERATE	IMPORTANT
symptom severity (self report): 9-11 month follow-up (Better indicated by lower values)												
2[11]	randomised trials	serious[12]	serious[13]	no serious indirectness	serious[5]	none	37	36	-	SMD 0.31 lower (0.79 lower to 0.17 higher)	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder: PTSD diagnosis after treatment												
7[14]	randomised trials	no serious risk of bias	serious[15]	no serious indirectness	no serious imprecision	none	119/266 (44.7%)	142/249 (57%)	RR 0.72 (0.5 to 1.05)	160 fewer per 1000 (from 285	□□□□ MODERATE	IMPORTANT

										fewer to 29 more)		
Presence of disorder: PTSD diagnosis: 3-5 month follow-up												
5[16]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	serious[18]	none	22/74 (29.7%)	31/67 (46.3%)	RR 0.64 (0.42 to 0.99)	167 fewer per 1000 (from 5 fewer to 268 fewer)	□□□□ LOW	IMPORTANT
Presence of disorder: PTSD diagnosis: 9-11 month follow-up												
2[19]	randomised trials	serious[20]	serious[21]	no serious indirectness	very serious[22]	none	7/28 (25%)	11/26 (42.3%)	RR 0.61 (0.27 to 1.36)	165 fewer per 1000 (from 309 fewer to 152 more)	□□□□ VERY LOW	IMPORTANT
Adverse effects: leaving the study early												
6[23]	randomised trials	no serious risk of bias	no serious inconsistency	serious[24]	no serious imprecision	none	48/266 (18%)	51/249 (20.5%)	RR 0.89 (0.63 to 1.26)	23 fewer per 1000 (from 76 fewer to 53 more)	□□□□ MODERATE	IMPORTANT

[1] From Analysis 1.1 of Roberts 2010a
[2] Visual inspection of forest plot highlights that confidence intervals do not overlap. I-squared = 75%.
[3] From Analysis 1.3 of Roberts 2010a
[4] Dropout rates exceeded 30% in one study (Foa 2006); in the other study it was unclear whether outcome assessment was performed by masked assessors (sijbrandij 2007).
[5] Confidence interval does not exclude the possibility of appreciable benefit of the experimental intervention.
[6] From Analysis 1.4 of Roberts 2010a
[7] Dropout rates exceeded 30% in one study (Foa 2006).
[8] Less than 100 patients included in this analysis. Confidence interval ranges does not exclude the possibility of appreciable benefit.

[9] From Analysis 1.5 of Roberts 2010.
[10] Confidence intervals do not overlap. I-squared = 84%
[11] From Analysis 1.7 of Roberts 2010.
[12] Dropout rates exceeded 30% in one study (Foa 2006).
[13] I-squared = 84%
[14] From Analysis 1.8 of Roberts 2010.
[15] I-squared = 71%
[16] From Analysis 1.10 of Roberts 2010.
[17] High dropout rates in one studies (Foa 2006); in the other study it was unclear whether outcome assessment was performed by masked assessors
[18] Less than 200 patients included. Confidence interval ranges from appreciable benefit to almost no benefit.
[19] From Analysis 1.11 of Roberts 2010.
[20] High dropout rates in one study (Foa 2006).
[21] I-squared = 70%
[22] Confidence interval ranges from appreciable benefit to no difference. Less than 100 patients included in the analysis.
[23] From Analysis 1.18 of Roberts 2010.
[24] Leaving the study early is only a proxy measure of the adverse effects associated with the experimental treatment.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	**Cognitive Behavioral Therapy with a trauma focus** There is evidence suggesting that early cognitive behavioral interventions (CBT) with a trauma focus in adults with acute traumatic stress symptoms have a beneficial effect in decreasing symptom severity after intervention. This beneficial effect has been demonstrated using clinician-rated as well as patient-rated outcome measures. The confidence in estimate is MODERATE. The effect is less evident at follow-up assessments. There is evidence suggesting that CBT with a trauma focus in adults with acute traumatic stress symptoms have a beneficial effect in preventing PTSD diagnosis. The confidence in estimate is MODERATE. The effect is less evident at follow-up assessments. **Problem-solving counseling,**

	The systematic review identified 1 study focused on supportive counseling, which did not find an effect of counseling on PTSD symptoms, anxiety or depression. **EMDR, relaxation, psycho-education** There is no systematic review on the potential benefits of EMDR as an early intervention. Although relaxation and psycho-education often are part of or precede CBT, there is no systematic review of evidence suggesting that each of these components on their own have a beneficial effect in decreasing symptom severity after intervention, preventing PTSD, or improvement of functioning. A recent systematic review of such interventions in LMIC humanitarian settings – all conducted more than one month after the potentially traumatic event - showed mixed evidence for psycho-education and counselling. Psycho-education was not effective in two out of three studies, and in one study adding PTSD psycho-education (i.e. discussion of PTSD symptoms) to reconciliation workshops produced worse outcomes than reconciliation workshops alone. Problem-solving counselling implemented by para-professionals was associated with minimal improvements in torture survivors in Nepal and Indonesia, and performed similarly positive to Narrative Exposure Therapy with refugees in Uganda. (Tol et al, 2011 Lancet 378: 1581-91). No separate evidence was found for relaxation.
Harms	**Cognitive Behavioral Therapy with a trauma focus** There is evidence suggesting that CBT with a trauma focus in adults with acute traumatic stress symptoms is acceptable; intervention was not associated with more people leaving the study early, a proxy measure of treatment acceptability. The confidence in estimate is MODERATE. **EMDR, problem-solving counseling, relaxation, psycho-education** There is no systematic review on the potential negative consequences of EMDR, problem solving counseling, relaxation and psycho-education as early interventions. However, a narrative review of the evidence on psycho-education found that there may be risks associated with psycho-education (Wessely et al, 2008; Psychiatry, 71, p.287)

Value and preferences	
In favour	The possibility of decreasing acute traumatic stress symptoms and preventing PTSD is an important value. Help-seekers from remote areas may have travelled long distances for treatment. If treatment is known to be effective, adopting a wait and see approach may be impractical and unethical as symptomatic, untreated and distressed persons may not return at a later date. On the other hand, if persons have travelled far they may not have resources to stay for an extended period (e.g. several weeks) of time to participate in multiple session psychotherapy.
Against	Many people with acute traumatic stress symptoms recover over time without intervention. It may be worthwhile (cf. NICE Guidelines) to wait 1-3 months to see who recovers naturally and only offer intervention to those who have disabling symptoms that remained the same or have worsened.

Feasibility (including economic consequences)	Most staff in PHC in LMIC have not received extensive training in communication skills and basic emotional support. Any additional training in cognitive behavioural therapy would require substantial resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources. Large numbers of PHC attenders suffer from acute traumatic stress symptoms (e.g. as a result of injury), especially after mass events that have numerous survivors. It would not be feasible to deliver CBT to all. Potentially those whose acute traumatic stress symptoms are associated with impairment in daily functioning should be prioritized for CBT. All studies supporting efficacy were implemented in high-income countries and in specialized treatment settings (specialized clinics, outpatient and inpatient clinics). Implementation of cognitive behavioural therapy in non-specialized settings by non-specialized staff may pose risks of harm due to the high levels of skills required and delicate nature of handling acute traumatic stress symptoms. Nevertheless, cognitive behavioural interventions have been successfully implemented in low-

	resource settings to treat maternal depression (Rahman et al, 2008 Lancet 372: 902–09) and post-traumatic stress disorder symptoms in adults and adolescents (Neuner et al, 2008 J Consult Clin Psychol 76(4): 686-94; Ertl et al, 2011 JAMA 306(5): 503-12) Although no or limited evidence was found for the value of relaxation and problem-solving counselling, it is noted that many CBT approaches require the person to be stable (i.e. reduced distress/symptoms) before using any form of exposure. CBT protocols often require psycho-education and relaxation and sometimes a problem-solving approach to achieve such stability.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X** For CBT **No X** **For other interventions**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes No
Are the expected values and preferences clearly in favour of the recommendation?	Yes No

Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 1

(i) Cognitive-behavioural therapy with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: standard
Quality of evidence: moderate

(ii) On the basis of available evidence, no specific recommendations can be made about stand-alone problem-solving counselling, eye movement desensitization and reprocessing (EMDR), relaxation, or psycho-education in the first month for adults with acute traumatic stress symptoms associated with significant impairment in daily functioning after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

SPE-Stress: Acute Traumatic Stress (first month); Psychological - Adults

Remarks

CBT with a trauma focus should only be offered in those contexts where individuals are competent (trained and supervised) to provide the therapy.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. When combined, these recommendations imply that psychological first aid should be considered in all adults with acute traumatic stress symptoms; and, where competent staff are available, CBT with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event. *In situations without sufficient resources to provide CBT with a trauma focus, other interventions such as stress management may be considered in addition to psychological first aid.*

2. Acute Traumatic Stress Symptoms (first month): Early Psychological Interventions – Children and Adolescents

Q2. For children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Acute traumatic stress symptoms in the current scoping question refer to symptoms of intrusion, avoidance and hyperarousal - when these are associated with significant impairment in daily functioning - in the first month after a potentially traumatic event. In terms of nosology, these symptoms can be part of

(a) DSM-IV Acute Stress Disorder (not included in ICD), which in DSM is limited to one month of the event and

(b) ICD-10 Posttraumatic Stress Disorder, which in ICD can be diagnosed within one month of the event.

Other symptoms of acute stress, including hyperventilation, conversion and dissociative symptoms, and secondary nonorganic nocturnal enuresis in children, are the focus of other evidence profiles of these guidelines.

There has been no demonstrated benefit in preventing Posttraumatic Stress Disorder, from either psychological debriefing or multiple-session psychological interventions, when applied universally (regardless of symptom levels) in the immediate aftermath of potentially traumatic events.[7] Access to psychological first aid – which despite its name involves largely social intervention - has been recommended by a WHO Guidelines Development Group in 2009 as an alternative to psychological debriefing.

[7] Roberts et al (2010b). Multiple session early psychological interventions for the prevention of posttraumatic stress disorder. Cochrane Database of Systematic Reviews, Issue 4.

An important question remains as to which other early psychological interventions may be effective in those with acute traumatic stress symptoms during the first month after the event. In this scoping question, *early psychological interventions* may include problem-solving counseling; relaxation; psycho-education; eye movement desensitization and reprocessing (EMDR) and cognitive behavioral therapy (CBT) applied during the first month after the event. Psycho-education refers to "the provision of information about the nature of stress, posttraumatic and other symptoms, and what to do about them".[8]

The term trauma-focused CBT (TF-CBT) has been used in different manners in the literature. For example, in the widely used NICE Guidelines, this term is used for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing of thoughts related to the event), while the same term is widely used for a very specific multi-component CBT protocol for children and adolescents developed by Cohen and colleagues. To avoid confusion, this guideline avoids the term TF-CBT and uses the term *CBT with a trauma focus* for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing).

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and adolescents with acute traumatic stress symptoms[9], within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Early psychological interventions[10]
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

[8] Wessely et al (2008). Does Psychoeducation help prevent post traumatic psychological distress? *Psychiatry*, 71(4), 287-302

[9] *Acute traumatic stress symptoms* in this scoping question refer to symptoms of intrusion, avoidance and hyperarousal associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

[10] *Early psychological interventions* may include problem-solving counseling; relaxation; psycho-education; and CBT

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("acute stress") AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "acute stress". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

The most recent systematic review that was identified (Brymer et al, 2009) concluded there are currently no sufficiently rigorous evaluation studies regarding this scoping question available and did not attempt meta-analysis because of study limitations. Therefore, no data were entered in the GRADE table. Rather, a narrative description of the most recent systematic review is provided.

NOTE: A pertinent systematic review and meta-analysis, published after the literature search was conducted, was identified during the external peer review process of this profile: Kramer DN, Landolt MA. Characteristics and efficacy of early psychological interventions in children and adolescents after single trauma: a meta-analysis. European Journal of Psychotraumatology 2011, 2: 7858.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

American Psychiatric Association (2004). Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder. Washington, DC: APA & Benedek, D.M., Friedman, M.J., Zatzick, D., Ursano, R.J. (2009). Guideline Watch (March 2009): Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder. Washington, DC: American Psychiatric Association
COMMENT: Benedek et al (2009) describe studies that have come out since the APA (2004) publication, but this is not a formal update of the guidelines. No update of ASD related studies is provided.

REASON FOR EXCLUSION: No formal meta-analysis reported. Only Medline and PILOTS searched; research on children and adolescents not aggregated

Australian Centre for Posttraumatic Mental Health (2007). Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder. Melbourne, Australia: ACPMH

COMMENT: aimed to update both the NICE and VA/DoD guidelines. P.103-114 focuses on adults without ASD symptoms, p.115-124 focus on people with ASD symptoms

REASON FOR EXCLUSION: More than 2 years old; research on children and adolescents not aggregated

Department of Veterans Affairs/ Department of Defense (2010). Clinical Practice Guideline for Management of Posttraumatic Stress. Washington, DC: VA/ DoD

REASON FOR EXCLUSION: No formal meta-analysis reported; research on children and adolescents not aggregated

Hofmann, S.G., Smits, J.A.J. (2008). Cognitive-Behavioral Therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *Journal of Clinical Psychiatry*, 69, 621-632

COMMENT: includes four studies by Bryant et al focused on ASD

REASON FOR EXCLUSION: More than 2 years old; research on children and adolescents not aggregated

Kornør, H., Winje, D. Ekeberg, Ø., Weisæth, L., Kirkehei1, I., Johansen, K., Steiro, A. (2008). Early trauma-focused cognitive-behavioural therapy to prevent chronic post-traumatic stress disorder and related symptoms: A systematic review and meta-analysis. *BMC Psychiatry*, 8(81), doi:10.1186/1471-244X-8-81

REASON FOR EXCLUSION: More than 2 years old; research on children and adolescents not aggregated

Litz, B.T. & Bryant, R.A. (2009). Early cognitive behavioral interventions for adults. In E.B. Foa, T.M. Keane, M.J. Friedman, J.A. Cohen (Eds). Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies 2nd Edition. New York: the Guilford Press

REASON FOR EXCLUSION: No formal meta-analysis reported; research on children and adolescents not aggregated

National Collaborating Centre for Mental Health (2005). The Management of PTSD in Adults and Children in Primary and Secondary Care. London, UK: Royal College of Psychiatrists & British Psychological Society

REASON FOR EXCLUSION: More than 2 years old

Ponniah, K., Hollon, S.D. (2009). Empirically supported psychological treatments for adult acute stress disorder and posttraumatic stress disorder: a review. *Depression and Anxiety*, 26, 1086-1109

REASON FOR EXCLUSION: No formal meta-analysis reported; research on children and adolescents not aggregated

Roberts, N.P., Kitchiner, N.J. Kenardy, J., Bisson, J.I. (2009). Systematic review and meta-analysis of multiple-session early interventions following traumatic events. *American Journal of Psychiatry*, 166, 293-301

REASON FOR EXCLUSION: Same author team published a more detailed report as a Cochrane review; research on children and adolescents not aggregated

Roberts, N.P., Kitchiner, N.J., Kenardy, J., Bisson, J.I. (2010a). Early psychological interventions to treat acute traumatic stress symptoms. Cochrane Database of Systematic Reviews, Issue 3.

REASON FOR EXCLUSION: research on children and adolescents not aggregated

Roberts, N.P., Kitchiner, N.J. Kenardy, J., Bisson, J.I. (2010b). Multiple session early psychological interventions for the prevention of posttraumatic stress disorder. *Cochrane Database of Systematic Reviews*, Issue 4.

REASON FOR EXCLUSION: focuses on psychological interventions for people without symptoms of acute stress; research on children and adolescents not aggregated

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Psychological interventions vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	No data

Narrative description of the studies that went into analysis

The most recent systematic review of relevant studies identified was: Brymer et al (2009). Acute interventions for children and adolescents. In E. Foa, T.M. Keane, M.J. Friedman, J.A. Cohen (2009). *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*. Guilford Press: New York, NY. This systematic review identified three randomized controlled trials with serious study limitations, and did not perform a meta-analysis. One trial (Yule, 1992) evaluated 1-day debriefing provided 10 days post a shipping disaster and followed children ($n_{treatment}$=24, $n_{control}$=15; aged 14-16 years) 5-9 months posttreatment, and found a between group effect size of 1.09 for PTSD symptoms. A second trial (Chapman et al, 2001) evaluated art

therapy treatment provided to children aged 7 to 17 years within days after exposure at a pediatric trauma unit. No statistically significant differences were found on PTSD symptoms between the treatment group (n=31) and a control group (n=27) at 1 week and 1-month periods. The third study (Stallard et al, 2006) evaluated a modified debriefing intervention delivered approximately 4 weeks after road traffic incidents. No statistically significant differences were found on PTSD symptoms between the treatment (n=82) and control group (n=76) at 8-month follow-up.

The systematic review and meta-analysis (Kramer and Landolt, 2011) identified by one of the peer reviewers of this profile included two studies investigating the efficacy of early psychological interventions based on the principles of CBT, and two studies investigating the efficacy of early psychological interventions based on the principles of psychoeducation.

Early psychological interventions based on the principles of CBT

The study carried out by Berkowitz and colleagues (2011) evaluated the efficacy of a four-session, caregiver-child intervention to prevent the development of chronic PTSD provided within 30 days of exposure to a potentially traumatic event. The study carried out by Zehnder and colleagues (2010) evaluated the efficacy of a single-session early psychological manualised intervention provided to the child and at least one parent around 10 days after the child's involvement in a road traffic accident.

Berkowitz and colleagues (2011) randomized 106 (53 experimental and 53 control intervention consisting of 4 sessions of a CBT-inspired parent-child intervention, including psycho-education, assessment of symptoms, improving parent-child communication and improving coping) children aged 7-17 years exposed to a potentially traumatic event, and outcomes were assessed at post-treatment and at 3 months. At follow-up, 23 out of 106 children were lost. In terms of efficacy, it found that the intervention group demonstrated significantly lower posttraumatic and anxiety scores than the comparison group, and significantly fewer full and partial PTSD diagnoses. Limitations of this study includes high attrition rate and use of the PTSD-RI instrument as both part of the intervention and an outcome measure.

Zehnder and colleagues (2010) randomized 101 (51 experimental and 50 control intervention consisting of standard medical care) children aged 7-16 years exposed to a road traffic accident, and outcomes were assessed at 2 and 6 months. At follow-up, only two patients were lost. In terms of efficacy, it found no significant differences concerning PTSD symptoms at 2 or 6 months. A subgroup analysis by age suggested that the intervention may be useful in preadolescent children in decreasing depressive symptoms and behavioral problems.

Early psychological interventions based on the principles of psychoeducation

The study carried out by Kenardy and colleagues (2008) evaluated the efficacy of information booklets (which normalize the common stress reaction in children following trauma and provide basic self-help advice) provided to participants within 72 hours of the initial trauma. The study carried out by Cox and colleagues (2010) evaluated the efficacy of an information provision web-based early intervention based on cognitive and resilience theories.

Kenardy and colleagues (2008) performed a cluster randomized trial with two hospitals: one provided the experimental intervention to 33 children (mean age 10 years) and the second one provided standard care to 70 children (mean age 10 years) admitted to pediatric units following accidental traumatic injury. Outcomes were assessed at 1 and 6 months. Only 65 out of 103 children were evaluated at follow-up. In terms of post-trauma symptoms of intrusion and avoidance, it found no efficacy of the experimental intervention. Limitations of this study includes high attrition rate and availability of two clusters only, which may have affected the randomization process as two clusters may be insufficient to assure random distribution of measured and unmeasured confounders.

Cox and colleagues (2010) randomized 85 (44 experimental and 41 control intervention consisting of standard care) children aged 7-16 years exposed to unintentionally injury, and outcomes were assessed at 4-6 weeks and at 6 months. At follow-up, outcome data were available for 29 out of 44 children randomized to the experimental intervention and for 27 out of 41 children randomized to the control intervention. In terms of efficacy, the analysis which included completers revealed that children in the experimental group reported improved anxiety, while the analysis which employed an intention-to-treat approach failed to reveal a positive effect of the intervention group. The main limitations of this study is the high attrition rate in both the experimental and control arm.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	A systematic review of evidence identified two studies investigating the efficacy of early psychological interventions based on the principles of CBT, and two studies investigating the efficacy of early psychological interventions based on the principles of psychoeducation. While the two studies on psychoeducation did not provide positive findings, one of the two studies on CBT suggested that an intervention consisting of 4 sessions of parent-child focused intervention may be

	effective in lowering posttraumatic and anxiety scores. Limitations of this study include a small sample size (106 children) and high attrition rate. The evidence is therefore inconclusive and it is uncertain if such interventions may have a beneficial effect in preventing disorders, decreasing symptom severity or improving functioning after intervention. One randomized study on art therapy did not find an effect of intervention and two studies on debriefing found conflicting results. All studies had serious limitations.
Harms	There is no systematic review of evidence on potential negative consequences of harmful effects of early psychological interventions in children and adolescents with acute traumatic stress symptoms.

Value and preferences	
In favour	The possibility of lowering acute traumatic stress symptoms and preventing PTSD is an important value.
Against	Many people with acute traumatic stress symptoms recover over time without intervention. It may be worthwhile waiting 1-3 months to see who recovers naturally and only offer intervention to those who have disabling symptoms that remained the same or have worsened (c.f. NICE Guidelines).

Feasibility (including economic consequences)	Most staff in PHC in LMIC have not received extensive training in communication skills and basic emotional support. Any additional training in early psychological interventions would require resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources. Large numbers of PHC attenders suffer from acute traumatic stress symptoms (e.g. as a result of injury), especially after mass events that have numerous survivors. It would not be feasible to deliver CBT to all. The limited available studies were conducted in industrialized countries.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes No
Are the expected values and preferences clearly in favour of the recommendation?	Yes No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 2

On the basis of available evidence, no specific recommendation can be made on early psychological interventions (covering problem-solving counseling; relaxation; psycho-education; eye movement desensitization and reprocessing (EMDR), and cognitive behavioural therapy (CBT) for children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

3. Acute Traumatic Stress Symptoms (first month): Pharmacological Interventions - Adults

Q3. For adults with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do pharmacological interventions (benzodiazepines and anti-depressants) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Acute traumatic stress symptoms in the current scoping question refer to symptoms of intrusion, avoidance and hyperarousal - when these are associated with significant impairment in daily functioning - in the first month after a potentially traumatic event. In terms of nosology, these symptoms can be part of

(a) DSM-IV Acute Stress Disorder (not included in ICD) , which in DSM is limited to one month of the event and

(b) ICD-10 Posttraumatic Stress Disorder, which in ICD can be diagnosed within one month of the event.

Other symptoms of acute stress, including hyperventilation, conversion and dissociative symptoms, and secondary nonorganic nocturnal enuresis in children, are the focus of other evidence profiles of these guidelines.

Pharmacological treatments, especially benzodiazepines, are commonly prescribed for people suffering symptoms of acute distress. However, there is currently no consensus on the effectiveness of pharmacological treatments between different clinical practice guidelines,[11] making this an important scoping question.

[11] Forbes et al (2010). A guide to guidelines for the treatment of PTSD and related conditions. Journal of Traumatic Stress, 23(5), 537-52

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with acute traumatic stress symptoms[12], within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Pharmacological interventions
- **Comparison:** Placebo/active pharmacological treatment (benzodiazepines and anti-depressants)
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

Details of commissioned systematic review

NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement, PTSD and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results of studies relevant to adults with acute traumatic stress symptoms are discussed.

Types of studies

All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTMH PTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated trauma focussed psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

[12] *Acute traumatic stress symptoms* in this scoping question refer to symptoms of intrusion, avoidance and hyperarousal associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

Types of participants

All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions

Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.

The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self-rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy

We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR "pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria
- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, presence of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Results

No RCTs of pharmacotherapy for adults with acute traumatic stress were identified.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Pharmacological interventions vs. Placebo/active pharmacological treatment	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	In adults with acute traumatic stress within the first month after experiencing a potentially traumatic stressor, there is no evidence on the effect of benzodiazepines and antidepressants on symptom

	severity, functioning and presence of disorder. A classic non-RCT study by Gelpin and colleagues (1996; J Clin Psychiatry) showed no benefits of benzodiazepines between 13 matched pairs of recent trauma survivors.
Harms	In adults with acute traumatic stress, there is no evidence on the adverse effects of benzodiazepines and antidepressants. For benzodiazepines, in addition to the evidence from randomized trials, data from observational and epidemiological studies highlighted a risk of tolerance and dependence. According to NICE UK, one of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (10–30% of chronic benzodiazepines users are physically dependent on them), and suffer a withdrawal syndrome when they stop taking them (50% of all users suffer withdrawal symptoms). The withdrawal syndrome includes anxiety, depression, nausea and perceptual changes. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects. The safety of psychotropic drugs in pregnancy and breastfeeding is not clearly established. In particular, exposure to benzodiazepines during the first trimester is associated with an increased risk of oral clefts, and exposure during the third trimester is associated with neonatal difficulties. For antidepressants, the risks of taking tricyclic antidepressants during pregnancy and when breastfeeding are better established than those of SSRIs and newer drugs. Antidepressants appeared not to be teratogenic, although SSRI exposure in late pregnancy may increase the risk of persistent pulmonary hypertension.

Value and preferences	

In favour	The possibility of decreasing symptoms of acute traumatic stress and improving functioning/coping in stressful environments are important values.
Against	Providing medication for acute traumatic stress may contribute to the medicalization of normal psychological reactions and contribute to dependence.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. To avoid the risks of harm referred to above, training of primary care practitioners may be necessary on responsible use of benzodiazepines. In many LMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge. Benzodiazepines are associated with low acquisition costs. Both generic tricyclic antidepressants and many generic selective serotonin reuptake inhibitors are associated with low acquisition costs. Diazepam (as a representative of the benzodiazepines) is included in the WHO list of essential medicines for the treatment of anxiety disorders. Amitriptyline (as a representative of the tricyclic antidepressants) and fluoxetine (*not* as a representative of SSRIs) are included in the WHO list of essential medicines for the treatment of depressive disorders. Diazepam is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies. Amitriptyline is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X (benzodiazepines & anti-depressants)**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X (benzodiazepines)** **No X (anti-depressants)**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X (benzodiazepines & anti-depressants)** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X (benzodiazepines & anti-depressants)** No

Final recommendation by the guideline panel

Recommendation 3

Benzodiazepines and antidepressants should not be offered to adults to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event

For benzodiazepines:
Strength of recommendation: strong
Quality of evidence: very low

For anti-depressants:
Strength of recommendation: standard
Quality of evidence: very low

Remarks

Clinicians should rule out concurrent disorders that may warrant treatment with benzodiazepines and antidepressants.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. In addition, question 1 (on psychological interventions for acute traumatic stress symptoms in adults) recommends that "cognitive-behavioural therapy (CBT) with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning." When combined, these recommendations imply that psychological first aid and (where resources exist) CBT should be considered in adults with acute traumatic stress symptoms associated with impairment in daily functioning in the first month after a potentially traumatic event.

4. Acute Traumatic Stress Symptoms (first month): Pharmacological Interventions – Children and Adolescents

Q4. For children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event, do pharmacological interventions (benzodiazepines and anti-depressants) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Acute traumatic stress symptoms in the current scoping question refer to symptoms of intrusion, avoidance and hyperarousal - when these are associated with significant impairment in daily functioning - in the first month after a potentially traumatic event. In terms of nosology, these symptoms can be part of

(a) DSM-IV Acute Stress Disorder (not included in ICD), which in DSM is limited to one month of the event and

(b) ICD-10 Posttraumatic Stress Disorder, which in ICD can be diagnosed within one month of the event.

Other symptoms of acute stress, including hyperventilation, conversion and dissociative symptoms, and secondary nonorganic nocturnal enuresis in children, are the focus of other evidence profiles of these guidelines.

Pharmacological treatments, especially benzodiazepines, are commonly prescribed for people suffering symptoms of acute distress. There is currently no consensus on the effectiveness of pharmacological treatments between different clinical practice guidelines,[13] making this an important scoping question.

[13] Forbes et al (2010). A guide to guidelines for the treatment of PTSD and related conditions. Journal of Traumatic Stress, 23(5), 537-52.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and adolescents with acute traumatic stress symptoms[14], within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Pharmacological interventions (benzodiazepines and anti-depressants)
- **Comparison:** Placebo/active pharmacological treatment
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

Details of commissioned systematic review

NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement, PTSD and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results studies relevant to children and adolescents with acute traumatic stress are discussed.

Types of studies

All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTMH PTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated trauma focussed psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded.

[14] *Acute traumatic stress symptoms* in this scoping question refer to symptoms of intrusion, avoidance and hyperarousal associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

Types of participants
All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions
Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.
The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy
We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR

"pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria
- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, presence of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Results

No RCTs of pharmacotherapy for children and adolescents with acute traumatic stress were identified.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Pharmacological interventions vs. placebo/active pharmacological treatment	Symptom severity	No data	
		Functioning	No data	
		Presence of disorder	No data	
		Adverse effects	No data	

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	In children and adolescents with acute traumatic stress, there is no evidence on the effect of benzodiazepines and antidepressants on symptom severity, functioning and presence of disorder.
Harms	In children and adolescents with acute traumatic stress, there is no evidence on the adverse effects of benzodiazepines and antidepressants. For benzodiazepines, in addition to the evidence from randomized trials, data from observational and epidemiological studies – mostly with adult populations - highlighted a risk of tolerance and dependence. According to NICE UK, one of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (10–30% of chronic benzodiazepines users are physically dependent on them), and suffer a withdrawal syndrome when they stop taking them (50% of all users suffer withdrawal symptoms). With regard to children and adolescents, very few rigorous studies have been conducted but dependency risks have been similarly reported (Witek et al, 2005, Psychiatric Quarterly, 76). The withdrawal syndrome includes anxiety, depression, nausea and perceptual changes. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects. For antidepressants, evidence collected in children with depression has highlighted safety and tolerability concerns, including the increased risk of suicide ideas and behaviour (see mhGAP, 2010) with some SSRIs. Tricyclics are not recommended in children and adolescents. No data on the long-term consequences of psychotropic drug exposure in children and adolescents

	are available.

Value and preferences	
In favour	
Against	Children and adolescents – still in development – should only be exposed to drugs if other effective treatment options have been tried, if the condition is sufficiently severe and treatment is likely to lead to a substantial improvement and if information about long-term consequences is available. Providing medication for acute stress may contribute to the medicalization of normal psychological reactions and may contribute to dependence.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. Training is required to properly assess acute stress in children and adolescents with due attention to any cultural variations that may exist. In many LAMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge. Benzodiazepines are associated with low acquisition costs. Both generic tricyclic antidepressants and many generic selective serotonin reuptake inhibitors are associated with low acquisition costs. Fluoxetine is included in the WHO list of essential medicines for the treatment of depressive disorders in adolescents only (> 8 years). Amitriptyline and diazepam are included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of

	people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 4

Benzodiazepines and antidepressants should not be offered to reduce acute traumatic stress symptoms associated with significant impairment in daily functioning in children and adolescents.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute traumatic stress symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event.

5. Acute (Secondary) Insomnia (first month): Early Psychological Interventions - Adults

Q5. For adults with acute (secondary) insomnia in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Insomnia is commonly associated with mood and anxiety disorders, including in the context of exposure to potentially traumatic events.[15] It is noted that insomnia may also have physical and other psychological causes, for example cardio vascular disorders, alcohol use disorder, and (prescription and non prescription) drug use disorder.

There is uncertainty how to treat adults with insomnia in the first month after a potentially traumatic event.[16] This type of insomnia is referred to as secondary insomnia (primary insomnia occurs when somatized tension and learned sleep-incompatible behaviors play a predominant role in the maintenance of poor sleep). Given the time-frame of this scoping question (within the first month of exposure to a potentially traumatic event), the focus is here on 'acute (secondary) insomnia'.[17] [18] This scoping question focuses on early psychological interventions, i.e. interventions delivered in the first month after exposure to a potentially traumatic event.

[15] Lamarche & De Koninck (2007). Sleep disturbance in adults with Posttraumatic Stress Disorder. *Journal of Clinical Psychiatry*, 68, 1257-70
[16] Harvey, Jones & Schmidt (2003). Sleep and Posttraumatic Stress Disorder: a review. *Clinical Psychology Review*, 23, 377-407
[17] Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
[18] Wang, Wang & Tsai (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults, after the first month of a potentially traumatic event
- **Interventions:** Early psychological interventions
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted on March 6th 2012 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("insomnia" AND "stress" OR "trauma"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "insomnia". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years), focusing on psychological and social treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword, and searched clinical practice guidelines related to managing acute stress reactions. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES (SEE BELOW: INCLUDED IN NARRATIVE DESCRIPTION)

De Niet, G.J., Tiemens, B.G., Kloos, M.W., Hutschemaekers, G.J.M. (2009). Review of systematic reviews about the efficacy of non-pharmacological interventions to improve sleep quality in insomnia. *International Journal for Evidence-Based Health Care*, 7, 233-42

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Aurora, R.N., Zak, R.S., Auerbach, S.H., Casey, K.R., Chowdhuri, S., Karippot, A., Maganti, R.K., Ramar, K., Kristo, D.A., Bista, S.R., Lamm, C.I., Morgenthaler, T.I. (2010). Best practice guide for the treatment of nightmare disorder in adults. *Journal of Clinical Sleep Medicine*, 6(4), 389-401
REASON FOR EXCLUSION: focuses on nightmares specifically, only searched PubMed, and identified only studies with chronic nightmares

Belleville, G., Cousineau, H., Levrier, K., St.-Pierre-Delorme, M. (2011). Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety. *Clinical Psychology Review*, 31, 638-52
REASON FOR EXCLUSION: This study focuses on effectiveness of treatment of insomnia on associated anxiety symptoms

Montgomery, P. & Dennis, J.A. (2009). Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*, 1
REASON FOR EXCLUSION: focuses on a specific population sub-group (elderly)

Montgomery, P. & Dennis, J.A. (2009). Physical exercise for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*, 1
REASON FOR EXCLUSION: focuses on a specific population sub-group (elderly)

Nappi, C.M., Drummond, S.P.A. & Hall, J.M.H. (in press). Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*, doi:10.1016/j.neuropharm.2011.02.029
REASON FOR EXCLUSION: no methodology of a systematic review is reported

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of Clinical Sleep Medicine, 15(5), 487-504
REASON FOR EXCLUSION: focuses on chronic insomnia

Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
REASON FOR EXCLUSION: no methodology of a systematic review is reported

Uchiyama, M., Inoue, Y., Uchimura, N., Kawamori, R., Kurabayashi, M., Kario, K., Watada, H. (2011). Clinical significance and management of insomnia. *Sleep and Biological Rhythms*, 9, 63-72
REASON FOR EXCLUSION: inclusion Japanese consensus statement, but no methodology of a systematic review is reported

Wang, M-Y, Wang, S-Y & Tsai, P-S. (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564
REASON FOR EXCLUSION: focuses on primary insomnia

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Early psychological intervention or acute secondary insomnia	Symptom severity (sleep quality) Functioning Presence of disorder Adverse effects	No data No data No data No data	No data

Narrative description of the studies that went into analysis

De Niet and colleagues provide a broad systematic review of previous systematic reviews and meta-analyses of diverse non-pharmacological treatments for insomnia, including secondary insomnia. Databases searched included Database of Abstracts of Reviews of Effects (2002-July 2008), the Cochrane Database of Systematic Reviews (200 – July 2008), and PubMed (1955 – July 2008), and identified reviews were rated using the Overview Quality Assessment Questionnaire. Of the reviews that were identified by this study that focused on insomnia (and not chronic or primary insomnia specifically), there was sufficient data to suggest the effectiveness of multicomponent cognitive behavioral therapy (CBT), paradoxical intention (consists of persuading a person to stay awake;. based on the assumption that performance anxiety prevents proper sleep), progressive muscle relaxation, relaxation training, and stimulus control (see below). All these comparisons were extracted from De Niet's review's reference #25: Murthag (1995). Identifying effective psychological treatments for insomnia: a meta-analysis. *Journal of Consulting & Clinical Psychology*, 63, 79-89. The studies included in Murthag (1995) were described in a way that would not allow entering results in a GRADE table. Therefore, the results of Murthag (1995) are described in a narrative style. These studies were not conducted with acutely traumatized adults in low and middle income countries, and evidence is therefore indirect.

Intervention descriptions of studies that went into analysis:

- Multicomponent CBT: aims to improve sleep by changing disadvantageous beliefs, attitudes, and behaviors. Includes cognitive therapy, one or more behavioral techniques, relaxation techniques and sleep hygiene education (a list of recommended behaviors and sleep-related factors assumed beneficial for a good night's rest)
- Paradoxical intention: persuading a person to engage in his/her most feared behavior – staying awake, based on the assumption that performance anxiety prevents proper sleep
- Progressive muscle relaxation: a method of tensing and relaxing different muscle groups throughout the body
- Relaxation training: can involve diverse methods aimed at reducing tension, e.g. autogenic training (daily visualization practice), biofeedback (use of electronic sensors that make state of relaxation visible), music-assisted relaxation.
- Stimulus control: a set of instructions designed to re-associate bed and bedroom temporal stimuli with rapid sleep onset

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	A total of 66 studies, including randomized and non-randomized trials, assessed the efficacy of multicomponent cognitive behavioral therapy, paradoxical intention, progressive muscle relaxation, relaxation training, and stimulus control. A total of 1,538 adults with insomnia received psychological interventions and 369 adults with insomnia received no treatment. According to the study authors, the meta-analysis indicated that psychological interventions (multicomponent cognitive behavioral therapy, paradoxical intention, progressive muscle relaxation, relaxation training, and stimulus control) produced considerable enhancement of sleep patterns (for definitions see above). Average treatment effect reduced sleep onset latency from 61 to 37 minutes, increased total sleep time from 5.65 to 6.18 hours, and decreased the number of awakenings from 1.63 to 0.44. Although it was not possible to analyze this meta-analysis in a GRADE table, the confidence in estimate may be VERY LOW, as data from randomized trials are lumped together with data from non-randomized studies. There is no systematic review with data for the outcomes functioning, presence of disorder and adverse effects
Harms	There is no systematic review of evidence on potential negative consequences of psychological interventions in adults with acute secondary insomnia in the first month after a potentially traumatic

	event.

Value and preferences	
In favour	Severe insomnia undermines the capacity of persons to carry out basic tasks for day to day living and may result in depression or self-medication such as using excess alcohol or other substances. Self-medication and substance use may continue even when insomnia, ASD or PTSD symptoms decrease over time. After certain recent events (e.g. exposure to war or natural disaster) it is important for the survivor to sleep sufficiently to be able to carry out essential day to day activities
Against	The overall impact on number of hours of sleep per night is limited (on average only half an hour per night).

Feasibility (including economic consequences)	Most staff in PHC in LMIC have not received extensive training in communication skills and basic emotional support. Any additional training in multicomponent cognitive behavioral therapy, paradoxical intention, progressive muscle relaxation, relaxation training, and stimulus control requires resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources. Multicomponent cognitive behavioral therapy (CBT) (which includes relaxation training, sleep hygiene and cognitive techniques), paradoxical intention, progressive muscle relaxation, relaxation training, and stimulus control differ in level of complexity. While relaxation training and sleep hygiene may be more easily learned and taught to persons, the cognitive techniques of CBT are more resource and time intensive. It is noted that relaxation training is already recommended in mhGAP as an adjunct treatment for depression, and would thus not necessary require additional investments.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 5

Relaxation techniques (e.g., progressive muscle relaxation or cultural equivalents) and advice about sleep hygiene (including advice about psychostimulants, such as coffee, nicotine, and alcohol) should be considered for adults with acute (secondary) insomnia in the first month after exposure to a potentially traumatic event.

Strength of recommendation: Standard
Quality of evidence: very low

Remarks

In many settings,relaxation may be made available through existing cultural practices.

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depressive disorder, and, in adolescents, alcohol or drug use disorder.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. When combined, these recommendations imply that psychological first aid, relaxation techniques and advice about sleep hygiene should be considered in adults with acute (secondary) insomnia in the first month after a potentially traumatic event.

6. Acute (Secondary) Insomnia (first month): Early Psychological Interventions – Children and Adolescents

Q6. For children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Insomnia is commonly associated with mood and anxiety disorders, including in the context of exposure to potentially traumatic events.[19] It is noted that insomnia may also have physical and other psychological causes, for example cardio vascular disorders, alcohol use disorder, and (prescription and non-prescription) drug use disorder.

There is uncertainty how to treat children and adolescents with insomnia in the first month of a potentially traumatic event.[20] This type of insomnia is referred to as secondary insomnia (primary insomnia occurs when somatized tension and learned sleep-incompatible behaviors play a predominant role in the maintenance of poor sleep). Given the time-frame of this scoping question (within the first month of exposure to a potentially traumatic event), the focus is here on 'acute (secondary) insomnia'.[21][22]

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and Adolescents after the first month of a potentially traumatic event
- **Interventions:** Early Psychological Interventions

[19] Lamarche & De Koninck (2007). Sleep disturbance in adults with Posttraumatic Stress Disorder. *Journal of Clinical Psychiatry*, 68, 1257-70
[20] Harvey, Jones & Schmidt (2003). Sleep and Posttraumatic Stress Disorder: a review. *Clinical Psychology Review*, 23, 377-407
[21] Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
[22] Wang, Wang & Tsai (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564

- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted on March 6th 2012 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("insomnia" AND "stress" OR "trauma"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "insomnia". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years), focusing on psychological and social treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword, and searched clinical practice guidelines related to managing acute stress reactions. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Bruni, O. & Novelli, L. (2010). Sleep disorders in children. *BMJ Clinical Evidence*, 9, 2304

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Aurora, R.N., Zak, R.S., Auerbach, S.H., Casey, K.R., Chowdhuri, S., Karippot, A., Maganti, R.K., Ramar, K., Kristo, D.A., Bista, S.R., Lamm, C.I., Morgenthaler, T.I. (2010). Best practice guide for the treatment of nightmare disorder in adults. *Journal of Clinical Sleep Medicine*, 6(4), 389-401
REASON FOR EXCLUSION: focuses on nightmares specifically, only searched PubMed, and identified only studies with chronic nightmares; focused on adults only.

Belleville, G., Cousineau, H., Levrier, K., St.-Pierre-Delorme, M. (2011). Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety. *Clinical Psychology Review*, 31, 638-52
REASON FOR EXCLUSION: earlier study found that CBT improves sleeping problems when treating anxiety disorders (no change in effect size for different anxiety disorders). This study focuses on effectiveness of treatment of insomnia on associated anxiety symptoms; focused on adults only.

De Niet, G.J., Tiemens, B.G., Kloos, M.W., Hutschemaekers, G.J.M. (2009). Review of systematic reviews about the efficacy of non-pharmacological interventions to improve sleep quality in insomnia. *International Journal for Evidence-Based Health Care*, 7, 233-42
REASON FOR EXCLUSION: Focused on adults only.

Montgomery, P. & Dennis, J.A. (2009). Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*, 1
REASON FOR EXCLUSION: Focused on adults only.

Montgomery, P. & Dennis, J.A. (2009). Physical exercise for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*, 1
REASON FOR EXCLUSION: Focused on adults only.

Nappi, C.M., Drummond, S.P.A. & Hall, J.M.H. (in press). Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*, doi:10.1016/j.neuropharm.2011.02.029
REASON FOR EXCLUSION: no methodology of a systematic review is reported; no studies with children and adolescents discussed

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of Clinical Sleep Medicine, 15(5), 487-504
REASON FOR EXCLUSION: focuses on chronic insomnia; focused on adults only.

Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
REASON FOR EXCLUSION: no methodology of a systematic review is reported

Uchiyama, M., Inoue, Y., Uchimura, N., Kawamori, R., Kurabayashi, M., Kario, K., Watada, H. (2011). Clinical significance and management of insomnia. *Sleep and Biological Rhythms*, 9, 63-72
REASON FOR EXCLUSION: inclusion Japanese consensus statement, but no methodology of a systematic review is reported

Wang, M-Y, Wang, S-Y & Tsai, P-S. (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564
REASON FOR EXCLUSION: focuses on primary insomnia

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Early psychological intervention for acute secondary insomnia	Symptom severity (sleep quality) Functioning Presence of disorder Adverse effects	Bruni & Novelli, 2010 No data No data No data	Bruni & Novelli provide a systematic review of RCTs with evidence evaluated through GRADE methodology

Narrative description

A systematic review conducted by Bruni & Novelli for Clinical Evidence, published by the British Medical Journal (Bruni & Novelli, 2010. Sleep disorders in Children. Clinical Evidence, 9, 2304) was identified. This systematic review searched the following databases up to September 2009: Medline, Embase, the Cochrane Library, as well as harm alerts from US and UK regulatory bodies. This review found 13 randomized controlled trials that met inclusion criteria (a focus on dyssomnia – defined as pediatric insomnia or excessive daytime sleepiness- and parasomnia). Evidence from these studies was subsequently evaluated using GRADE methodology. The systematic review identified 3 randomized controlled trials relevant to this scoping question:

- 2 RCTs evaluating extinction (through a standardized sleep program) and graduated extinction vs no treatment (in otherwise healthy children) (32, 34)
- 1 RCT evaluating sleep hygiene vs no treatment (in otherwise healthy children) (38)

No studies concerned children with insomnia in the first month after exposure to potentially traumatic events, and the evidence must therefore be considered indirect.

In this systematic review:

- *Standardized sleep program* (reference 32) (based on extinction) consisted of: “8 page booklet — "Parent Guide" (that involved organised bedtime routines, procedures for settling the child, and for the handling of crying, calling out, and getting out of bed) plus a 1-hour interview. Telephone calls each day at first, then as needed. Total staff attention: 2 to 3 hours/family”

& 8-page booklet "Parent Guide" (that involved organized bedtime routines, procedures for settling the child, and for the handling of crying, calling out, and getting out of bed) plus any questions answered. Total staff attention: 5 to 10 minutes/family

- *Graduated extinction* (reference 34) consisted of: “Parents put the child to bed after pre-bedtime routines, said "good night", and left the room. If the child cried or fussed, the parents could make a brief (30 seconds) check after 5 minutes, then left the room. Brief checks could be made after another 10 minutes, then at 15-minute intervals if the child was still crying. No checks were made after the child stopped crying. Checking intervals were lengthened by 5 minutes each night. If the child left the bedroom, he/she was given 1 warning each night. If the child left the bedroom a second time, the parent held the door closed for a short interval each time. The intervals were progressively lengthened until the child stayed in bed. Once the child stayed in bed, the door was left open. Parents explained the routine to the child before treatment, and the child's successful behaviour was rewarded with praise and small rewards.” & (reference 35) “The therapist discussed certain techniques with the parent: Extinction and graduated extinction procedures such as checking and gradual withdrawal, and stimulus-control procedures and positive reinforcement.”
- *Extinction* (reference 34) consisted of: “Parents put the child to bed after pre-bedtime routines, said "good night", left the room, and did not return. Parents could check the child briefly in the night if they work, then leave and not return. If the child left the bedroom, they were given 1 warning each night. If the child left the bedroom a second time, they were kept in the room by the parents by closing the door or using a child gate. The door was kept closed until the child was asleep. Parents explained the routine to the child before treatment, and the child's successful behavior was rewarded with praise and small rewards”
- *Sleep hygiene* (reference 38) consisted of a bed time routine: “The bedtime routine included one week of usual routine, followed by 2 weeks of a 3-step bedtime routine of bathing, applying lotion, and quiet activities such as cuddling with the lights out within 30 minutes of the end of the bath”.

GRADE Table

Author(s): C Barbui and W Tol
Date: 2012-09-18
Question: Should sleep hygiene vs no treatment be used in children and adolescents after the first month of a potentially traumatic event?
Settings:
Bibliography: Mindell 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sleep hygiene**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Symptom severity[1,2] (Better indicated by lower values)												
1[3]	randomised trials	very serious[4]	no serious inconsistency[5]	no serious indirectness	no serious imprecision	none	0[6]	-	-	MD 0 higher (0 to 0 higher)[1,2]	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Prevention of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] Infant Study: Sleep latency (min) at week 3: Control 14.9 (8.69), Intervention 12.4 (9.65). Number of night wakings: Control 1.4 (0.97), Intervention 1.0 (0.76) Duration of night wakings (min): Control 18.9 (21.33), Intervention 12.6 (11.79). On the basis of these results the authors concluded that instituting a consistent nightly bedtime routine is beneficial in improving multiple aspects of infant sleep, resulting in shorter sleep onset latency, decreased wakefulness after sleep onset, and increased sleep consolidation.

[2] Toddlers Study: Sleep latency (min): Control 2.6 (13.50), Intervention 16.3 (12.05). Number of night wakings: Control 1.0 (1.01), Intervention 0.6 (0.71). Duration of night wakings (min): Control 13.3 (15.65), Intervention 8.2 (9.85). On the basis of these results the authors concluded that instituting a consistent nightly bedtime routine is beneficial in improving multiple aspects of toddler sleep, resulting in shorter sleep onset latency, decreased wakefulness after sleep onset, and increased sleep consolidation.

[3] Mindell 2009 as identified by BMJ Clinical Evidence 2010

[4] Two age-specific 3-week studies are described. In the first it is reported that "134 families were assigned" and the term random allocation is not mentioned. In the second it is reported that 133 families were randomly assigned. No further details are reported.

[5] Only one study included in the analysis.

[6] There were originally 209 families in the infant study who completed the study; of these, 206 (98.6%) had complete data. Similarly, there were complete data for 199 (94.8%) of the original 210 families in the toddler study.

Author(s): C. Barbui, W. Tol
Date: 2012-09-24
Question: Should extinction/graduated extinction vs no treatment be used in children and adolescents after the first month of a potentially traumatic event?
Settings:
Bibliography: Reid 1999, Seymour 1989 (from BMJ Clinical Evidence 2010)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Extinction/graduated extinction**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	0[5]	-	-	MD 0 higher (0 to 0 higher)[6]	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Prevention of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence					none	0	-	-	MD 0 higher (0		IMPORTANT

	available									to 0 higher)		

[1] Reid 1999, Seymour 1989 (from BMJ Clinical Evidence 2010)
[2] random assignement and concealment of allocation not described, no blindness.
[3] Two studies included in the analysis but no meta-analysis was carried out.
[4] Small samples in both groups.
[5] Reid 1999: 43 participants. Seymour 1989: 45 participants.
[6] Seymour 1989, experimental group (standardized sleep programme, i.e. an 8-page Parent Guide plus an hour long interview to establish the programme, followed by telephone calls each day at first and as needed thereafter): Minutes awake each night 15.2 (SD 15.2). Control group (no treatment): Minutes awake each night 41.5 (SD 32.9). Reid 1999, experimental group (standard ignoring treatment/graduated ignoring treatment): Average Weekly Number of Good Bedtimes: 5.36 (1.91). Control group (no treatment): Average Weekly Number of Good Bedtimes: 0.62 (1.63).

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	The evidence is very limited, so the clinical benefit of organizing bedtime routines, procedures for settling the child and for the handling of crying is unclear.
Harms	The evidence is very limited, so the harms of organizing bedtime routines, procedures for settling the child and for the handling of crying are unclear.

Value and preferences	
In favour	Severe insomnia undermines the capacity of persons to carry out basic tasks for day to day living. After some recent potentially traumatic event (e.g. exposure to war or natural disaster) it is important for the survivor to sleep sufficiently to be able to carry out essential survival tasks
Against	

Feasibility (including economic consequences)	

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits*	Yes **No X**
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 6

On the basis of available evidence, no specific recommendation can be made for early psychological interventions in children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: low

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. This includes assessment of the child's perception as to why insomnia may be present. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

Relaxation techniques and advice about sleep hygiene (see question 5 on psychological interventions for insomnia in adults) may be safe, feasible and potentially effective strategies in adolescents (age 10-17 years).

Health care providers should explain that insomnia is common after exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessedfor other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depressive disorder, and, in adolescents, alcohol or drug use disorder.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made, psychological first aid should be considered in children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

7. Acute (Secondary) Insomnia (first month): Pharmacological Interventions – Adults

Q7. For adults with acute (secondary) insomnia in the first month after a potentially traumatic event, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Insomnia is commonly associated with mood and anxiety disorders, including in the context of exposure to potentially traumatic events.[23] It is noted that insomnia may also have physical and other psychological causes, for example cardio vascular disorders, alcohol use disorder, and (prescription and non prescription) drug use disorder.

There is uncertainty how to treat adults with insomnia in the first month of a potentially traumatic event.[24] This type of insomnia is referred to as secondary insomnia (primary insomnia is diagnosed when somatized tension and learned sleep-incompatible behaviors play a predominant role in the maintenance of poor sleep). Given the time-frame of this scoping question (within the first month of exposure to a potentially traumatic event), the focus is here on 'acute insomnia'.[25,26]

Although benzodiazepines are commonly used, health care providers have expressed worries on iatrogenic effects of these drugs,[27] making this an important scoping question.

[23] Lamarche & De Koninck (2007). Sleep disturbance in adults with Posttraumatic Stress Disorder. *Journal of Clinical Psychiatry*, 68, 1257-70
[24] Harvey, Jones & Schmidt (2003). Sleep and Posttraumatic Stress Disorder: a review. *Clinical Psychology Review*, 23, 377-407
[25] Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
[26] Wang, Wang & Tsai (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564
[27] De Niet et al (2009). Review of systematic reviews about the efficacy of non-pharmacological interventions to improve sleep quality in insomnia. *Interational Journal for Evidence Based Healthcare*, 7, 233-42

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with insomnia, within the first month of a potentially traumatic event
- **Interventions:** Benzodiazepines
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted on March 6th 2012 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("insomnia" AND "stress" OR "trauma"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "insomnia". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years), focusing on psychological and social treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Nappi, C.M., Drummond, S.P.A. & Hall, J.M.H. (2012). Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*, doi:10.1016/j.neuropharm.2011.02.029
Note: This review does not provide a meta-analysis, but identifies less recent systematic reviews that included relevant meta-analyses

Van Liempt, S., Vermetten, E., Geuze, E. & Westenberg, H.G.M. (2006). Pharmacotherapy for disordered sleep in post-traumatic stress disorder: a systematic review. *International Clinical Psychopharmacology*, 21, 193–202
Note: Older than 2 years, but this seems the most up-to-date relevant review with data reported

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Alessi, C. & Vitiello, M.V. (201). Insomnia (primary) in older people. *Clinical Evidence*, 10, 2302
REASON FOR EXCLUSION: focuses on primary insomnia, and on a specific population sub-group (older adults)

Aurora, R.N., Zak, R.S., Auerbach, S.H., Casey, K.R., Chowdhuri, S., Karippot, A., Maganti, R.K., Ramar, K., Kristo, D.A., Bista, S.R., Lamm, C.I., Morgenthaler, T.I. (2010). Best practice guide for the treatment of nightmare disorder in adults. *Journal of Clinical Sleep Medicine*, 6(4), 389-401
REASON FOR EXCLUSION: focuses on nightmares specifically, only searched PubMed, and identified only studies with chronic nightmares

Buscemi, N., Vandermeer, B, Friesen, C., Bialy, C., Tubman, M., Ospina, M., Klassen, T.P., Witmans, M. (2007). The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs
REASON FOR EXCLUSION: focuses on chronic insomnia, more than 2 years old

Dündar, Y., Boland, A., Strobl, J., Dodd, S., Haycox, A., Bagust, A., Bogg, J., Dickson, R & Walley, T. (2004). Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation. *Health, Technology, Assessment*, 8(24)
REASON FOR EXCLUSION: older than 2 years old

Hirst, A. & Sloan, R. (2009). Benzodiazepines and related drugs for insomnia in palliative care. *Cochrane Database of Systematic Reviews*, 4
REASON FOR EXCLUSION: focuses specifically on interventions in palliative care

National Institute for Clinical Excellence (2004). Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia.
REASON FOR EXCLUSION: older than 2 years Lack of actual data in the guidelines

Riemann, D. & Perlis, M.L. (2009). The treatments of chronic insomnia: A review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Medicine Reviews*, 13, 205-14
REASON FOR EXCLUSION: focuses specifically on chronic insomnia

Sateia, M.J. & Dowell, P.D. (2004). Insomnia. *Lancet*, 364, 1959-73
REASON FOR EXCLUSION: focuses specifically on chronic insomnia, and older than 2 years

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of Clinical Sleep Medicine, 15(5), 487-504
REASON FOR EXCLUSION: focuses on chronic insomnia, and older than 2 years

Silber, M.H. (2005). Chronic insomnia. *New England Journal of Medicine*, 353, 803-10
REASON FOR EXCLUSION: focuses on chronic insomnia, older than 2 years, and no systematic review methodology reported

Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
REASON FOR EXCLUSION: no methodology of a systematic review is reported

Uchiyama, M., Inoue, Y., Uchimura, N., Kawamori, R., Kurabayashi, M., Kario, K., Watada, H. (2011). Clinical significance and management of insomnia. *Sleep and Biological Rhythms*, 9, 63-72
REASON FOR EXCLUSION: inclusion Japanese consensus statement, but no methodology of a systematic review is reported

Wilson, S.J., Nutt, D.J. Alford, C., Argyropoulos, S.V. Baldwin, D.S., Bateson, A.N. et al (2009). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *Journal of Psychopharmacology*, 24(11), 1577-1600
REASON FOR EXCLUSION: represents a comprehensive and recent effort to make practice guidelines, consensus was reached where evidence was insufficient. However, data is not included in this paper and the Nappi et al (2012) review is more recent

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Pharmacological intervention for acute secondary insomnia	Symptom severity Functioning Presence of disorder Adverse effects	Van Liempt 2006 and Nappi 2012 identified Nowell 1996 and Holbrook 2000.	Nowell 1996 provides data on the efficacy of benzodiazepines versus placebo in chronic insomnia in general patient populations. Although there is an issue with directness (the focus here is on acute insomnia in the context of exposure to trauma) it

				represents the most recent meta-analysis with a focus on double-blind placebo-controlled trials only. Holbrook 2000 provides data on adverse effects.

Narrative description of the studies that went into analysis

Van Liempt and colleagues (2006) provide a systematic review of the efficacy of PTSD-related drugs, including benzodiazepines for PTSD-related sleep complaints. Forty eight articles were identified through searches in Medline, EMBASE, and the Cochrane Library from 1980 onwards. The authors conclude there is little evidence to support the use of benzodiazepines for trauma-related nightmares and insomnia. Nappi, Drummond and Hall (2012) published an update of this review, which identified two further studies: one small randomized controlled trial comparing zolpidem with hypnotherapy in persons already receiving SSRIs and supportive psychotherapy (hypnotherapy was more effective with regard to sleep quality and PTSD symptoms); and one 6-month cohort study with Australian Vietnam Veterans in which no pre-post differences were identified. This systematic review does not provide a meta-analysis of these data.

GRADE Table

Author(s): Corrado Barbui
Date: 2012-03-10
Question: Should benzodiazepines vs placebo be used in adults with insomia after the first month of a potentially traumatic event?
Settings:
Bibliography: Nowell 1996; Holbrook 2000

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Placebo	Relative (95% CI)	Absolute		
Sleep onset latency (Better indicated by higher values)												
18[1]	randomised trials	no serious risk of bias[2]	serious[3]	serious[4]	no serious imprecision	none	0[5]	-	-	Cohen's d 0.56 higher (0.41 to 0.71 higher)	□□□□ LOW	IMPORTANT
Total sleep time (Better indicated by higher values)												
17[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[6]	no serious imprecision	none	0[5]	-	-	Cohen's d 0.71 higher (0.55 to 0.87 higher)	□□□□ MODERATE	IMPORTANT
Number of awakenings (Better indicated by higher values)												
10[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[6]	no serious imprecision	none	0[5]	-	-	Cohen's d 0.65 higher (0.48 to 0.82	□□□□ MODERATE	IMPORTANT

										higher)		
Sleep quality (Better indicated by higher values)												
14[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[6]	no serious imprecision	none	0[5]	-	-	Cohen's d 0.62 higher (0.45 to 0.79 higher)	□□□□ MODERATE	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
adverse effects												
11[7]	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	298/506 (58.9%)	222/502 (44.2%)	OR 1.8 (1.4 to 2.4)	146 more per 1000 (from 84 more to 213 more)	□□□□ MODERATE	IMPORTANT

[1] From Table 5 of Nowell 1996.
[2] Only double-blind placebo-controlled studies were included.
[3] Forest plot not reported. Heterogeneity of effect size p 0.09.
[4] No explanation was provided
[5] Unclear.
[6] The focus of this scoping question is "Adults with insomnia, after the first month of a potentially traumatic event." However, Nowell 1996 is focused on primary insomnia.
[7] From Figure 2 of Holbrook 2000.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	There is indirect evidence (based on studies with adults with chronic insomnia without exposure to a traumatic event) suggesting that benzodiazepines in adults with insomnia have a beneficial effect in terms of sleep onset latency, total sleep time, number of awakenings, sleep quality. The confidence in estimate is MODERATE (LOW for the outcome sleep onset latency). There is no systematic review of evidence on the effect of benzodiazepines on functioning and presence of disorder.

Harms	There is evidence suggesting that benzodiazepines in adults with insomnia are associated with more persons leaving the study early, a proxy measure of treatment acceptability (58.9% versus 44.2%). The confidence in estimate is MODERATE. In addition to the evidence from randomized trials, data from observational and epidemiological studies highlighted a risk of tolerance and dependence. According to NICE UK, one of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (10–30% of chronic benzodiazepines users are physically dependent on them), and suffer a withdrawal syndrome when they stop taking them (50% of all users suffer withdrawal symptoms). The withdrawal syndrome includes anxiety, depression, nausea and perceptual changes. Rebound insomnia may occur and is characterised by a worsening of the original insomnia symptoms. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects. The safety of psychotropic drugs in pregnancy and breastfeeding is not clearly established. In particular, exposure to benzodiazepines during the first trimester is associated with an increased risk of oral clefts, and exposure during the third trimester is associated with neonatal difficulties (Dolovich et al, 1998, BMJ 317: 839-43). A number of consensus-based guidelines and narrative reviews argue against the use of benzodiazepines for posttraumatic stress symptoms (see http://www.ptsd.va.gov/professional/pages/clinicians-guide-to-medications-for-ptsd.asp)

Value and preferences	
In favour	Severe insomnia undermines the capacity of persons to carry out basic tasks for day to day living and may result in depression or self-medication such as using excess alcohol or other substances. Self-medication and substance use may continue even when insomnia, ASD or PTSD symptoms decrease over time. After certain recent events (e.g. exposure to war or natural disaster) it is important for the survivor to sleep sufficiently to be able to carry out essential survival tasks.
Against	There is evidence that simple non pharmacological methods: sleep hygiene and relaxation are effective at reducing acute insomnia and have no long term ill effects (scoping question 14). Stressor-related anxiety should be addressed before initiating benzodiazepines.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. In many low income countries, continuous availability of psychotropic drugs in non-specialized health care is a challenge. Benzodiazepines are associated with low acquisition costs, but shorter acting benzodiazepines are not generally available in low income countries. Diazepam (as a representative of the benzodiazepines) is included in the WHO list of essential medicines for the treatment of anxiety disorders. Diazepam is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X** No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 7

Benzodiazepines should not be offered to adults with insomnia in the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: moderate

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

There are alternatives to pharmacological treatment (see (a) recommendation 5 on psychological interventions for insomnia in adults and (b) WHO (2010) mhGAP recommendations on psychological first aid).

In exceptional cases when psychologically oriented interventions are not feasible, short-term treatment (3-7 days) with benzodiazepines may be considered as a treatment option for insomnia that interferes severely with daily functioning. The following precautions should be considered (a) there are possible interactions with other drugs, (b) necessary precautions should be taken when prescribing to elderly populations and pregnant or breastfeeding women and (c) use of benzodiazepines can quickly lead to dependence in some people. Accordingly benzodiazepines should only be prescribed for insomnia in exceptional cases and for a very short time period. Benzodiazepines are often overprescribed.

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month, the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depression, and alcohol or drug use disorder.

8. Acute (Secondary) Insomnia (first month): Pharmacological Interventions – Children and Adolescents

Q8. For children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

Insomnia is commonly associated with mood and anxiety disorders, including in the context of exposure to potentially traumatic events.[28] It is noted that insomnia may also have physical and other psychological causes, for example cardio vascular disorders, alcohol use disorder, and (prescription and non prescription) drug use disorder.

There is uncertainty how to treat children and adolescents with insomnia in the first month of a potentially traumatic event.[29] This type of insomnia is referred to as secondary insomnia (primary insomnia is diagnosed when somatized tension and learned sleep-incompatible behaviors play a predominant role in the maintenance of poor sleep). Given the time-frame of this scoping question (within the first month of exposure to a potentially traumatic event), the focus is here on 'acute insomnia'.[30,31]

Although benzodiazepines are commonly used, health care providers have expressed worries on iatrogenic effects of these drugs,[32] making this an important scoping question.

[28] Lamarche & De Koninck (2007). Sleep disturbance in adults with Posttraumatic Stress Disorder. *Journal of Clinical Psychiatry*, 68, 1257-70
[29] Harvey, Jones & Schmidt (2003). Sleep and Posttraumatic Stress Disorder: a review. *Clinical Psychology Review*, 23, 377-407
[30] Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
[31] Wang, Wang & Tsai (2005). Cognitive behavioural therapy for primary insomnia: a systematic review. *Journal of Advanced Nursing*, 50(5), 553–564
[32] De Niet et al (2009). Review of systematic reviews about the efficacy of non-pharmacological interventions to improve sleep quality in insomnia. *Interational Journal for Evidence Based Healthcare*, 7, 233-42

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and adolescents with insomnia, within the first month of a potentially traumatic event
- **Interventions:** Benzodiazepines
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted on March 6th 2012 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("insomnia" AND "stress" OR "trauma"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "insomnia". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years), focusing on pharmacological treatments. In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES
We identified a systematic review conducted by Bruni & Novelli for Clinical Evidence, published by the British Medical Journal (Bruni & Novelli, 2010. Sleep disorders in Children. Clinical Evidence, 9, 2304). This systematic review searched the following databases up to September 2009: Medline, Embase, the Cochrane Library, as well as harm alerts from US and UK regulatory bodies. This review identified 13 randomized controlled trials that met inclusion criteria (a focus on dyssomnia – defined as pediatric insomnia or excessive daytime sleepiness- and parasomnia). Evidence from these studies was subsequently evaluated using GRADE methodology. However, no studies evaluating benzodiazepines were identified.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Alessi, C. & Vitiello, M.V. (201). Insomnia (primary) in older people. *Clinical Evidence*, 10, 2302
REASON FOR EXCLUSION: focuses on primary insomnia, and on a specific population sub-group (older adults)

Aurora, R.N., Zak, R.S., Auerbach, S.H., Casey, K.R., Chowdhuri, S., Karippot, A., Maganti, R.K., Ramar, K., Kristo, D.A., Bista, S.R., Lamm, C.I., Morgenthaler, T.I. (2010). Best practice guide for the treatment of nightmare disorder in adults. *Journal of Clinical Sleep Medicine*, 6(4), 389-401
REASON FOR EXCLUSION: focuses on nightmares specifically, only searched PubMed, and identified only studies with chronic nightmares; no studies focused on children and adolescents

Buscemi, N., Vandermeer, B, Friesen, C., Bialy, C., Tubman, M., Ospina, M., Klassen, T.P., Witmans, M. (2007). The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs
REASON FOR EXCLUSION: focuses on chronic insomnia, more than 2 years old; no studies focused on children and adolescents

Dündar, Y., Boland, A., Strobl, J., Dodd, S., Haycox, A., Bagust, A., Bogg, J., Dickson, R & Walley, T. (2004). Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation. *Health, Technology, Assessment*, 8(24)
REASON FOR EXCLUSION: older than 2 years

Hirst, A. & Sloan, R. (2009). Benzodiazepines and related drugs for insomnia in palliative care. *Cochrane Database of Systematic Reviews*, 4
REASON FOR EXCLUSION: focuses specifically on interventions in palliative care

Nappi, C.M., Drummond, S.P.A. & Hall, J.M.H. (2012). Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*, doi:10.1016/j.neuropharm.2011.02.029
REASON FOR EXCLUSION: This review does not provide a meta-analysis; no studies focused on children and adolescents

National Institute for Clinical Excellence (2004). Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia.
REASON FOR EXCLUSION: older than 2 years; Lack of actual data in the guidelines

Riemann, D. & Perlis, M.L. (2009). The treatments of chronic insomnia: A review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Medicine Reviews*, 13, 205-14
REASON FOR EXCLUSION: focuses specifically on chronic insomnia

Sateia, M.J. & Dowell, P.D. (2004). Insomnia. *Lancet*, 364, 1959-73
REASON FOR EXCLUSION: focuses specifically on chronic insomnia, and older than 2 years

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of Clinical Sleep Medicine, 15(5), 487-504
REASON FOR EXCLUSION: focuses on chronic insomnia, and older than 2 years

Silber, M.H. (2005). Chronic insomnia. *New England Journal of Medicine*, 353, 803-10
REASON FOR EXCLUSION: focuses on chronic insomnia, older than 2 years, and no systematic review methodology reported

Toward Optimized Practice (TOP) Program (2007). Clinical Practice Guideline Adult Insomnia: Assessment to Diagnosis. http://www.centreforsleep.com/assets/images/pdf/insomnia_assessment_guideline07.pdf
REASON FOR EXCLUSION: no methodology of a systematic review is reported

Uchiyama, M., Inoue, Y., Uchimura, N., Kawamori, R., Kurabayashi, M., Kario, K., Watada, H. (2011). Clinical significance and management of insomnia. *Sleep and Biological Rhythms*, 9, 63-72
REASON FOR EXCLUSION: inclusion Japanese consensus statement, but no methodology of a systematic review is reported

Van Liempt, S., Vermetten, E., Geuze, E. & Westenberg, H.G.M. (2006). Pharmacotherapy for disordered sleep in post-traumatic stress disorder: a systematic review. *International Clinical Psychopharmacology*, 21, 193–202
REASON FOR EXCLUSION: Older than 2 years, but this seems the most up-to-date relevant review with data reported; no studies focused on children and adolescents

Wilson, S.J., Nutt, D.J. Alford, C., Argyropoulos, S.V. Baldwin, D.S., Bateson, A.N. et al (2009). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *Journal of Psychopharmacology*, 24(11), 1577-1600
REASON FOR EXCLUSION: represents a comprehensive and recent effort to make practice guidelines, consensus was reached where evidence was insufficient. However, data is not included in this paper.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Pharmacological intervention for acute secondary insomnia	Symptom severity Functioning Presence of disorder	No data No data No data	No data

		Adverse effects	No data	

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	A systematic review found no evidence on the benefit of benzodiazepines for children and adolescents with acute secondary insomnia with regard to symptom severity, presence of disorder or functioning.
Harms	There is no systematic review of evidence on the potential negative consequences of benzodiazepines for children and adolescents with acute secondary insomnia. However, the NICE guidelines state the following with regard to adults: "One of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (both physically and psychologically), and suffer a withdrawal syndrome when they stop taking them. The withdrawal syndrome may be prolonged and may develop at any time up to 3 weeks after cessation of a long acting benzodiazepine, or a few hours after cessation of a short-acting one. The syndrome includes anxiety, depression, nausea and perceptual changes. 'Rebound insomnia' also occurs and is characterised by a worsening of the original insomnia symptoms. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects." "It has been estimated that 10–30% of chronic benzodiazepines users are physically dependent on them and 50% of all users suffer withdrawal symptoms. Factors potentially associated with an increased risk of developing dependency include short duration of action, long-term use, high dose, high potency, alcoholism and other drug dependency, personality disorders and use without medical supervision." Similarly, clinical guidelines by the British Medical Journal report "paucity of evidence about

	effective treatments for sleep disorders in children, especially parasomnias, but behavioural interventions may be the best first-line approach." (p.2)

Value and preferences	
In favour	
Against	Consensus statements on the use of hypnotic medications in children all recommend the use of behavioural interventions as a first line approach.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. Benzodiazepines may not be continuously available in LMIC settings. To avoid the risks of harm referred to above, training of primary care practitioners may be necessary on responsible use of benzodiazepines.

Judgements to inform the decision on the strength of the recommendation

Factor	**Decision**
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?*	**Yes X** No

In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation8

Benzodiazepines should not be offered to children and adolescents with acute (secondary) insomnia in the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

It is important to always assess for and manage other possible physical causes for insomnia, even when the insomnia starts within one month of a potentially traumatic event. Where possible, environmental causes for insomnia (e.g. noisy environments) should be addressed.

There are alternatives to pharmacological treatment (see question 6's remarks on psychological interventions for insomnia in children and adolescents).

Health care providers should explain that insomnia is common after recent exposure to extreme stressors. If insomnia persists for more than one month the person should be re-assessed for other conditions that may need treatment, including anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder), depression, and, in adolescents, alcohol or drug use disorder.

9. Secondary Nonorganic Enuresis (first month): Early Psychological Interventions – Children

Q9. In children with secondary nonorganic enuresis after a potentially traumatic recent event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines. This scoping question covers bedwetting in the first month after a potentially traumatic event.

The ICD10 describes nonorganic enuresis as "involuntary voiding of urine, by day and/or by night which is abnormal in relation to the individual's mental age and which is not a consequence of a lack of bladder control due to any neurological disorder, to epileptic attacks or to any structural abnormality of the urinary tract." (p. 285). Nonorganic enuresis may be primary (in children who never were completely continent) or secondary (in children who experience a period of acquired bladder control). Furthermore, nonorganic enuresis may be mono-symptomatic (i.e. be the main complaint) or poly-symptomatic (may be one complaint among more emotional/ behavioral problems). Enuresis is a common complaint in primary care for children recently exposed to potentially traumatic events.[33] and may have important harmful mental and social consequences, including decreased self-esteem, anxiety, and harsh punitive parental reactions[34].

[33] Al-Jawadi, A.A. & Abdul-Rhman, S. (2007). Prevalence of childhood and early adolescence mental disorders among children attending primary health care centers in Mosul, Iraq: a cross-sectional study. *BMC Public Health*, 7, 274

[34] Sapi, M.C., Vasconcelos, J.S.P., Silva, F.G., Damião, R., da Silva, E.A. (2009). Assessment of domestic violence against children and adolescents with enuresis. *Jornal de Pediatria*, 85(5), 433-37

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children with nonorganic (secondary) enuresis in the first month after a potentially traumatic event
- **Interventions:** Any psychological and social intervention
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("enuresis" OR "bedwetting") AND "systematic review"). In addition, in the PILOTS database the keywords dissociation and conversion were used. In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keywords "bedwetting" and "enuresis". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years), focusing on psychological and social treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

National Clinical Guideline Centre (NICE) (2010). Nocturnal Enuresis: The Management of bedwetting in Children and Young People. London: National Clinical Guideline Centre. Available from www.nice.org.uk

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

American Academy of Child and Adolescent Psychiatry (2004). Practice parameter for the assessment and treatment of children and adolescents with enuresis. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(12), 1540-1550
REASON FOR EXCLUSION: More than 2 years old

Butler, R.J., Gasson, S.L. (2005). Enuresis alarm treatment. *Scandinavian Journal of urology and Nephrology*, 39, 349-357
REASON FOR EXCLUSION: More than 2 years old

Evans, J.H.C. (2001). Evidence based management of nocturnal enuresis. *British Medical Journal*, 323, 1167–1169
REASON FOR EXCLUSION: More than 2 years old

Glazener, C.M.A., Evans, J.H.C. (2009). Simple behavioural and physical interventions for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*, Issue 1
REASON FOR EXCLUSION: the NICE (2010) performed more recent searches

Glazener, C.M.A., Evans, J.H.C., Cheuk, D.K.L. (2009). Complementary and miscellaneous interventions for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*, Issue 1
REASON FOR EXCLUSION: the NICE (2010) performed more recent searches

Glazener, C.M.A., Evans, J.H.C., Peto, R.E. (2004). Treating nocturnal enuresis in children. *Journal of Wound Ostomy and Continence Care*, 31(4), 223-34
REASON FOR EXCLUSION: More than 2 years old, and summarizes Cochrane review which was updated in the meantime

Glazener, C.M.A., Evans, J.H.C., Peto, R.E. (2008). Complex behavioural and educational interventions for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*, Issue 3
REASON FOR EXCLUSION: the NICE (2010) performed more recent searches

Glazener, C.M.A., Evans, J.H.C., Peto, R.E. (2009). Alarm interventions for enuresis in children. *Cochrane Database of Systematic Reviews*, Issue 1
REASON FOR EXCLUSION: the NICE (2010) performed more recent searches

Glazener, C.M.A., Peto, R.E., Evans, J.H.C. (2003). Effects of interventions for the treatment of nocturnal enuresis in children. *Quality and Safety in Health Care*, 12, 390-394
REASON FOR EXCLUSION: More than 2 years old, and summarizes Cochrane review which was updated in the meantime

Hjalmas, K., Arnold, T., Bower, W., Caione, P., Chiozza, L.M., von Gontard, A., Han, S.W., Husman, D.A., Kawauchi, A., Läckgren, G., Lottmann, H., Mark, S., Rittig, S., Robson, L., Vande Walle, J., Yeung, C.K. on behalf of the International Children's Continence Society (2004). Nocturnal enuresis: An international evidence based management strategy. *The Journal of Urology*, 171, 2545-2561

REASON FOR EXCLUSION: More than 2 years old

Hodgkinson, B., Josephs, K., Hegney, D. (2010). Best practice in the management of primary nocturnal enuresis in children: a systematic review. *JBI Library of Systematic Reviews*; 8(5): 173-254

REASON FOR EXCLUSION: No formal meta-analysis reported

Jindal, V., Ge, A., Mansky, P.J. (2008). Safety and efficacy of acupuncture in children: A review of the evidence. *Journal of Pediatric Hematology & Oncology*, 30, 431-442

REASON FOR EXCLUSION: More than 2 years old

Kiddoo, D. (2007). Nocturnal enuresis. *Clinical Evidence*, 10, 305

REASON FOR EXCLUSION: More than 2 years old

Mathew, J.L. (2010). Evidence-based management of nocturnal enuresis: An overview of systematic reviews. *Indian Pediatrics*, 777-780

REASON FOR EXCLUSION: reports on existing systematic reviews and meta-analses. Searched Cochrane Database and Medline searched, no new meta-analysis conducted.

Kristensen, G. & Jensen, I.N. (2003). Meta-analyses of alarm treatment for nocturnal enuresis -- reporting practice, criteria, and frequency of bedwetting. Scandinavian Journal of Urology and Nephrology, 37(3), 232-238

REASON FOR EXCLUSION: More than 2 years old

Neveus, T. Eggert, P., Evans, J., Macedo, A. Rittig, S., Tekgül, S. Vande Walle, J.,Yeung, C.K., Robson, L. (2010). Evaluation of and treatment for monosymptomatic enuresis: A standardization document from the International Children's Continence Society. *The Journal of Urology*, 83, 441-447

REASON FOR EXCLUSION: No methods for systematic review reported

Nunes, V.N., O'Flynn, N., Evans, J., Sawyer, L. on behalf of the Guideline Development Group (2010). Management of bedwetting in children and young people: summary of NICE guidance. *British Medical Journal*, 341, c5399

REASON FOR EXCLUSION: Summarizes NICE guidelines which were included

Paediatric Society New Zealand (PSNZ) (2005). Best Practice Evidence Based Guideline: Nocturnal Enuresis 'Bedwetting'. Wellington: PSNZ

REASON FOR EXCLUSION: More than 2 years old

Tekgül, S., Riedmiller, H., Gerharz, E., Hoebeke, P., Kocvara, R., Nijman, R. Radmayr, C., Stein, R. (2011). Guidelines on Paediatric Urology. Arnhem, the Netherlands: European Society for Paediatric Urology

REASON FOR EXCLUSION: No systematic review methodology described, except for a reference to searching MEDLINE

van Dyk, J.C., Duvenhage, F., Coetzee, L.J.E., Segone, A.M., Fockema, M., Smart, D., Haffejee, M., Lefakane, S.B.I., Roos, J., Stellmacher, G., McGillevray, D., Bereczky, Z. (2003). South African guidelines for the management of nocturnal enuresis. *South African Medical Journal*, 93(5), 338-340
REASON FOR EXCLUSION: More than 2 years old

Wespes, E. (2010).Enurésie : les traitements soumis à l'épreuve EBM. *Rev Med Brux*, 31, 351-355
REASON FOR EXCLUSION: based on guidelines by the European Urological Association and the International Children's Continence Society (Neveus et al, 2010). No systematic review methodology reported.

COMMENT: Glazener, Evans & Peto (2008), Glazener, Evans & Cheuk (2009), Glazener, Evans & Peto (2009), and NICE (2010) are all rigorous systematic reviews and meta-analysis of strong quality, focusing on specific psychological and social interventions for enuresis. However, NICE (2010) performed searches more recently (in April 2009, vs. 22 November 2005, 20 March 2008, 16 November 2006, and 28 February 2007, for Glazener and team reviews respectively). NICE (2010) additionally provides GRADEd evidence.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	GRADE
1	Fluid and diet restriction vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010), Glazener 2009 included Bhatia 1990 No data No data No data	NICE (2010) provides the most recent high quality systematic review and meta-analysis of psychological and social treatments for enuresis. Note: NICE (2010) does not focus specifically on treatments in the first month of a potentially traumatic event(s). Bhatia 1990: Our calculation

				of the comparison between: Imipramine and simple behavioral intervention (waking, fluid restriction, avoiding parental punishment) vs. imipramine alone
2	Lifting and waking vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010), Glazener 2009 included Fournier 1987 and Turner 1970 No data No data No data	
3	Bladder training and retention control vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010), Glazener 2009 included Harris 1977 No data No data No data	Harris 1977 is the only RCT that compared retention training versus waiting list
4	Star charts vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010), Glazener 2009 included Fava 1981 No data No data	

5	Dry bed training[35] vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010) No data No data No data	NICE (2010): Dry bed training without an alarm compared to no treatment; Dry bed training with an alarm compared to no treatment
6	Alarms vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010) No data No data No data	
7	Other psychological treatments vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010) No data No data No data	Only one study compared psychological interventions with no treatment: CBT compared to no treatment (other studies are head-to-head comparisons)
8	Information and educational interventions vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010) No data No data NICE (2010)	No studies available comparing information and educational interventions vs. no treatment/ control (only head-to-head)

[35] Dry-bed training is a training program that may include combinations of a number of different behavioral interventions, and that may include rewards, punishment, training routines and waking routines, and may be undertaken with or without an alarm (NICE, 2010)

9	Alternative treatments (hypnosis) vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	NICE (2010) No data No data NICE (2010)	No studies comparing hypnosis with no treatment/ control (only head-to-head)

Narrative description of the studies that went into analysis

NICE provides clinical guidelines based on a thorough systematic review of evidence for both pharmacological and psychological interventions. NICE included randomized controlled trials comparing active treatments with treatment as usual or control conditions, as well as randomized controlled trials comparing active treatment conditions. Here, randomized controlled trials with a treatment as usual or control condition are included in GRADE tables. These studies were not conducted with acutely traumatized children in low and middle income countries. The following studies were included in NICE:

- Fluid and diet restriction (i.e., restriction of fluids particularly before bed will have been tried by many families before they seek professional help. Children with bedwetting may also have daytime urinary symptoms and fluid restriction during the day may be used by children and young people themselves to manage symptoms of frequency and urgency when out of the home. The hypothesis that dietary restrictions may be beneficial to children with bedwetting is based on the idea that food allergies may provoke bladder instability) : 1 randomized controlled trial
- Lifting and waking (i.e. lifting is described as lifting the child from their bed while they sleep or walking the child to the bathroom to pass urine, without necessarily waking the child. Waking is described as waking the child from their sleep and taking them to the bathroom to pass urine. Children can be woken at either set times or randomly during the night.): 6 randomized controlled trials
- Bladder training (also described as bladder retraining, bladder drill, bladder re-education, bladder discipline) (i.e. involves the individual in attempting to increase the interval between the desire to void and actual void): 5 randomized controlled trials
- Star charts (i.e. star charts and rewards systems are the giving of some reward either for a dry night or for the correct toileting behavior, regardless of the child actually being dry overnight. The rewards can range from stars on charts in the child's room or in a family room, to pocket money or time-earnt for a preferred activity such as gaming): 6 randomized controlled trials

- Dry bed training (the dry bed training procedure was described as a first night of intensive training which included positive practice one hour before bedtime, being given fluid at bed time, an alarm, hourly waking, and cleanliness training when the child was wet. After the initial nights treatment, post training supervision was given which continued to include an alarm, positive practice if the child was wet the night before, waking the child when parent went to bed, cleanliness training if the child wet the bed, and praise if the child was dry in the morning. If the child was dry for 7 consecutive dry nights the alarm was removed, and the parent would continue to check the bed in the morning. If the child was wet, cleanliness training would be used and positive practice was given the following evening. If the child was wet twice in a week, then post training supervision was started again.): 5 randomized controlled trials
- Enuresis alarm (i.e. a battery powered alarm that is triggered by urine coming into contact with the alarm sensor. Alarms come in 2 main groups: bed alarms where the sensor pad is placed under a draw sheet and body worn alarms where the sensor is placed e.g. between two pairs of snugly fitting underpants. The alarms can generate various noises or sometimes pre recorded sounds. Some body worn alarms can be set to vibration with or without sound.): 10 randomized controlled trials

GRADE Tables

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should fluid and diet restriction vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis?
Settings:
Bibliography: Bhatia 1990 as described in NICE 2010 and in Glazener 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluid and diet restriction	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity: number not achieving 14 dry nights												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	serious[4]	serious[5]	none	2/20 (10%)	8/20 (40%)	RR 0.25 (0.06 to 1.03)[6]	300 fewer per 1000 (from 376	□□□□ VERY LOW	IMPORTANT

										fewer to 12 more)		
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] Bhatia 2009 as described in NICE 2010 and in Glazener 2009, page 14.
[2] High dropout rate due to inadequate follow up.
[3] Only one study included in this analysis.
[4] It is unclear if children were included in the first month after a potentially traumatic event.
[5] Only 40 patients included in this analysis.
[6] Our calculation with Cochrane RevMan Software.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should lifting and waking vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: Fournier 1987 and Turner 1970 as described in NICE 2010 and in Glazener 2009

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lifting and waking	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity: number not achieving 14 consecutive dry nights												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[4]	none	14/15 (93.3%)	13/17 (76.5%)	RR 1.22 (0.91 to 1.64)	168 more per 1000 (from 69 fewer to 489 more)	□□□□ VERY LOW	IMPORTANT
Symptom severity: mean wet nights on treatment (Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency[3]	no serious indirectness	very serious[7]	none	8	8	-	MD 0 higher (0 to 0 higher)[8]	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 3.2 of Glazener 2009.
[2] Allocation was by means of stratification based on age and sex, but children who dropped out were replaced by the next child referred to the clinic.
[3] Only one study included in the analysis.
[4] Only 32 patients included in this analysis. Confidence interval ranges from no benefit to appreciable harm.
[5] From Analysis 3.5 of Glazener 2009.
[6] This study failed to provide standard deviations for continuous data.

[7] Only 16 patients included in is analysis.
[8] Not reported as standard deviations were not available.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should bladder training and retention control vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: Harris 1977 and Turner 1970 as described in NICE 2010 and in Glazener 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bladder training and retention control	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity: mean wet nights on treatment (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[4]	none	9	9	-	MD 0 higher (0 to 0 higher)[5]	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												

0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.5 of Glazener 2009.
[2] Groups were not comparable at baseline.
[3] Only one study included in the analysis.
[4] Only 18 patients included in the analysis.
[5] No data.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should star charts vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis?
Settings:
Bibliography: Fava 1981 and Turner 1970 as described in NICE 2010 and in Glazener 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Star charts**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity: number not achieving 14 consecutive dry nights												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/10 (20%)	9/10 (90%)	RR 0.22 (0.06 to 0.78)	702 fewer per 1000 (from 198 fewer to 846 fewer)	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												

0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.2 of Glazener 2009.
[2] Baseline comparison of measurements of wetting were not reported. Children with physical causes for their enuresis were not explicitly excluded (the criterion was notmentioned).
[3] Only 20 patients included in this analysis.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should dry bed training vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: NICE 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dry bed training**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity: number of children who achieved 14 consecutive dry nights												
2[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[4]	none	7/30 (23.3%)	2/30 (6.7%)	RR 2.9 (0.75 to 11.14)[5]	127 more per 1000 (from 17 fewer to 676 more)	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0		IMPORTANT

										to 0 higher)		
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From NICE 2010 Appendix H, page 18.
[2] Unclear allocation concealment in Bollard 1981 and Bollard 1982. Bollard 1981 did not report method of blinding.
[3] From NICE 2010 Appendix H, page 18.
[4] Only 60 patients included in the analysis (see NICE 2010, full Guidance, page 186). Confidence interval ranges from no benefit to appreciable benefit.
[5] From NICE 2010, page 186.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should dry bed training with an alarm vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: NICE 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dry bed training with an alarm**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity: number of children who achieved 14 consecutive dry nights												
2[1]	randomised	serious[2]	no serious	no serious	serious[4]	none	29/30	2/30	RR 9.34	556 more	□□□□	IMPORTANT

	trials		inconsistency[3]	indirectness			(96.7%)	(6.7%)	(3.2 to 27.27)[5]	per 1000 (from 147 more to 1000 more)	LOW	
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From NICE 2010, Appendix H, page 20.
[2] Unclear allocation concealment in Bollard 1981 and Bollard 1982. Bollard 1981 did not report method of blinding
[3] From NICE 2010, Appendix H, page 21.
[4] Only 60 patients included in the analysis. Very wide confidence interval, but suggesting a clinical benefit.
[5] From NICE 2010 Full Guidance, page 189.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should enuresis alarms vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: NICE 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enuresis alarms	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity: number of children who achieved 14 consecutive dry nights												
6[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	108/141 (76.6%)	3/135 (2.2%)	RR 16.9 (7.17 to 39.85)[4]	353 more per 1000 (from 137 more to 863 more)	□□□□ MODERATE	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From NICE 2010 Appendix H, page 30.
[2] Unclear allocation concealment and blinding.
[3] From NICE 2010 Appendix H, page 30.
[4] From NICE 2010 Full Guidance, page 214.

Author(s): Corrado Barbui
Date: 2012-02-27
Question: Should other psychological treatments (CBT) vs treatment as usual or no treatment/waitlist be used in children and adolescents with nonorganic (secondary) enuresis ?
Settings:
Bibliography: Ronen 1992 as described in NICE 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Other psychological treatments (CBT)**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity: number of children who became dry for 3 weeks												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	15/20 (75%)	0/18 (0%)	RR 28.05 (1.8 to 437.4)	-	□□□□ LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0		IMPORTANT

										higher)		

[1] From NICE 2010 Appendix H, page 95.
[2] Unclear allocation concealment and blinding.
[3] Only one study included in the analysis.
[4] Only 38 patients included in the analysis. Confidence interval ranges from minimal benefit to clinically appreciable benefit.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	**Fluid and diet restriction:** There is one study only suggesting a beneficial effect, although the confidence in estimate is VERY LOW (the 95% confidence interval ranges from substantial benefit of the intervention to no benefit at all). No evidence is available for the outcomes functioning and presence of disorder. **Lifting and waking:** There is one study only suggesting lack of benefit. The confidence in estimate is VERY LOW. No evidence is available for the outcomes functioning and presence of disorder. **Bladder training and retention:** There is one study only suggesting lack of benefit. The confidence in estimate is VERY LOW. No evidence is available for the outcomes functioning and presence of disorder. **Star charts:** There is one study only suggesting a statistically significant beneficial effect, although the confidence in estimate is VERY LOW. No systematic review of evidence is available for the outcomes functioning and presence of disorder. **Dry bed training:** There are two small studies only suggesting a beneficial effect, although the confidence in estimate is VERY LOW (the 95% confidence interval ranges from substantial benefit of the intervention to no

	benefit at all). No systematic review of evidence is available for the outcomes functioning and presence of disorder. **Dry bed training with an alarm:** There are two small studies only suggesting a statistically significant beneficial effect, although the confidence in estimate is VERY LOW. No systematic review of evidence is available for the outcomes functioning and presence of disorder. **Enuresis alarm:** There is evidence (six studies) suggesting that enuresis alarm is effective in terms of number of children who achieved 14 consecutive dry nights (76.6% versus 2.2%). The confidence in estimate is MODERATE. No systematic review of evidence is available for the outcomes functioning and presence of disorder. **Other psychological treatments (CBT):** There is one study only suggesting a statistically significant beneficial effect, although the confidence in estimate is LOW. No systematic review of evidence is available for the outcomes functioning and presence of disorder.
Harms	No systematic review of evidence is available for adverse effects in any of the studied psychological treatments.

Value and preferences	
In favour	Effective psychological interventions are preferable over potentially harsh and counterproductive punitive measures by caregivers and others that may be elicited by nonorganic secondary enuresis. Difficult living conditions and lack of access to water for washing make alleviation of symptoms preferable to waiting for natural recovery.
Against	Some regression in development – potentially involving bed-wetting but also separation anxiety is common after recent exposure to traumatic events and natural recovery may be expected in most cases

Feasibility (including economic consequences)	Most staff in PHC in LAMIC have not received extensive training in communication skills and basic emotional support. Any additional training in specific psychological interventions would require some resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources. Provision of alarms may not be feasible in all resource-constrained settings. Behavioural interventions (e.g. reward systems) may be simpler and quicker to train and easily understood by parents and staff (NICE, 2010).

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X for alarm** **No X for other interventions**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** (for psychoeducation) **No X** (for other interventions)
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** (for psychoeducation) **No X** (for other

	interventions)
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** (for psychoeducation) **No X** (for other interventions)

Final recommendation by the guideline panel

Recommendation 9

(i) Psycho-education about the negative effects of punitive responses should be given to caregivers of children with secondary nonorganic enuresis in the first month after a potentially traumatic event.

Strength of recommendation: strong
Quality of evidence: very low

(ii) Parenting skills training and the use of simple behavioural interventions (i.e. star charts, toileting before sleep and rewarding having nights without wetting the bed) should be considered. In addition, where resources permit, alarms should be considered.

Strength of recommendation: standard
Quality of evidence: moderate for alarms, low or very low for other behavioural interventions

Remarks

Medical causes of bedwetting should be assessed and managed to ensure that the bedwetting is indeed secondary to a potentially traumatic event.

Health care providers should explain that bedwetting is common after recent exposure to extreme stressors. If the bed-wetting persists for more than one month the child should be re-asssesed for other disorder that may need treatment.

10. Symptoms of Dissociative (Conversion) Disorders (first month): Early Psychological Interventions – Adults

Q10. For adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

This scoping question covers both psychological and somatoform dissociation in adults in the first month after a potentially traumatic event. Dissociative (conversion) disorders[36] are described by ICD10 as "being associated closely in time with traumatic events, insoluble and intolerable problems, or disturbed relationships." Dissociative symptoms have been observed in varying ways (e.g. expressed through different idioms of distress) in various cultures.[37]

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with symptoms of dissociative (conversion) disorders, within one month of exposure to a potentially traumatic event(s)

[36] *Dissociative (conversion) disorders* in ICD10 include dissociative amnesia (F44.0), dissociative fugue (F44.1), dissociative stupor (F44.2), trance and possession disorders (F44.3), dissociative disorders of movement and sensation (F44.4 - F44.7), mixed and other dissociative (conversion) disorders (Ganser's syndrome, multiple personality disorder, transient dissociative disorders occurring in childhood and adolescence). The DSMIV lists conversion disorder (cf. ICD10 F44.4-F44.7) within the category of somatoform disorders.

[37] Van Duijl, M., Nijenhuis, E., Komproe, I.H., Gernaat, H.B.P.E., de Jong, J.T.V.M. (2010). Dissociative Symptoms and Reported Trauma Among Patients with Spirit Possession and Matched Healthy Controls in Uganda, *Culture Medicine & Psychiatry*, 34, 380–400

- **Interventions:** Any psychological interventions
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("dissociative disorder" OR "conversion disorder") AND "systematic review"). In addition, in the PILOTS database the keywords dissociation and conversion were used. In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keywords "dissociative disorder" and "conversion disorder". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Ruddy, R., House, A. (2009). Psychosocial interventions for conversion disorder. Cochrane Database of Systematic Reviews, Issue 1

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

During, E.H., Elahi, F.M., Taieb, O., Moro, M., Baubet, T. (2011). A critical review of dissociative trance and possession disorders: etiological, diagnostic, therapeutic and nosological issues. *Canadian Journal of Psychiatry*, 56(4), 235-242
REASON FOR EXCLUSION: Systematic review of all study types, not only evaluation studies. Does not list inclusion/ exclusion criteria, quality appraisal, or formal meta-analysis for evaluation studies.

International Society for Study of Dissociation [Chu, J.A., Loewenstein, R., Dell, P.F., Barach, P.M., Somer, E., Kluft, R.P., Gelinas, D.J., Van der Hart, O., Dalenberg, C.J., Nijenhuis, E.R.S., Bowman, E.S., Boon, S., Goodwin, J., Jacobson, M., Ross, C.A., Sar, V, Fine, C.G., Frankel, A.S., Coons, P.M., Courtois, C.A., Gold, S.N., & Howell, E.] (2005). Guidelines for Treating Dissociative Identity Disorder in Adults. Journal of Trauma and Dissociation, 6(4), 69-149
REASON FOR EXCLUSION: Methods of systematic review not reported. The guidelines state that no research with comparison groups exist.

Kroenke, K. (2007). Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. *Psychosomatic Medicine*, 69, 881-888
REASON FOR EXCLUSION: systematic review of all somatoform disorders according to DSMIV, including conversion disorder. Identified same studies as Ruddy & House (2009), which is more recent.

Poole, N.A., Wuerz, A., Agrawal, N. (2010). Abreaction for conversion disorder: systematic review with meta-analysis. *British Journal of Psychiatry*, 197, 91-95
REASON FOR EXCLUSION: focuses specifically on drug interviews as intervention

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Psychological interventions vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Ruddy & House (2009) (physical signs and mental state) No data No data Ruddy & House (2009) (drop-out as proxy)	Ruddy & House (2009) is the most recent systematic review meeting inclusion criteria, but does not apply a one-month-after-event limit and identified 3 studies of poor methodological quality. No meta-analysis was attempted.

Narrative description of the studies that went into analysis

Ruddy & House (2009) systematically searched for randomized controlled trials evaluating psychological and social treatments for dissociative (conversion disorders) as defined by ICD10 and DSMIV, without age, nationality or gender limitations. Three studies met inclusion criteria of the review, with altogether 119 participants:

- 1 study (Ataoglu, 2003) compared paradoxical intention therapy (two sessions a day for three weeks) for inpatients with diazepam for outpatient adults (mean age 27 years) with non-epileptic seizures in Turkey. Outcomes were: no statistically significant differences for physical signs and drop-out, and better outcome for the psychological treatment on anxiety.
- 1 study (Moene, 2002) compared an inpatient treatment program (including group psychotherapy, social skills training, a planning group, creative therapy, sports, as well as physiotherapy) for adults (mean age 37 years) with conversion disorder (motor type) with and without hypnosis (eight one-hour weekly sessions) in the Netherlands. Outcomes were: no statistically significant difference on drop-out (physical and mental variables not reported).
- 1 study (Moene, 2003) compared outpatient hypnosis (eight one-hour weekly sessions) for adults (mean age 37 years) with conversion disorder (motor type) with a waitlist control group in the Netherlands. Outcomes were: no statistically significant differences on mental state and drop-out, and treatment benefits for physical signs (no numerical data for physical disability).

The studies were judged to be of poor methodological quality, and they were not combined in a statistical meta-analysis because of differences in intervention and control groups across studies. The authors conclude that psychological and social interventions for people with dissociative (conversion) disorders "should be viewed as experimental, with slight evidence in favor of help rather than harm in terms of engagement, mental state and physical functioning".

GRADE Table

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-27
Question: Should psychological interventions vs treatment as usual or no treatment/waitlist be used in adults with symptoms of dissociative (conversion) disorders?
Settings:
Bibliography: Ruddy 2009

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Psychological interventions**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity (inpatient paradoxical intention therapy) (Better indicated by lower values)												
1[1,2]	randomised trials	serious[3]	no serious inconsistency[4]	serious[5]	serious[6]	none	15	15	-	MD 3.73 lower (6.96 to 0.5 lower)	□□□□ VERY LOW	IMPORTANT
Functioning (inpatient paradoxical intention therapy) (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of Disorder (inpatient paradoxical intention therapy) (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects: leaving the study early (inpatient paradoxical intention therapy)												
1[2,7]	randomised trials	serious[3]	no serious inconsistency[4]	serious[5]	serious[6]	none	0/15 (0%)	0/15 (0%)	-	-	□□□□ VERY LOW	IMPORTANT
Symptom severity (outpatient hypnosis versus waiting list) (Better indicated by lower values)												
1[8]	randomised trials	serious[9]	no serious inconsistency[4]	serious[5]	very serious[10]	none	20	23	-	MD 12.30 lower (44.28 lower to 19.68 higher)	□□□□ VERY LOW	IMPORTANT
Functioning (outpatient hypnosis versus waiting list) (Better indicated by lower values)												
0	no					none	0	-	-	MD 0		IMPORTANT

	evidence available									higher (0 to 0 higher)		
Presence of disorder (outpatient hypnosis versus waiting list) (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effect: leaving the study early (outpatient hypnosis versus waiting list)												
1[11]	randomised trials	serious[9]	no serious inconsistency[4]	serious[5]	very serious[12]	none	4/24 (16.7%)	2/25 (8%)	RR 2.08 (0.42 to 10.34)	86 more per 1000 (from 46 fewer to 747 more)	□□□□ VERY LOW	IMPORTANT

[1] From Analysis 1.2 of Ruddy 2009.
[2] The included study compared paradoxical intention therapy as an inpatient with outpatient follow-up and diazepam for pseudoseizures.
[3] In the included study the two groups had a different length of treatment (three weeks for the inpatients and 45 days for the outpatients) but they were all followed up at six weeks.
[4] Only one study included in this analysis.
[5] Included patients were adults with symptoms of dissociative (conversion) disorders, but the occurrence of symptoms within one month of exposure to a potentially traumatic event was not an inclusion criterion.
[6] Only 30 patients included in this analysis (all but one female, all suffering pseudoseizures).
[7] From Analysis 1.3 of Ruddy 2009.
[8] From Analysis 3.2 of Ruddy 2009.
[9] In the included study there is information about the number of people who were lost to follow up but there is no specific information about why they were lost.
[10] Only 43 patients included. Confidence interval ranges from appreciable benefit to appreciable harm.
[11] From Analysis 3.4 of Ruddy 2009.
[12] Only 49 patients included. Confidence interval ranges from appreciable benefit to appreciable harm.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	The evidence is indirect (people with conversion disorder but not after exposure to a traumatic event), limited and inconclusive and so it is uncertain if psychological interventions may be beneficial in people with dissociative (conversion) disorders within one month of exposure to a traumatic event. The confidence in estimate from the two studies that were GRADEd is VERY LOW.
Harms	The two studies that were GRADEd provided inconclusive findings on leaving the study early, a proxy measure of treatment acceptability. The confidence in estimates is VERY LOW.

Value and preferences	
In favour	
Against	It has been argued that dissociative symptoms (e.g. medically unexplained paralysis and other forms of somatoform dissociation) often take the form of culturally sanctioned idioms of distress. People suffering dissociative symptoms often seek care in the non-formal health sector (e.g. religious and traditional healing settings) (see Van Duijl et al, Cult Med Psychiatry 2010, 34(2):380-400). As such, making interventions (for which there is inconclusive evidence of effectiveness) available through formal health care settings may not provide additional value to these existing community resources. International consensus-based guidelines on mental health practices in emergency settings advocate learning about and, where appropriate, collaborating with local, indigenous and traditional health systems, but also warn against the risk that such services may do harm (IASC, 2007).

Feasibility (including economic consequences)	Most staff in PHC in LAMIC have not received extensive training in communication skills and basic emotional support. Any additional training in paradoxical intention therapy and hypnosis would require resources, including supervision. The tested psychological interventions were evaluated in specialized settings (inpatient and outpatient clinics) and it is not known to what extent they can be applied in PHC.

	Psychological interventions require time to be delivered, which is important in the context of strained human resources.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes **No X**
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 10

On the basis of available evidence no specific recommendation can be made on psychological interventions for adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

Possible physical causes for dissociation should be ruled out or managed.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made: psychological first aid should be considered in adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

For somatoform dissociation (i.e. conversion disorder), existing WHO guidance on the management of somatic medically unexplained symptoms may be considered (see Other Significant Emotional or Medically Unexplained Complaints module ofthe mhGAP Intervention Guide (WHO, 2010)).

Health care providers should explain that these symptoms can sometimes occur after recent exposure to extreme stressors. When interacting with people with conversion disorder, clinicians should acknowledge suffering and maintain a relationship of respect with the person. At the same time they should carefully avoid reinforcing any secondary gain that the person may get from somatoform dissociation (conversion). The use of culturally appropriate interventions that are not harmful may be considered.

11. Symptoms of Dissociative (Conversion) Disorders (first month): Early Psychological Interventions – Children and Adolescents

Q11. For children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event, do early psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

This scoping question covers both psychological and somatoform dissociation in children and adolescents in the first month after a potentially traumatic event. Dissociative (conversion) disorders[38] are described by ICD10 as "being associated closely in time with traumatic events, insoluble and intolerable problems, or disturbed relationships." Dissociative symptoms have been observed in varying ways (e.g. expressed through different idioms of distress) in various cultures.[39]

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

[38] *Dissociative (conversion) disorders* in ICD10 include dissociative amnesia (F44.0), dissociative fugue (F44.1), dissociative stupor (F44.2), trance and possession disorders (F44.3), dissociative disorders of movement and sensation (F44.4 - F44.7), mixed and other dissociative (conversion) disorders (Ganser's syndrome, multiple personality disorder, transient dissociative disorders occurring in childhood and adolescence). The DSMIV lists conversion disorder (cf. ICD10 F44.4-F44.7) within the category of somatoform disorders.

[39] Van Duijl, M., Nijenhuis, E., Komproe, I.H., Gernaat, H.B.P.E., de Jong, J.T.V.M. (2010). Dissociative Symptoms and Reported Trauma Among Patients with Spirit Possession and Matched Healthy Controls in Uganda, *Culture Medicine & Psychiatry*, 34, 380–400

- **Population:** Children and adolescents with symptoms of dissociative (conversion) disorders, within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Any psychological interventions
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("dissociative disorder" OR "conversion disorder") AND "systematic review"). In addition, in the PILOTS database the keywords dissociation and conversion were used. In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keywords "dissociative disorder" and "conversion disorder". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

The most rigorous and recent systematic review that was identified (Ruddy and House, 2009) looked for but did not find any studies with children and adolescents pertaining to this scoping question.

Ruddy, R., House, A. (2009). Psychosocial interventions for conversion disorder. Cochrane Database of Systematic Reviews, Issue 1

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

During, E.H., Elahi, F.M., Taieb, O., Moro, M., Baubet, T. (2011). A critical review of dissociative trance and possession disorders: etiological, diagnostic, therapeutic and nosological issues. *Canadian Journal of Psychiatry*, 56(4), 235-242
REASON FOR EXCLUSION: Systematic review of all study types, not only evaluation studies. Does not list inclusion/ exclusion criteria, quality appraisal, or formal meta-analysis for evaluation studies.

International Society for Study of Dissociation [Chu, J.A., Loewenstein, R., Dell, P.F., Barach, P.M., Somer, E., Kluft, R.P., Gelinas, D.J., Van der Hart, O., Dalenberg, C.J., Nijenhuis, E.R.S., Bowman, E.S., Boon, S., Goodwin, J., Jacobson, M., Ross, C.A., Sar, V, Fine, C.G., Frankel, A.S., Coons, P.M., Courtois, C.A., Gold, S.N., & Howell, E.] (2005). Guidelines for Treating Dissociative Identity Disorder in Adults. Journal of Trauma and Dissociation, 6(4), 69-149
REASON FOR EXCLUSION: Methods of systematic review not reported. The guidelines state that no research with comparison groups exist.

Kroenke, K. (2007). Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. *Psychosomatic Medicine*, 69, 881-888
REASON FOR EXCLUSION: systematic review of all somatoform disorders according to DSMIV, including conversion disorder. Identified same studies as Ruddy & House (2009), which is more recent.

Poole, N.A., Wuerz, A., Agrawal, N. (2010). Abreaction for conversion disorder: systematic review with meta-analysis. *British Journal of Psychiatry*, 197, 91-95
REASON FOR EXCLUSION: focuses specifically on drug interviews as intervention

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Psychological interventions vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	No data

Narrative description of the studies that went into analysis

NA

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	A recent systematic review found no evidence on the benefit of psychological interventions in children and adolescents with dissociative (conversion) disorders in the first month of a potentially traumatic event with regard to symptom severity, presence of disorder or functioning.
Harms	There is no systematic review on the potential harms of psychological interventions for children and adolescents with dissociative (conversion) disorders in the first month of a potentially traumatic event.

Value and preferences	
In favour	
Against	It has been argued that dissociative symptoms (e.g. medically unexplained paralysis and other forms of somatoform dissociation) often take the form of culturally sanctioned idioms of distress. People suffering dissociative symptoms often seek care in the non-formal health sector (e.g. religious and traditional healing settings) (see Van Duijl et al, Cult Med Psychiatry 2010, 34(2):380-400), who may or may not provide effective services. International consensus-based guidelines on mental health practices in emergency settings advocate learning about and, where appropriate, collaborating with local, indigenous and traditional health systems, but also warn against the risk that such services may do harm (IASC, 2007).

Feasibility (including economic consequences)	Most staff in PHC in LAMIC have not received extensive training in communication skills and basic emotional support. Any additional training in paradoxical intention therapy and hypnosis would require resources, including supervision. The tested psychological interventions were evaluated in specialized settings (inpatient and outpatient clinics) and it is not known to what extent they can be applied in PHC. Psychological interventions require time to be delivered, which is important in the context of strained human resources.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes **No X**
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 11

On the basis of available evidence, no specific recommendation can be made for children and adolescents with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

Possible physical causes for dissociation should be ruled out or managed.

There is already a WHO (2010) mhGAP recommendation to offer access to psychological first aid to people who have been recently exposed to potentially traumatic events. Therefore, as no further specific recommendation can be made psychological first aid should be considered in adults with symptoms of dissociative (conversion) disorders in the first month after a potentially traumatic event.

For somatoform dissociation (i.e. conversion disorder), existing WHO guidance on the management of somatic medically unexplained symptoms may be considered (see Other Significant Emotional or Medically Unexplained Complaints module of the mhGAP Intervention Guide (WHO, 2010)).

Health care providers should explain that these symptoms can sometimes occur after recent exposure to extreme stressors. When interacting with people with conversion disorder, clinicians should acknowledge suffering and maintain a relationship of respect with the person. At the same time they should carefully avoid reinforcing any secondary gain that the person may get from somatoform dissociation (conversion). The use of culturally specific interventions that are not harmful may be considered.

12. Hyperventilation (first month): Rebreathing into a Bag – Adults and Adolescents

Q12. For adolescents and adults with hyperventilation in the first month after a potentially traumatic event, does rebreathing into a paper bag when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

This scoping question covers hyperventilation in adolescents and adults in the first month after a potentially traumatic event. Around half of populations exposed to potentially traumatic events have been reported to experience panic symptoms during the first month after the event.[40] Indeed, clinical experience suggests that in the immediate aftermath of potentially traumatic events, help-seeking for hyperventilation is common. Because symptoms are associated with hypocapnia, clinicians frequently encourage persons to increase their CO2 levels by re-breathing into a paper bag.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adolescents and adults with hyperventilation, within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Re-breathing into a paper bag
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up

[40] Nixon & Bryant (2003). Peritraumatic and persistent panic attacks in acute stress disorder. *Behavior Research & Therapy*, 41(10), 1237-42; Bryant & Panasetis (2001). Panic symptoms during trauma and acute stress disorder. *Behavior Research & Therapy*, 39(8), 961-6

- Presence of mental disorder post intervention and at follow-up
- Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 29 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ((("hyperventilation") AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "hyperventilation". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adolescents (10-18 years) and adults (>18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

Given that no systematic reviews were identified, a systematic review was conducted in week 24 of 2012. This systematic review searched the Cochrane Library; Medline; EMBASE; CINAHL; and PsycInfo for studies with the following keywords: ("traumatic event" or "acute stress" or PTSD) and "hyperventilation". This review returned 81 records: 3 in Cochrane; 31 in Medline; 43 in EMBASE; 3 in CINAHL; and 1 in PsycInfo (where the randomized controlled trial function was selected). These results were hand-searched for relevant studies, but none were identified.

INCLUDED IN GRADE TABLES OR FOOTNOTES

The systematic review did not identify any studies that could be entered in GRADE tables.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Australian Resuscitation Council (2008). Guideline 9.2.8. The first aid management of hyperventilation syndrome.
REASON FOR EXCLUSION: Older than 2 years; no systematic review methodology described; no meta-analysis reported

Warwick University (2006). Hyperventilation syndrome: specific treatment options. Available at http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/prehospitalcare/jrcalcstakeholderwebsite/guidelines/hyperventilation_syndrome_2006.pdf . Last accessed April 24th 2012.

REASON FOR EXCLUSION: Older than 2 years; no systematic review methodology described; no meta-analysis reported

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Rebreathing into a paper bag vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	No data

Narrative description of the studies that went into analysis

NA

Evidence to recommendation table

Benefits	No studies were available to suggest benefits of rebreathing into a paper bag for adolescents and adults with hyperventilation in the first month after exposure to traumatic stress, with regard to symptom severity, presence of disorder, and quality of life.
Harms	No studies were available to evaluate whether rebreathing into a paper bag for adolescents and adults with hyperventilation in the first month after exposure to traumatic stress may do harm.

Value and preferences	

In favour	A common approach to dealing with hyperventilation caused by stress may be rebreathing in a paper bag. Anecdotal clinical experience has suggested some effectiveness.
Against	Clinical guidelines recommend *not* rebreathing into a paper bag in pre-hospital settings. Rebreathing Co2 rather than providing oxygen may be dangerous for adolescents and adults with medical conditions that resemble hyperventilation (e.g. heart attacks and asthma).

Feasibility (including economic consequences)	Making a recommendation *not* to carry out a specific intervention is feasible.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Judgements to inform the decision on the strength of the recommendation

Factor	**Decision**
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes No
Are the expected values and preferences clearly in favour of the recommendation?	Yes No

Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 12

No specific recommendation can be made on the basis of available evidence on rebreathing into a paper bag for adolescents and adults with hyperventilation in the first month after exposure to a potentially traumatic event.

Strength of recommendation: not applicable
Quality of evidence: very low

Remarks

There are significant risks if this technique is used in specific populations (e.g. people with heart disease and asthma).

Health care providers should always rule out physical causes before considering psychological intervention for hyperventilation. They should maintain a calm approach, where possible remove sources of anxiety and coach respirations (i.e. encourage normal breathing, not deeper and quicker than usual).

Health care providers should explain that hyperventilation can sometimes occur after recent exposure to extreme stressors. Acute stress should be managed using psychological first aid as per WHO (2010) mhGAP guidelines. Moreover, as per question 1 (on

psychological interventions for acute traumatic stress symptoms in adults), cognitive-behavioural therapy with a trauma focus should be considered in adults with acute traumatic stress symptoms associated with significant impairment in daily functioning.

13. Hyperventilation (first month): Rebreathing into a Bag – Children

Q13. For children with hyperventilation in the first month after a potentially traumatic event, does rebreathing into a bag when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic events is common, and symptoms of acute stress in the aftermath of such events are frequently reported. A range of symptoms of acute stress exist, such as intrusion, avoidance, hyperarousal, hyperventilation, dissociation, insomnia, and – in children - bedwetting. These symptoms are covered in different evidence profiles of these guidelines.

This scoping question covers hyperventilation in children in the first month after a potentially traumatic event. Around half of populations exposed to potentially traumatic events have been reported to experience panic symptoms during the first month after the event.[41] Indeed, clinical experience suggests that in the immediate aftermath of potentially traumatic events, help-seeking for hyperventilation is common. Because symptoms are associated with hypocapnia, clinicians frequently encourage persons to increase their CO2 levels by re-breathing into a paper bag.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children with hyperventilation, within one month of exposure to a potentially traumatic event(s)
- **Interventions:** Re-breathing into a paper bag
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up

[41] Nixon & Bryant (2003). Peritraumatic and persistent panic attacks in acute stress disorder. *Behavior Research & Therapy*, 41(10), 1237-42; Bryant & Panasetis (2001). Panic symptoms during trauma and acute stress disorder. *Behavior Research & Therapy*, 39(8), 961-6

- Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 29 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (("hyperventilation") AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "hyperventilation". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children (<10 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

Given that no systematic reviews were identified, a systematic review was conducted in week 24 of 2012. This systematic review searched the Cochrane Library; Medline; EMBASE; CINAHL; and PsycInfo for studies with the following keywords: ("traumatic event" or "acute stress" or PTSD) and "hyperventilation". This review returned 81 records: 3 in Cochrane; 31 in Medline; 43 in EMBASE; 3 in CINAHL; and 1 in PsycInfo (where the randomized controlled trial function was selected). These results were hand-searched for relevant studies, but none were identified.

INCLUDED IN GRADE TABLES OR FOOTNOTES

The systematic review did not identify any studies that could be entered in GRADE tables.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Australian Resuscitation Council (2008). Guideline 9.2.8. The first aid management of hyperventilation syndrome.
REASON FOR EXCLUSION: Older than 2 years; no systematic review methodology described; no meta-analysis reported

Warwick University (2006). Hyperventilation syndrome: specific treatment options. Available at http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/prehospitalcare/jrcalcstakeholderwebsite/guidelines/hyperventilation_syndrome_2006.pdf . Last accessed April 24th 2012.
REASON FOR EXCLUSION: Older than 2 years; no systematic review methodology described; no meta-analysis reported

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Rebreathing into a bag vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	No data

Narrative description of the studies that went into analysis

NA

Evidence to recommendation table

Benefits	No studies were available and therefore it is not possible to ascertain whether rebreathing into a bag has a beneficial effect in children with hyperventilation in the first month after exposure to traumatic stress, with regard to symptom severity, presence of disorder, and quality of life.
Harms	No studies were available to evaluate whether rebreathing into a bag for children with hyperventilation in the first month after exposure to traumatic stress may do harm.

Value and preferences	
In favour	A common approach to dealing with hyperventilation caused by stress may be rebreathing into a paper bag. Anecdotal clinical experience has demonstrated some effectiveness.
Against	Clinical guidelines recommend *not* rebreathing into a paper bag in pre hospital settings. Rebreathing Co2 rather than providing oxygen may be dangerous for children e with medical conditions that

	resemble hyperventilation (e.g. asthma).

Feasibility (including economic consequences)	Making a recommendation *not* to carry out a specific intervention is feasible.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes **No X**
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the*	Yes **No X**

benefits are worth the costs of the resources being consumed? *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	

Final recommendation by the guideline panel

Recommendation 13

Rebreathing into a paper bag should not be considered for children with hyperventilation in the first month after a potentially traumatic event.

Strength of recommendation: standard
Quality of evidence: very low

Remarks

Health care providers should always rule out physical causes before considering psychological intervention. They should maintain a calm approach, where possible remove sources of anxiety and coach respirations (i.e., encourage normal breathing, not deeper and quicker than usual).

Health care providers should explain that hyperventilation can sometimes occur after recent exposure to extreme stressors. Acute stress in children should be managed using psychological first aid as per WHO (2010) mhGAP guidelines.

14. Posttraumatic Stress Disorder (PTSD): Psychological Interventions – Adults

Q14. For adults with posttraumatic stress disorder (PTSD), do psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Posttraumatic stress disorder (PTSD) is the most studied disorder after exposure to potentially traumatic events, with prevalence rates ranging from 0.3% to 6.1% in general populations globally and 15.4% in conflict-affected populations,[42] and can be associated with significant impairment in functioning. Much has been written about best practices in treatment of PTSD.

This scoping question focuses on psychological interventions (individual and group cognitive behavioral therapy (CBT), eye movement desensitization and reprocessing (EMDR), stress management) for adult PTSD.

A large amount of research trials have been conducted on (a) cognitive behavior therapy (CBT) with a trauma focus (with most research on prolonged exposure therapy and cognitive processing therapy) and on (b) eye movement desensitization and reprocessing (EMDR).

With respect to CBT, this guideline does not use the term trauma-focused CBT (TF CBT), because this term has been used in different manners in the international literature. For example, in NICE/ Cochrane, this term is used for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing of thoughts related to the event), while the same term is also widely used for a very specific multi-component CBT protocol for children and adolescents developed by Cohen and colleagues. To avoid confusion, this guideline avoids the term TF CBT and uses the term *CBT with a trauma focus* for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing). The term *CBT with a trauma focus* is thus synonymous to the term TF-CBT as used in NICE/Cochrane.

[42] Kessler, R.C., & Üstün, T. B. (Eds.). (2008).*The WHO World Mental Health Surveys: global perspectives on the epidemiology of mental disorders*. New York: Cambridge University Press, 1-580; Steel, Z., Chey, T., Silove, D., Marnane, C., Bryant, R.A., van Ommeren, M. (2009) Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement. Journal of the American Medical Association, 302(5), 537-549.

EMDR is a new treatment developed in the late 1980s. Proponents of EMDR usually do not consider EMDR as a type of cognitive behaviour therapy. This is in contrast to many proponents of CBT, who consider EMDR to be a form of CBT.

Traditional CBT PTSD-treatments involve teaching an individual skills to change unhelpful thoughts and behaviors to more helpful or productive thoughts and behaviors, leading the person to feel better. These treatments utilize procedures that directly target the person's beliefs and behaviors (e.g., prolonged exposure, challenging of beliefs). EMDR procedures focus on spontaneous associative processing of memories with a component of bilateral stimulation (e.g., eye movements). Unlike traditional CBT PTSD-treatments, EMDR therapy (a) does not involve the direct procedural targeting of beliefs or behaviors, (b) does not use daily homework (although the person may be encouraged to test themselves in previously feared situations near the end of the treatment when symptoms already have reduced), and (c) involves treatment that is conducted without detailed descriptions of the event and without direct challenging of beliefs and without extended exposure. Relative to CBT, the underlying theoretical treatment mechanisms of EMDR are still largely speculative and this has been a source of controversy.

It should be noted that exposure treatment (which often is part of CBT with a trauma focus) is very different from psychological debriefing (i.e., promotion of ventilation by requesting a person to briefly but systematically recount perceptions, thoughts, and emotional reactions experienced during the event). The latter does not involve enough sufficient exposure to the traumatic memory to reduce symptoms (see mhGAP Guidelines 2009).

Consistent with the NICE Guidelines for adults, in these guidelines the term *stress management* refers to psychological treatments that use cognitive or behavioral techniques that do not focus on trauma (e.g. relaxation, stress inoculation training).

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with PTSD, after the first month of a potentially traumatic event
- **Interventions:** individual and group CBT with a trauma focus, EMDR, stress management
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 30 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("PTSD" AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "PTSD". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years), focusing on psychological treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

COMMENT: The above search identified 28 relevant systematic reviews. Given the large amount of reviews, and in accordance with the WHO Handbook on Guideline development, only reviews published in the last two years (>2009) are discussed here (other reviews are available upon request).

INCLUDED IN GRADE TABLES OR FOOTNOTES

Bisson, J., Andrew, M., Cooper, R., Lewis, C. Psychological treatment of chronic post-traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*, in in preparation. COMMENT*: this is an update of the 2007 Cochrane review on the same topic. This update has the same conclusions as the previous review.*

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Amstadter, A.B., Broman-Fulks, J., Zinzow, H., Ruggiero, K.J., Cercone, J. (2009). Internet-based interventions for traumatic stress-related mental health problems: A review and suggestion for future research. *Clinical Psychology Review*, 29, 410-420
REASON FOR EXCLUSION: Focuses on interventions delivered in a specific modality

Crumlish, N., O'Rourke, G. (2010). A systematic review of treatments for post-traumatic stress disorder among refugees and asylum seekers. *Journal of Nervous and Mental Disease*, 198, 237-251
REASON FOR EXCLUSION: Focuses on specific population sub-group of refugees and asylum-seekers, and does not report a formal meta-analysis

Cuijpers, P., Marks, I.M., van Straten, A., Cavanagh, K., Gega, L., Anderson, G. (2009). Computer-aided psychotherapy for anxiety disorders: A meta-analytic review. *Cognitive Behaviour Therapy*, 38(2), 66-82
REASON FOR EXCLUSION: Focuses on interventions delivered in a specific modality

Department of Veterans Affairs Health Services Research & Development Service (2009). The assessment and treatment of individuals with history of traumatic brain injury and post-traumatic stress disorder: A systematic review of the evidence
REASON FOR EXCLUSION: Focuses on specific population sub-group

Lawrence, S., De Silva, M., Henley, R. (2010). Sports and games for posttraumatic stress disorder (PTSD). *Cochrane database of Systematic Reviews*, Issue 1
REASON FOR EXCLUSION: did not identify any studies that met inclusion criteria

Mulligan, K., Fear, N.T., Jones, N., Wessely, S., Greenberg, N. (2011). Psycho-educational interventions designed to prevent deployment-related psychological ill health in Armed Forces personnel: A review. *Psychological Medicine*, 41, 673-686
REASON FOR EXCLUSION: Focuses on specific population sub-group and does not report formal meta-analysis

Palic, S., Elklit, A. (2011). Psychosocial treatment of posttraumatic stress disorder in adult refugees: A systematic review of prospective treatment outcome studies and a critique. *Journal of Affective Disorders*, 131, 8-23
REASON FOR EXCLUSION: Focuses on specific population sub-group

Ponniah, K., Hollon, S.D. (2009). Empirically supported psychological treatments for adult acute stress disorder and posttraumatic stress disorder: a review. *Depression and Anxiety*, 26, 1086-1109
REASON FOR EXCLUSION: No formal meta-analysis reported

Possemato, K. (2011). The current state of intervention research for posttraumatic stress disorder within the primary care setting. *Journal of Clinical Psychology in Medical Settings*, DOI 10.1007/s10880-011-9237-4
REASON FOR EXCLUSION: No systematic review methodology reported

Powers, M.B., Halpern, J.M., Ferenschak, M.P., Gillihan, S.J., Foa, E. (2010). A meta-analytic review of prolonged exposure for posttraumatic stress disorder. *Clinical Psychology Review*, 30, 635-641
REASON FOR EXCLUSION: Focuses on one specific form of CBT. i.e. prolonged exposure therapy

Sloan, D.M., Gallagher, M.W., Feinstein, B.A., Lee, D.J., Pruneau, G.M. (2011). Efficacy of Telehealth Treatments for Posttraumatic Stress-Related Symptoms: A Meta-Analysis, *Cognitive Behaviour Therapy*, 40(2), 111-125
REASON FOR EXCLUSION: Focuses on interventions delivered in a specific modality

Stewart, C.L., Wrobel, T.A. (2009). Evaluation of the efficacy of pharmacotherapy and psychotherapy in the treatment of combat-related post-traumatic stress disorder: A meta-analytic review of outcome studies
REASON FOR EXCLUSION: Focuses on specific population sub-group

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Individual CBT with a trauma focus vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Bisson et al (in in preparation) (severity of PTSD symptoms) No data Bisson et al (in in preparation) (PTSD diagnosis) Bisson et al (in in preparation) (proxy drop-out)	Bisson et al (in in preparation) is the most recent review of high quality. Limitations: This Cochrane review focuses on PTSD from the 3rd month after a potentially traumatic event, and does not specifically address treatments in non-specialized health care settings.
2	Group CBT with a trauma focus vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Bisson et al (in in preparation) (severity of PTSD symptoms) No data Bisson et al (in in preparation) (PTSD diagnosis) Bisson et al (in in preparation) (proxy drop-out)	See above

3	EMDR vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Bisson et al (in in preparation) (severity of PTSD symptoms) No data Bisson et al (in in preparation) (PTSD diagnosis) Bisson et al (in in preparation) (proxy drop-out)	See above
4	Stress management vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Bisson et al (in in preparation) (severity of PTSD symptoms) No data Bisson et al (in in preparation) (PTSD diagnosis) Bisson et al (in in preparation) (proxy drop-out)	See above

Narrative description of the studies that went into analysis

Bisson et al (in in preparation) is a recent update (searches up to December 31st 2010) of the Bisson & Andrew (2007) Cochrane review. This study identified 61 randomized controlled trials, out of which 39 studies included individual CBT with a trauma focus, 9 studies included group CBT with a trauma focus, and 16 studies included EMDR. The review identified 7 studies

including stress management (2 including Stress Inoculation Training, 2 including unspecified forms of relaxation 1 including biofeedback-assisted relaxation, and 1 including progressive relaxation training), and 7 studies considering other therapies. The latter included non-directive counseling, psychodynamic therapy, hypnotherapy, and person-centered therapy. No studies covered rows 6, 7, and 8. There was no significant statistical heterogeneity ($I^2 < 50\%$) on outcomes for stress management and other therapies, so fixed effects models were applied in meta-analysis. The quality of the studies addressing CBT with a trauma focus was variable: 8 studies were evaluated to have low risk of bias, 7 studies were judged to have a high risk of bias, and for 24 studies this was unclear. Of the 9 studies that focused on group CBT with a trauma focus, 2 studies were evaluated to have low risk of bias, 1 study was judged to have high risk of bias, and for the remaining 6 there was insufficient information. None of the 16 studies focused on EMDR were rated as having low risk of bias, 2 had a high risk of bias, and for 14 this was uncertain.

Altogether, the systematic review only identified a few large randomized controlled trials with sample sizes over 100. There was significant statistical heterogeneity ($I^2 > 50\%$) on most outcomes across comparisons, so random effects models were applied in meta-analysis. There was insufficient information to judge the risk of bias in a majority of the included studies. In addition, a funnel plot showed some evidence of publication bias.

The authors conclude that individual CBT with a trauma focus, EMDR, stress management, group CBT with a trauma focus are effective in the treatment of PTSD. In addition: “There was some evidence that individual CBT with a trauma focus and EMDR are superior to stress management in the treatment of PTSD at between 1 and 4 months following treatment, and also that CBT, EMDR and stress management are more effective than other therapies.”

NOTE: systematic reviews conducted by Crumlish & Rourke (2010) and Palic & Elklit (2011) were excluded, because they focused on refugees and asylum seekers. It is noted that these studies came to similar conclusions as the Cochrane review that was GRADEd. Crumlish & Rourke found 10 randomized controlled trials (generally small and with inadequate allocation concealment and blinding), and concluded that: “No treatment was firmly supported, but there was evidence for narrative exposure therapy and cognitive-behavioral therapy”. Palic & Elklit (2011) identified 12 RCTs and conclude that: “…indicating a broad suitability of CBT in the treatment of core symptoms of PTSD in adult refugees” and “There are few studies of treatments alternative to CBT and they are less methodologically rigorous than the CBT studies”

GRADE Table

Author(s): Corrado Barbui
Date: 2012-03-09
Question: Should individual CBT with a trauma focus vs treatment as usual or no treatment/waitlist be used in adults with PTSD?
Settings:
Bibliography: Bisson Cochrane Review in preparation.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual CBT	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity - clinician (Better indicated by lower values)												
15[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	284	269	-	SMD 1.27 lower (1.82 to 0.73 lower)	□□□□ MODERATE	CRITICAL
Symptom severity - clinician (1-4 month follow-up) (Better indicated by lower values)												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	146	131	-	MD 17.68 lower (19.68 to 15.68 lower)	□□□□ HIGH	CRITICAL
Symptom severity - clinician (5-8 month follow-up) (Better indicated by lower values)												
2[4]	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	none	65	85	-	MD 8.52 lower (15.37 to 1.67 lower)	□□□□ LOW	CRITICAL
Symptom severity - clinician (9-12 month follow-up) (Better indicated by lower values)												
1[7]	randomised trials	serious[8]	no serious inconsistency[9]	no serious indirectness	serious[6]	none	62	47	-	MD 22.28 lower (32.2 to 12.36 lower)	□□□□ LOW	CRITICAL

Symptom severity - self report (Better indicated by lower values)												
11[10]	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	no serious imprecision	none	258	215	-	SMD 1.56 lower (1.98 to 1.14 lower)	□□□□ MODERATE	CRITICAL
Symptom severity - self report (1-4 month follow-up) (Better indicated by lower values)												
2[12]	randomised trials	serious[1] [3]	no serious inconsistency	no serious indirectness	serious[6]	none	91	90	-	MD 11.03 lower (12.1 to 9.96 lower)	□□□□ LOW	CRITICAL
Symptom severity - self report (9-12 month follow-up) (Better indicated by lower values)												
1[14]	randomised trials	serious[1] [5]	no serious inconsistency[9]	no serious indirectness	serious[6]	none	61	60	-	MD 12.64 lower (16.29 to 8.99 lower)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder - PTSD diagnosis after treatment												
18[16]	randomised trials	no serious risk of bias	serious[17]	no serious indirectness	no serious imprecision	none	242/522 (46.4%)	322/362 (89%)	RR 0.52 (0.41 to 0.65)	427 fewer per 1000 (from 311 fewer to 525 fewer)	□□□□ MODERATE	IMPORTANT
Adverse effects												
22[18]	randomised trials	no serious risk of bias	no serious inconsistency	serious[19]	no serious imprecision	none	211/853 (24.7%)	76/564 (13.5%)	RR 1.72 (1.33 to 2.22)	97 more per 1000 (from 44 more to 164 more)	□□□□ MODERATE	IMPORTANT

[1] From Analysis 1.1.1 of Bisson Cochrane Review in in preparation.
[2] Visual inspection of forest plot suggests heterogeneity. I-squared = 87%.
[3] From Analysis 1.2.1 of Bisson Cochrane Review in in preparation.
[4] From Analysis 1.8 of Bisson Cochrane Review in in preparation.
[5] I-squared = 56%
[6] Less than 200 patients contributed to this analysis.

[7] From Analysis 1.10 of Bisson Cochrane Review in in preparation.
[8] Quote: "Independent raters who were not otherwise involved in the project conducted assessments of treatment adherence and therapist competence."
[9] Only one study contributed to the analysis.
[10] From Analysis 1.1.2 of Bisson Cochrane Review in in preparation.
[11] Visual inspection of forest plot suggests heterogeneity. I-squared = 71%.
[12] From Analysis 1.12 of Bisson Cochrane Review in in preparation.
[13] Unclear risk of bias in one study. In the second one: quote: "Independent raters who were not otherwise involved in the project conducted assessments of treatment adherence and therapist competence."
[14] From Analysis 1.16 of Bisson Cochrane Review in in preparation.
[15] Unclear random allocation.
[16] From Analysis 1.6 of Bisson Cochrane Review in in preparation.
[17] Visual inspection of forest plot suggests heterogeneity. I-squared = 83%.
[18] From Analysis 1.5 of Bisson Cochrane Review in in preparation.
[19] Total dropouts are only a proxy measure of adverse effects.

Author(s): Corrado Barbui
Date: 2012-03-09
Question: Should group CBT with a trauma focus vs treatment as usual or no treatment/waitlist be used in adults with PTSD?
Settings:
Bibliography: Bisson Cochrane Review in in preparation.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Group CBT**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity - clinician (Better indicated by lower values)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	0[6]	-	-	MD 0 higher (0 to 0 higher)[6]	□□□□ VERY LOW	CRITICAL
Symptom severity - clinician (1-4 month follow-up) (Better indicated by lower values)												
0[7]	no					none	0	-	-	MD 0		CRITICAL

	evidence available									higher (0 to 0 higher)		
Symptom severity - clinician (5-8 month follow-up) (Better indicated by lower values)												
1[8]	randomised trials	serious[9]	no serious inconsistency[10]	no serious indirectness	serious[11]	none	45	52	-	MD 18.79 lower (28.98 to 8.6 lower)	□□□□ LOW	CRITICAL
Symptom severity - clinician (9-12 month follow-up) (Better indicated by lower values)												
0[12]	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Symptom severity - self report (Better indicated by lower values)												
5[13]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	125	125	-	SMD 1.15 lower (1.72 to 0.58 lower)	□□□□ MODERATE	CRITICAL
Symptom severity - self report (1-4 month follow-up) (Better indicated by lower values)												
1[14]	randomised trials	serious[15]	no serious inconsistency[10]	no serious indirectness	serious[11]	none	53	24	-	MD 11.24 lower (18.11 to 4.37 lower)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder - PTSD diagnosis after treatment												

1[16]	randomised trials	no serious risk of bias	no serious inconsistency[10]	no serious indirectness	very serious[17]	none	9/24 (37.5%)	16/24 (66.7%)	RR 0.56 (0.31 to 1.01)	293 fewer per 1000 (from 460 fewer to 7 more)	□□□□ LOW	IMPORTANT
Adverse effects												
5[18]	randomised trials	no serious risk of bias	no serious inconsistency	serious[19]	no serious imprecision	none	50/199 (25.1%)	38/181 (21%)	RR 1.19 (0.82 to 1.74)	40 more per 1000 (from 38 fewer to 155 more)	□□□□ MODERATE	IMPORTANT

[1] From Analysis 4.2 of Bisson Cochrane Review in in preparation.
[2] Studies did not provide full details of the method of allocation.
[3] Visual inspection of forest plot suggests significant heterogeneity.
[4] The study populations were varied and not directly comparable. All studies included individuals at least three months following the trauma.
[5] Less than 200 patients included in the analysis.
[6] No overall treatment estimate was calculated.
[7] No data according to Analysis 4.7 of Bisson Cochrane Reveiw in in preparation.
[8] From Analysis 4.11 of Bisson Cochrane Reveiw in in preparation.
[9] Unclear allocation concealment.
[10] Only one study included in the analysis.
[11] Less than 100 patients included in the analysis.
[12] No data according to Analysis 4.12 of Bisson Cochrane Reveiw in in preparation.
[13] From Analysis 4.1 of Bisson Cochrane Reveiw in in preparation.
[14] From Analysis 4.8 of Bisson Cochrane Review in in preparation.
[15] Outcomes rated by patients only.
[16] From Analysis 4.6 of Bisson Cochrane Review in in preparation.
[17] Less than 100 patients included. Confidence interval ranges from appreciable benefit to no benefit.
[18] From Analysis 4.5 of Bisson Cochrane Review in in preparation.
[19] Total droputs are a proxy measure of adverse effects.

Author(s): Corrado Barbui
Date: 2012-03-09

Question: Should EMDR vs treatment as usual or no treatment/waitlist be used in adults with PTSD?
Settings:
Bibliography: Bisson Cochrane Review in in preparation.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMDR	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity - clinician (Better indicated by lower values)												
6[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	93	90	-	MD 13.24 lower (16.39 to 10.1 lower)	□□□□ LOW	CRITICAL
Symptom severity - self report (Better indicated by lower values)												
6[4]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	84	75	-	MD 15.97 lower (19.86 to 12.08 lower)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder												

6[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/107 (48.6%)	97/102 (95.1%)	OR 0.05 (0.02 to 0.14)	459 fewer per 1000 (from 220 fewer to 671 fewer)	□□□□ HIGH	IMPORTANT
Adverse effects												
7[1,6]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	no serious imprecision	none	24/120 (20%)	19/107 (17.8%)	OR 1.07 (0.54 to 2.11)	10 more per 1000 (from 73 fewer to 135 more)	□□□□ MODERATE	IMPORTANT

[1] From Analysis 9.1 of Bisson Cochrane Review in in preparation.
[2] Visual inspection of forest plot suggested significant heterogeneity.
[3] Less than 200 patients included in the analysis.
[4] From Analysis 9.2 of Bisson Cochrane Review in in preparation.
[5] From Analysis 9.6 of Bisson Cochrane Review in in preparation.
[6] From Analysis 9.5 of Bisson Cochrane Review in in preparation.
[7] Total dropouts are only a proxy measure of adverse effects.

Author(s): Corrado Barbui
Date: 2012-03-10
Question: Should stress management vs treatment as usual or no treatment/waitlist be used in adults with PTSD?
Settings:
Bibliography: Bisson Cochrane Review in in preparation.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stress management**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		

Symptom severity - clinician (Better indicated by lower values)												
3[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	44	42	-	SMD 1.14 lower (1.62 to 0.67 lower)	□□□□ LOW	CRITICAL
Symptom severity - self report (Better indicated by lower values)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	12	12	-	SMD 0.33 higher (0.47 lower to 1.14 higher)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder												
4[7]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3,8]	none	41/67 (61.2%)	54/54 (100%)	RR 0.65 (0.5 to 0.86)	350 fewer per 1000 (from 140 fewer to 500 fewer)	□□□□ LOW	IMPORTANT
Adverse effects												

4[9]	randomised trials	no serious risk of bias	no serious inconsistency	serious[10]	very serious[8]	none	12/67 (17.9%)	4/54 (7.4%)	RR 2.19 (0.71 to 6.73)	88 more per 1000 (from 21 fewer to 424 more)	□□□□ VERY LOW	IMPORTANT

[1] From Analysis 2.1.1 of Bisson Cochrane Review in in preparation.
[2] Visual inspection of forest plots suggests some heterogeneity.
[3] Less than 100 patients included in the analysis.
[4] From Analysis 2.2.2 of Bisson Cochrane Review in in preparation.
[5] Only one study contributed to the analysis.
[6] Only 24 patients contributed to the analysis. Confidence interval ranges from appreciable benefit to appreciable harm.
[7] From Analysis 2.6 of Bisson Cochrane Review in in preparation.
[8] Less than 200 patients included in the analysis. Confidence interval ranges from appreciable benefit to appreciable harm.
[9] From Analysis 2.5 of Bisson Cochrane Review in in preparation.
[10] Total dropouts are only a proxy measure of adverse effects.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	**Individual-CBT with a trauma focus**: There is evidence suggesting that individual CBT with a trauma focus in adults with PTSD has a beneficial effect in decreasing symptom severity after intervention. This beneficial effect has been demonstrated using clinician-rated as well as service user-rated outcome measures. The confidence in this estimate is MODERATE. The effect persists at follow-up assessments, although the confidence in estimates at follow-up is LOW. There is evidence suggesting that individual CBT with a trauma focus in adults with PTSD has a beneficial effect in reducing PTSD diagnosis after treatment (individuals with PTSD diagnosis at follow-up: 46.4% (CBT) versus 89% (control group)). The confidence in this estimate is MODERATE.

	There is no systematic review of the evidence on the effect of CBT with a trauma focus on functioning. **Group CBT with a trauma focus** : There is evidence suggesting that Group CBT with a trauma focus in adults with PTSD has a beneficial effect in decreasing symptom severity after intervention. This beneficial effect has been demonstrated using patient-rated outcome measures only. The confidence in estimate is MODERATE. The effect may persist at follow-up assessments, although the confidence in estimates at follow-up is LOW. There is some evidence, from one trial only, suggesting that Group CBT with a trauma focus in adults with PTSD have a beneficial effect in reducing PTSD diagnosis after treatment (individuals with PTSD diagnosis at follow-up: 37.5% (Group CBT with a trauma focus) versus 66.7% (control group)). The confidence in estimate is LOW. There is no systematic review of evidence on the effect of Group CBT on functioning. **EMDR:** There is evidence suggesting that EMDR in adults with PTSD has a beneficial effect in decreasing symptom severity after intervention. This beneficial effect has been demonstrated using clinician-rated as well as patient-rated outcome measures. The confidence in estimate is LOW. It is uncertain if the effect persists at follow-up assessments, as no systematic review of evidence is available. There is evidence suggesting that EMDR in adults with PTSD has a beneficial effect in reducing PTSD diagnosis after treatment (individuals with PTSD diagnosis at follow-up: 48.6% (EMDR) versus 95.1% (control group)). The confidence in this estimate is HIGH. There is no systematic review of evidence on the effect of EMDR on functioning.

	Stress management: There is evidence suggesting that stress management in adults with PTSD has a beneficial effect in decreasing symptom severity after intervention. This beneficial effect has been demonstrated using clinician-rated outcome measures only. The confidence in estimate is LOW. It is unclear if the effect persists at follow-up assessments, as no evidence is available. There is evidence suggesting that stress management in adults with PTSD has a beneficial effect in decreasing PTSD diagnosis after treatment (individuals with PTSD diagnosis at follow-up: 61.2% (stress management) versus 100% (control group)). The confidence in estimate is LOW. There is no systematic review of evidence on the effect of stress management on functioning.
Harms	**Individual CBT with a trauma focus**: There is evidence suggesting that CBT with a trauma focus in adults with PTSD *is* associated with more persons leaving the study early, a proxy measure of treatment acceptability (24.7% versus 13.5%). The confidence in estimate is MODERATE. **Group CBT with a trauma focus**: There is evidence suggesting that Group CBT with a trauma focus in adults with PTSD is *not* associated with more people leaving the study early, a proxy measure of treatment acceptability (25.1% versus 21%). The confidence in estimate is MODERATE. **EMDR**: There is evidence suggesting that EMDR in adults with PTSD is *not* associated with more people leaving the study early, a proxy measure of treatment acceptability (20% versus 17.8%). The

	confidence in estimate is MODERATE. **<u>Stress management</u>**: There is evidence suggesting that stress management in adults with PTSD is associated with more people leaving the study early, a proxy measure of treatment acceptability (17.9% versus 7.4%), although this difference does not reach statistical significance. The confidence in estimate is VERY LOW.

Value and preferences	
In favour	The possibility of decreasing PTSD symptoms and enhancing recovery from PTSD is an important value. Psychological treatment based on CBT principles, including stress management and exposure-based CBT with a trauma focus, has value in that it may possibly build life skills in the person to address stressors in the long-term. Skills applied in these treatments may be applied for treatment of other disorders. Psychological treatment based on EMDR does not require the person to verbalize details of the traumatic event. Compared to CBT, this makes treatment easier when the traumatic event (e.g. sexual violence) carries social stigma; and when therapists are at risk for burn out. Psychological treatment based on stress management has value in it that can be learnt relatively easily by paraprofessionals
Against	Prolonged exposure therapy involves being extensively exposed to frightening or horrific memories that one is trying to avoid, and as such, can be counter-intuitive to the person. Some clinicians and many help-seekers prefer treatments that are easier to endure. (A counter argument is that despite

	such preferences, research using exposure for all types of anxiety disorders shows large effect sizes for reduction in symptoms. Discomfort remembering traumatic memories may be likened to medical procedures where an individual has to undergo discomfort to heal an injury.) EMDR can involve the person suddenly thinking about other traumatic memories, which they may not welcome. Relative to CBT, EMDR's underlying treatment mechanisms are largely unknown. Although a number of studies have reported positive results with EMDR in diverse situations (e.g., evidence exists from Iran and Mexico)[43], EMDR used in certain cultural situations has been interpreted as witchcraft and increased the stress and anxiety in some of the recipients (Melville A, *Psychosocial Interventions: Psychosocial evaluation of UNICEF supported projects (1999-2001),* UNICEF Indonesia, 2003). (A counter argument is that public health experience with other interventions (e.g. vaccinations) suggests that such cultural interpretations can become a significant barrier to implementation, but do not necessarily constitute sufficient reason for deciding to not make the intervention available.)

[43] Abbasnejad, M., Mahani, K. N., & Zamyad, A. (2007). Efficacy of "eye movement desensitization and reprocessing" in reducing anxiety and unpleasant feelings due to earthquake experience. Psychological Research, 9, 104-117; Jarero, I., Artigas, L., & Luber, M. (2011). The EMDR protocol for recent critical incidents: Application in a disaster mental health continuum of care context. Journal of EMDR Practice and Research, 5, 82-94

Feasibility (including economic consequences)	Most studies supporting efficacy were implemented in high-income countries (except two published CBT with a trauma focus studies in Turkey and one unpublished EMDR study in Pakistan) and by trained clinicians. All three non-western studies had positive findings. Most staff in PHC in LMIC have not been extensively trained in communication skills and basic emotional support. Any additional training in delivery of CBT with a trauma focus and EMDR would require substantial resources, including supervision. CBT with a trauma focus and EMDR are both specialized techniques. The clinician using these techniques should also have additional capacities to help the person, including (a) the ability to make differential diagnosis, (b) problem-solving techniques, (c) relaxation/ stabilizing techniques. The likelihood that full time PHC clinicians have the time to learn and practice all these techniques is limited. Given the delicate and technical nature of CBT with a trauma focus and EMDR, implementation by para-professionals may carry risks. Nevertheless, cognitive behavioural interventions have been successfully implemented in low-resource settings by paraprofessionals (e.g. community health workers) to treat maternal depression (Rahman et al, 2008 Lancet 372: 902–09) and post-traumatic stress disorder symptoms in adults and adolescents (Neuner et al, 2008 J Consult Clin Psychol 76(4): 686-94; Ertl et al, 2011 JAMA 306(5): 503-12). There is no randomized evidence that EMDR can feasibly implemented by non-specialized health staff. The EMDR Institute requires prospective trainees to “have a masters degree or higher in the mental health field and are licensed or certified through a state or national board which authorizes independent practice.” Stress management training can be carried out relatively simply and practised on a regular group basis by paraprofessionals. It has value across a range of disorders.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X** **CBT/EMDR** **No X** **Group CBT/Stress management**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 14

Individual or group cogntive-behavioural therapy (CBT) with a trauma focus, eye movement desensitization and reprocessing (EMDR), or stress management should be considered for adults with PTSD

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, EMDR; low for group CBT, stress management

Remarks

Individual and group CBT with a trauma focus and EMDR should only be offered in those contexts where individuals are competent (i.e. trained and supervised) to provide the therapies. Although studies show that individual CBT with a trauma focus is more effective than stress management, in resource constrained settings stress management may be the most feasible treatment option.

15. Posttraumatic Stress Disorder (PTSD): Psychological Interventions – Children and Adolescents

Q15. For children and adolescents with posttraumatic stress disorder (PTSD), do psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

This scoping question focuses on psychological interventions (individual and group cognitive behavioral therapy (CBT), eye movement desensitization and reprocessing (EMDR), stress management, and psycho-education) for child and adolescent PTSD.

With respect to CBT, this guideline does not use the term trauma-focused CBT (TF CBT), because this term has been used in different manners in the international literature. For example, in the widely used NICE Guidelines, this term is used for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing of thoughts related to the event), while the same term is also widely used for a very specific multi-component CBT protocol for children and adolescents developed by Cohen and colleagues. To avoid confusion, this guideline avoids the term TF CBT and uses the term *CBT with a trauma focus* for all CBT interventions that involve a trauma focus (e.g. through exposure or cognitive processing). The term *CBT with a trauma focus* is thus synonymous to the term TF-CBT as used in the NICE Guidelines.

EMDR is a new treatment developed in the late 1980s. Proponents of EMDR usually do not consider EMDR as a type of cognitive behaviour therapy. This is in contrast to many proponents of CBT, who consider EMDR to be a form of CBT.

Traditional CBT PTSD-treatments involve teaching an individual skills to change unhelpful thoughts and behaviors to more helpful or productive thoughts and behaviors, leading the person to feel better. These treatments utilize procedures that directly target the person's beliefs and behaviors (e.g., exposure, challenging of beliefs), EMDR procedures focus on spontaneous associative processing of memories with a component of bilateral stimulation (e.g., eye movements). Unlike traditional CBT PTSD-treatments, EMDR therapy (a) does not involve the direct procedural targeting of beliefs or behaviors, (b) does not use daily homework (although the person may be encouraged to test themselves in previously feared situations near the end of the treatment when symptoms already have reduced), and (c) involves treatment that is conducted without detailed descriptions of the event and without direct challenging of beliefs and without extended exposure. Relative to CBT, the underlying theoretical treatment mechanisms of EMDR are still largely speculative, and this has been a source of controversy.

It should be noted that exposure treatment (which often is part of CBT with a trauma focus) is very different from psychological debriefing (i.e., promotion of ventilation by requesting a person to briefly but systematically recount perceptions,

thoughts, and emotional reactions experienced during the event). The latter does not involve enough sufficient exposure to the traumatic memory to reduce symptoms (see mhGAP Guidelines 2009).

Consistent with the NICE Guidelines for adults, the term *stress management* refers in this guidelines to psychological treatments that use cognitive or behavioral techniques that do not focus on trauma (e.g. relaxation, stress inoculation training)

Psycho-education refers in this guideline to "the provision of information about the nature of stress, posttraumatic and other symptoms, and what to do about them."

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and adolescents with PTSD, after the first month of a potentially traumatic event
- **Interventions:** Individual and group CBT with trauma focus, EMDR, stress management, psycho-education
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention
  - Functioning/ quality of life post intervention
  - Presence of mental disorder at 6 to 12 month follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 30 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ("PTSD" AND "systematic review"). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option, and used only the keyword "PTSD". We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years), focusing on psychological and social treatments. We did not include systematic reviews of pharmacological and manual therapies (e.g. massage therapy, acupuncture, spinal manipulation). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE using the same keyword. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Kowalik, J., Weller, J., Venter, J., Drachman, D. (2011). Cognitive behavioral therapy for the treatment of pediatric posttraumatic stress disorder: A review and meta-analysis. *Journal of Behavior Therapy & Experimental Psychiatry*, 42, 405-413

Rodenburg, R., Benjamin, A., de Roos, C., Meijer, A., Stams, G. (2009). Efficacy of EMDR in children: A meta-analysis. *Clinical Psychology Review*, 29, 599-606

Rolfsnes, E.S., Idsoe, T.E. (2011). School-based intervention programs for PTSD symptoms: A review and meta-analysis. *Journal of Traumatic Stress*, 24(2), 155-165

Silverman, W.K., Ortiz, C.D., Viswesvaran, C., Burns, B, Kolko, D.J., Putnam, F., Amaya-Jackson, L., (2008). Evidence-based psychosocial treatments for children and adolescents exposed to traumatic events. *Journal of Clinical Child & Adolescent Psychology*, 37(1), 156-183

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

American Academy of Child & Adolescent Psychiatry (AACAP) (2010). Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(4), 414-430

REASON FOR EXCLUSION: Minimal description of systematic review methodology, e.g. no description of quality appraisal of studies, and no formal meta-analysis reported

Cartwright-Hatton, S., Roberts, C., Chitsabesan, P., Fothergill, C., Harrington, R. (2004). Systematic review of the efficacy of cognitive behaviour therapies for childhood and adolescent anxiety disorders. *British Journal of Clinical Psychology*, 43, 421-436

REASON FOR EXCLUSION: More than 2 years old, excluded trials solely focusing on PTSD

Cohen, J.A., Mannarino, A.P. (2010). Psychotherapeutic options for traumatized children. *Current Opinion in Pediatrics*, 22, 605-609

REASON FOR EXCLUSION: No systematic review methodology is described

Ehntholt, K., Yule, W. (2006). Practitioner Review: Assessment and treatment of refugee children and adolescents who have experienced war-related trauma. *Journal of Child Psychology & Psychiatry*, 47(12), 1197-1210

REASON FOR EXCLUSION: More than 2 years old, no systematic review methodology is described

Macdonald, G., Higgins, J., Ramchandi, P. (2006). Cognitive-behavioral interventions for children who have been sexually abused. *Campbell Systematic Reviews*, DOI 10.4073/csr.2006.10

REASON FOR EXCLUSION: More than 2 years old, focused on specific population sub-group

Peltonen, K., Punamäki, R. (2010). Preventive interventions among children exposed to trauma of armed conflict: A literature review. *Aggressive Behavior*, 36, 95-116

REASON FOR EXCLUSION: Focused on specific population sub-group; missed studies published in recent years

Taylor, T.L., Chemtob, C.M. (2004). Efficacy of treatment for child and adolescent traumatic stress. *Archives of Pediatrics and Adolescent Medicine*, 158, 786-791

REASON FOR EXCLUSION: More than 2 years old, no formal meta-analysis reported

Trask, E.V., Walsh, K., DiLillo, D. (2011). Treatment effects for common outcomes of child sexual abuse: A current meta-analysis. *Aggression and Violent Behavior*, 16, 6-19

REASON FOR EXCLUSION: Focused on specific population sub-group

Wethington, H.R., Hahn, R.A., Fuqua-Whitley, D.S., Sipe, T.A., Crosby, A.E., Johnson, R.L., Liberman, A.M., Mos´cicki, E., Price, L.N., Tuma, F.K. Kalra, G., Chattopadhyay, S.K., Task Force on Community Preventive Services (2008). The effectiveness of interventions to reduce psychological harm from traumatic events among children and adolescents: A systematic review. American Journal of Preventive Medicine, 35(3), 287-313 & Task Force on Community Preventive Services (2008). Recommendations to reduce psychological harm from traumatic events among children and adolescents. *American Journal of Preventive Medicine*, 35(3), 314-316

REASON FOR EXCLUSION: excluded studies in middle-income and low-income countries (no further details on reports excluded for this reason), and merged EMDR within the CBT category

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Individual CBT vs. no treatment/ control	Symptom severity	Silverman et al (2008) for PTSD symptoms; Kowalik et al (2011) for internalizing/ externalizing problems	Silverman and colleagues is older than 2 years, but reviews interventions that are not reviewed elsewhere. This review is supplemented by the more recent Kowalik et al (2011) study for other than PTSD outcomes.
		Functioning	No data	
		Presence of disorder	No data	

		Adverse effects	No data	
2	Group CBT vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Rolfsnes & Idsoe (2011) No data No data No data	Rolfsnes & Idsoe (2011) is the most recent review of group CBT interventions, but also included non-randomized controlled studies.
3	EMDR vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	Rodenburg et al (2009) No data No data No data	Rodenburg et al (2009) is the most recent high quality systematic review and meta-analysis including EMDR as a separate intervention
4	Stress management vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	
5	Psycho-education[b] vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	

Narrative description of the studies that went into analysis

Silverman and coworkers' (2008) review is older than two years, but is the most recent systematic review and meta-analysis that reviewed a variety of psychosocial/psychological interventions of interest to this scoping question (e.g., the Task Force on Community Preventive Services [2008] merged EMDR within a CBT category). Altogether, the review identified 21 randomized controlled trials. Most studies evaluated individual or group CBT with trauma focus. Included studies focused on children exposed to a variety of traumatic stressors, with a large group of studies focused on sexual abuse and maltreatment. Two separate studies (total N=324) were found that focused on group CBT, both implemented in school settings in the United States. Meta-analysis focused on the variables treatment (CBT vs non-CBT), parent involvement, and type of trauma. The authors conclude that significant effect sizes were found favoring CBT treatment and treatment of sexually abused children.

Kowalik and colleagues (2011) identified a similar group of studies as Silverman and colleagues (2008) (n=21, no studies dated past 2007). Subsequent to observing that the CBCL was a measure consistently used, authors focused on meta-analyses of the three subscales of this measure (total problems, internalizing and externalizing problems).

For a more up-to-date review of group CBT, Rolfsnes & Idsoe's (2011) review of school-based interventions was selected. This review included 19 studies, out of which 16 applied a form of CBT. However, this review also included non-randomized controlled studies.

Rodenburg and colleagues (2009) systematic review and meta-analysis of EMDR for the treatment of PTSD in children and adolescents identified 7 randomized controlled trials. These studies included children experiencing a range of trauma's (dominantly one-off events), who were offered between 3 and 8 sessions of EMDR. Meta-analysis focused on PTSD symptoms post-treatment as few studies assessed longitudinal changes. Altogether, EMDR was effective with a medium effect size (Cohen's *d* .56), and found to be more effective than CBT treatments when comparing effect sizes. The variation in effect sizes between studies was partly explained by both treatment and study methodology factors, including year of publication (more recent studies associated with lower effect sizes), type of informant (parent-child reports associated with higher effect sizes than studies using only child reports), drop-out (more drop-out associated with lower effect sizes), type of comparison (comparison with established treatments associated with lower effect sizes), and number of sessions (less sessions associated with higher effect sizes).

GRADE Tables

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-27
Question: Should individual CBT vs treatment as usual or no treatment/waitlist be used in children and adolescents with PTSD?
Settings:
Bibliography: Silverman 2008, Kowalik 2011

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Individual CBT**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
PTSD symptoms (Better indicated by higher values)												
16[1]	randomised trials	no serious risk of bias[2]	serious[3]	no serious indirectness	no serious imprecision	none	0[2]	-	-	sample size weighted average effect size 0.50 higher (0.03 to 0.98 higher)	□□□□ MODERATE	CRITICAL
Comorbid internalizing symptoms (Better indicated by lower values)												

7[4]	randomised trials	serious[5]	no serious inconsistency[6]	no serious indirectness	no serious imprecision[7]	none	0[2]	-	-	Average effect size 0.314 lower (0.505 to 0.122 lower)	□□□□ MODERATE	CRITICAL
Comorbid externalizing symptoms (Better indicated by lower values)												
8[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0[2]	-	-	Average effect size 0.192 lower (0.376 to 0.008 lower)	□□□□ MODERATE	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Silverman 2008, table 5.
[2] Not clearly reported.
[3] Funnel plot not available, but significant variability among effect sizes is reported.

[4] From Kowalik 2011.
[5] From Table 1 of Kowalik 2011.
[6] I-squared = 20.3%.
[7] Overall number of patients included in this analysis not reported.

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-27
Question: Should group CBT vs treatment as usual or no treatment/waitlist be used in children and adolescents with PTSD?
Settings:
Bibliography: Rolfsnes 2011

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group CBT	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity (Better indicated by higher values)												
19[1]	observational studies	very serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision[4]	none	0[5]	-	-	Cohen's d 0.68 higher (0 to 0 higher)[5]	□□□□ VERY LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												

0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Rolfsnes 2011, page 163.
[2] Randomized trials were pooled together with non-randomized trials.
[3] Not reported.
[4] Overall number of included patients not reported.
[5] CI not reported. SD = 0.41

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-27
Question: Should EMDR vs treatment as usual or no treatment/waitlist be used in children and adolescents with PTSD?
Settings:
Bibliography: Rodenburg 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EMDR**	**Treatment as usual or no treatment/waitlist**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by higher values)												
7[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	0[4]	-	-	Cohen's d 0.56 higher (0.42 to 0.7 higher)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												

0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Rodenburg 2009, table 3.
[2] Unclear random allocation and concealment of allocation.
[3] Funnel plot not available but inconsistency reported by the authors.
[4] Overall sample size is 209.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	**Individual CBT with trauma focus**: There is evidence suggesting that individual CBT with trauma focus in children with PTSD has a beneficial effect in decreasing symptom severity after intervention. The confidence in estimate is MODERATE. It is unclear if the effect persists at follow-up assessments, as no systematic review of evidence is available. There is no systematic review of evidence on the effect of individual trauma-focused CBT on presence of disorder and functioning. **Group CBT with trauma focus**: There is evidence suggesting that Group CBT with trauma focus in children with PTSD may have a beneficial effect in decreasing symptom severity after intervention. However, the confidence in

	estimate is VERY LOW (randomized controlled trials were meta-analyzed together with non-randomized controlled trials). It is unclear if the effect persists at follow-up assessments, as no systematic review of evidence is available. There is no systematic review of evidence on the effect of Group CBT with trauma focus on presence of disorder and functioning. **EMDR**: There is evidence suggesting that EMDR in children with PTSD may have a beneficial effect in decreasing symptom severity after intervention. However, the confidence in estimate is LOW. It is unclear if the effect persists at follow-up assessments, as no systematic review of evidence is available. There is no systematic review of evidence on the effect of EMDR on functioning, presence of disorder and adverse effects. **Other psychological treatments:** There is no systematic review of evidence on the effect of other psychological interventions (stress management, dealing with current stressors, psycho-education) on decreasing PTSD symptoms, reducing PTSD or functioning.
Harms	There is no systematic review of evidence available to evaluate if CBT with trauma focus, EMDR or other psychological interventions may do harm for children and adolescents with PTSD.

Value and preferences	

In favour	The possibility of decreasing PTSD symptoms and decreasing presence of PTSD is an important value. Psychological treatment based on CBT principles has value in that it may possibly build life skills in the person to address stressors in the long-term. Skills applied in these treatments may be applied for treatment of other disorders. Psychological treatment based on EMDR does not require the child or adolescent to verbalize details of the traumatic event. Compared to CBT, this makes treatment easier when the traumatic event (e.g. sexual violence) carries social stigma; when the child has for any other reason (e.g. developmental stage) difficulties verbalizing what has happened; and when therapists are at risk for burn out.
Against	Trauma focused CBT include imaginal or in vivo exposure. Exposure therapy involves being exposed to frightening or horrific memories that one is trying to avoid (e.g. through drawing, stories), and as such, can be counter-intuitive to the child or adolescent. Some clinicians and many help-seekers prefer treatments that are easier to endure. (A counter argument is that despite such preferences, research using exposure for all types of anxiety disorders shows large effect sizes for reduction in symptoms. Discomfort remembering traumatic memories may be likened to medical procedures where an individual has to undergo discomfort to heal an injury.) EMDR can involve the person suddenly thinking about other traumatic memories, which they may not welcome. Relative to CBT, the underlying treatment mechanisms of EMDR are largely unknown. Although a number of studies (with adults) have reported positive results with EMDR in diverse situations (eg from Iran[44])), EMDR used in certain cultural situations has been interpreted as witchcraft and increased the stress and anxiety in some of the recipients (Melville A, Psychosocial Interventions: Psychosocial evaluation of UNICEF supported projects (1999-2001), UNICEF Indonesia, 2003). Public health experience with other interventions (e.g. vaccinations) suggests that

[44] Jaberghaderi, N., Greenwald, R., Rubin, A., Dolatabadim S., & Zand, S.O. (2004). A comparison of CBT and EMDR for sexually abused Iranian girls. Clinical Psychology and Psychotherapy, 11, 358-368.;

	such cultural interpretations can become a significant barrier to implementation, but do not necessarily constitute sufficient reason for deciding to not make the intervention available.

Feasibility (including economic consequences)	Most studies supporting efficacy were implemented in high-income countries and by trained clinicians. Most staff in PHC in LMIC have not received extensive training in communication skills and basic emotional support. Any additional training in CBT and EMDR would require substantial resources, including supervision. CBT and EMDR are both specialized techniques. The clinician using these techniques should also have additional capacities to help the person, including (a) the ability to make differential diagnosis, (b) problem-solving techniques, (c) relaxation/ stabilizing techniques, and (d) working with children. The likelihood that full time PHC clinicians have the time to learn and practice all these techniques is limited. CBT and EMDR involve thinking about trauma-related reminders. Given the delicate nature of this process, implementation by para-professionals may carry risks. Nevertheless, cognitive behavioural interventions have been successfully implemented in low-resource settings by paraprofessionals (e.g., community health workers) to treat maternal depression (Rahman et al, 2008 Lancet 372: 902–09) and post-traumatic stress disorder symptoms in adults and adolescents (Neuner et al, 2008 J Consult Clin Psychol 76(4): 686-94; Ertl et al, 2011 JAMA 306(5): 503-12). There is no randomized evidence that EMDR can feasibly implemented by non-specialized health staff. The EMDR Institute requires prospective trainees to “have a masters degree or higher in the mental health field and are licensed or certified through a state or national board which authorizes independent practice.”

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X individual CBT** **No X group CBT/ EMDR**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X individual CBT** **No X group CBT/ EMDR**
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 15

Individual or group cogntive-behavioural therapy (CBT) with a trauma focus or eye movement desensitization and reprocessing (EMDR) should be considered for children and adolescents with PTSD.

Strength of recommendation: standard
Quality of evidence: moderate for individual CBT, low for EMDR, very low for group CBT

Remarks

Individual and group CBT with a trauma focus and EMDR should only be offered in those contexts where individuals are competent (i.e. trained and supervised) to provide the therapies. Stress management may also be beneficial for children and adolescents with PTSD.

16. Posttraumatic Stress Disorder (PTSD): Pharmacological Interventions – Adults

Q16. For adults with posttraumatic stress disorder (PTSD), do tricyclic antidepressants (TCAs) or selective serotonin re-uptake inhibitors (SSRIs) when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic stressors is common. Posttraumatic stress disorder (PTSD) is the most studied disorder after exposure to potentially traumatic events, with prevalence rates ranging from 0.3% to 6.1% in general populations globally and 15.4% in conflict-affected populations,[45] [46] and can be associated with significant impairment in functioning.

Pharmacological treatments, especially anti-depressants, are commonly prescribed for people suffering PTSD. However, there is currently no consensus on the effectiveness of pharmacological treatments between different clinical practice guidelines, [47] making this an important scoping question.

The question is limited to those pharmacological treatments that are most likely available now or in the next 5 years in non-specialized health care in low and middle income countries. Amitriptyline (as a representative of the tricyclic antidepressants) and fluoxetine (*not* as a representative of SSRIs) are included in the WHO model list of essential medicines for the treatment of depressive disorders. The scoping question will address: (a) Tricyclic antidepressants (TCAs, as a category of antidepressants), (b) Selective serotonin re-uptake inhibitors (SSRIs, as a category of antidepressants), and (c) fluoxetine (*not* as a representative of SSRIs)

[45] Kessler, R.C., & Üstün, T. B. (Eds.). (2008).*The WHO World Mental Health Surveys: global perspectives on the epidemiology of mental disorders*. New York: Cambridge University Press, 1-580

[46] Steel, Z., Chey, T., Silove, D., Marnane, C., Bryant, R.A., van Ommeren, M. (2009) Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement. Journal of the American Medical Association, 302(5), 537-549.

[47] Forbes, D., Creamer, M., Bisson, J., Cohen, J.A., Crow, B.E., Foa, E., Friedman, M.J., Keane, T.M., Kudler, H.S., Ursano, R.J. (2010). A guide to guidelines for the treatment of PTSD and related conditions. *Journal of Traumatic Stress*, 23(5), 537-552

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Adults with PTSD, after the first month of a potentially traumatic event
- **Interventions:** Antidepressants
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

Details of commissioned systematic review

NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results of studies relevant to adults with PTSD symptoms are discussed.

Types of studies

All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated trauma focussed psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

Types of participants

All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions

Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.

The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy

We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR "pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria
- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, presence of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Narrative description of the studies that went into analysis

All but one of the studies employed a placebo comparator arm, Spivak 2006 being the exception (reboxetine versus fluvoxamine). There were 22 comparisons in 7 SSRI trials, 2 of which included sertraline (Friedman 2007, Panahi 2011), 2 fluoxetine (Martenyi 2007, van der Kolk 2007), 1 escitalopram (Shalev 2011) and 1 fluvoxamine (Spivak 2006). One trial compared the SNRI venlafaxine against placebo (Davidson 2006). One trial assessed the atypical antipsychotic risperidone (Padala 2006). One trial included the mood stabiliser divalproex (Davis 2008). Two trials assessed the anticonvulsant topiramate (Tucker 2007, Yeh 2010) and 1 trial considered tiagabine (Davidson 2007). Matthew 2011 assessed a novel new selective neurokinin-1 receptor antagonist called GR205171.

All but 2 of the trials were between 8-12 weeks of treatment duration, Davidson 2006 compared venlafaxine to placebo over 6 months and Shalev 2011 compared escitalopram to placebo over 5 months. No RCTs of pharmacotherapy for ASD or grief reactions. No RCTs for PTSD, ASD or grief reactions in children or adolescents were found.

Risk of bias assessments

Eight of the studies included enough information on adequate random sequence generation to be judged as having a low risk of bias, the remainder were unclear. Only 2 studies included an adequate description of allocation concealment. All 14 studies described themselves as double blind but a total of 8 provided sufficient information to judge the blinding of participants, personnel and outcome assessors as low risk. Incomplete outcome data was addressed adequately in 5 studies. Ten of the studies were deemed to be free of selective reporting.

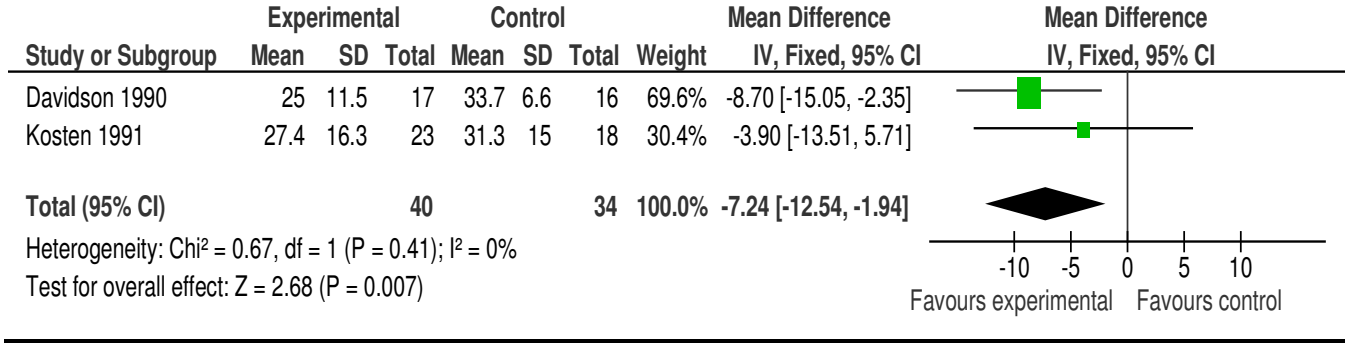
PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	TCA versus placebo	Symptom severity Functioning Presence of disorder Adverse effects	Bisson review No data No data Bisson review	
2	SSRI versus placebo	Symptom severity Functioning Presence of disorder Adverse effects	Bisson review No data No data Bisson review	
3	Fluoxetine versus placebo	Symptom severity Functioning Presence of disorder Adverse effects	Bisson review No data No data Bisson review	

TCA versus placebo

Efficacy: self rated IES (Impact of events scale, total score)

Davidson 1990 = amitriptyline
Kosten 1991 = imipramine

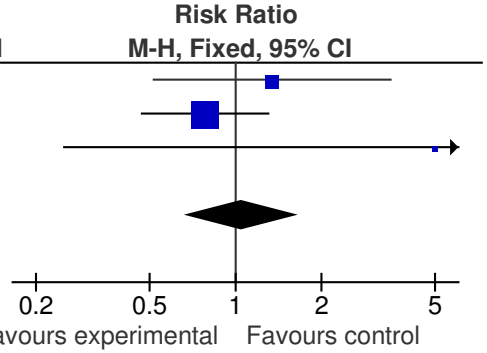


Leaving the study early

Davidson 1990 = amitriptyline
Kosten 1991 = imipramine
Reist 1989 = desipramine

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Davidson 1990	8	25	5	21	28.0%	1.34 [0.52, 3.49]
Kosten 1991	12	23	12	18	69.4%	0.78 [0.47, 1.30]
Reist 1989	2	27	0	27	2.6%	5.00 [0.25, 99.51]
Total (95% CI)		**75**		**66**	**100.0%**	**1.05 [0.66, 1.66]**
Total events	22		17			

Heterogeneity: Chi² = 2.57, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.20 (P = 0.84)

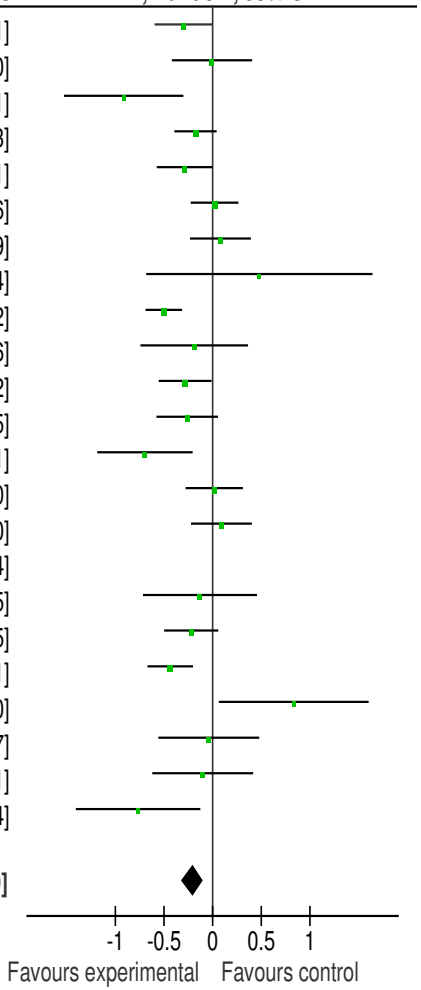


SSRI versus placebo Efficacy: PTSD symptom severity (any continuous outcome).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brady 2000	43.4	28.1	93	51.9	28.7	90	5.6%	-0.30 [-0.59, -0.01]
Brady 2004	32.56	15.69	49	32.7	28.75	45	4.2%	-0.01 [-0.41, 0.40]
Connor 1999	10.1	9.8	25	20.5	12.6	22	2.5%	-0.91 [-1.52, -0.31]
Davidson	-39.4	27.12	173	-34.5	28.42	179	6.9%	-0.18 [-0.39, 0.03]
Davidson 2001c	-33	23.8	98	-26.2	23.46	104	5.8%	-0.29 [-0.56, -0.01]
Ely lily	-10.42	7.5	323	-10.59	10.21	88	6.5%	0.02 [-0.21, 0.26]
Friedman 2007	-13.1	27.5	84	-15.4	28.07	82	5.5%	0.08 [-0.22, 0.39]
Hertzberg 2000	47	8	6	42	11	6	0.9%	0.48 [-0.68, 1.64]
Marshall 2001	-38.75	27.24	365	-25.3	25.8	186	7.3%	-0.50 [-0.68, -0.32]
Marshall 2004	55.6	33.4	25	62.8	40.8	27	2.9%	-0.19 [-0.73, 0.36]
Martenyi 2002A	-34.6	28.1	226	-26.8	26.1	75	6.1%	-0.28 [-0.54, -0.02]
Martenyi 2007	-42.9	23.1	114	-36.6	25.7	64	5.4%	-0.26 [-0.57, 0.05]
Panahi 2011	-22.7	7.3	35	-17.5	7.5	35	3.4%	-0.69 [-1.18, -0.21]
Pfizer588	-27.4	27.12	94	-27.9	28.42	94	5.7%	0.02 [-0.27, 0.30]
Pfizer589	-13.1	21.12	84	-15.4	28.42	82	5.5%	0.09 [-0.21, 0.40]
Robb 2010	-17.7	1.9	67	-20.8	2.1	61	0.0%	1.54 [1.15, 1.94]
Shalev 2011	-31.12	29.63	23	-27.8	20.13	23	2.7%	-0.13 [-0.71, 0.45]
SKB627	-36.5	26.1	109	-30.8	25.37	103	5.9%	-0.22 [-0.49, 0.05]
Tucker 2001	-35.5	24.58	151	-24.7	24.98	156	6.6%	-0.43 [-0.66, -0.21]
Tucker 2003	60.28	26.15	25	29.07	55.5	10	1.8%	0.83 [0.07, 1.60]
van der Kolk 2004	42.7	22.1	30	43.6	22.6	29	3.2%	-0.04 [-0.55, 0.47]
van der Kolk 2007	-33.23	22.11	30	-30.95	22.6	29	3.2%	-0.10 [-0.61, 0.41]
Zohar 2002	-18.7	6.7	23	-13.5	6.6	19	2.4%	-0.77 [-1.40, -0.14]
Total (95% CI)			**2185**			**1548**	**100.0%**	**-0.20 [-0.32, -0.09]**

Heterogeneity: Tau² = 0.04; Chi² = 50.64, df = 21 (P = 0.0003); I² = 59%

Test for overall effect: Z = 3.51 (P = 0.0005)

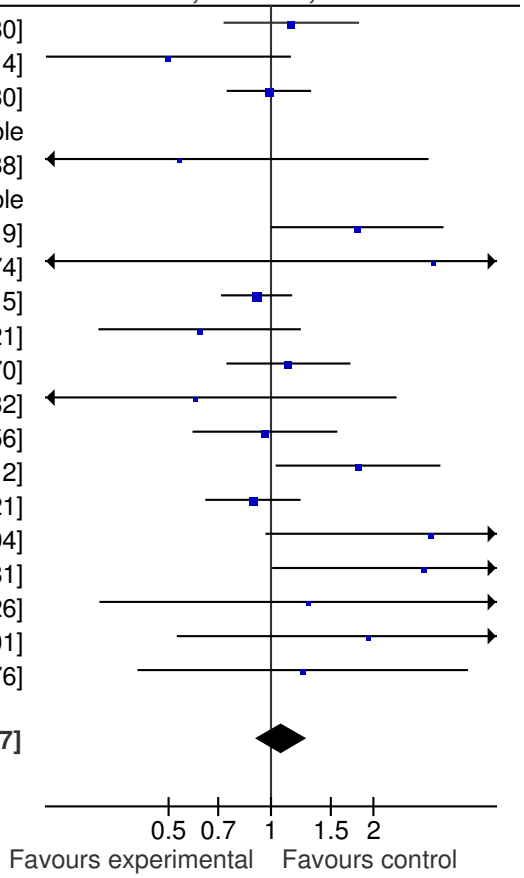


Leaving the study early

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Brady 2000	29	94	25	93	8.5%	1.15 [0.73, 1.80]
Connor 1999	6	27	12	27	3.6%	0.50 [0.22, 1.14]
Davidson	62	173	65	179	13.4%	0.99 [0.75, 1.30]
Davidson 2001	0	0	0	0		Not estimable
Davidson 2001c	2	100	4	108	1.0%	0.54 [0.10, 2.88]
Davidson 2003	0	0	0	0		Not estimable
Friedman 2007	26	86	14	83	6.2%	1.79 [1.01, 3.19]
Hertzberg 2000	1	6	0	6	0.3%	3.00 [0.15, 61.74]
Marshall 2001	127	369	69	182	15.1%	0.91 [0.72, 1.15]
Marshall 2004	8	25	14	27	4.9%	0.62 [0.31, 1.21]
Martenyi 2007	50	163	24	88	9.4%	1.12 [0.75, 1.70]
Panahi 2011	3	35	5	35	1.5%	0.60 [0.16, 2.32]
Pfizer588	24	95	25	95	7.8%	0.96 [0.59, 1.56]
Pfizer589	28	86	15	83	6.6%	1.80 [1.04, 3.12]
SKB627	49	160	56	162	12.2%	0.89 [0.65, 1.21]
Tucker 2001	12	163	4	160	2.1%	2.94 [0.97, 8.94]
van der Kolk 1994	12	33	4	31	2.5%	2.82 [1.02, 7.81]
van der Kolk 2004	4	30	3	29	1.4%	1.29 [0.32, 5.26]
van der Kolk 2007	6	30	3	29	1.6%	1.93 [0.53, 7.01]
Zohar 2002	6	23	4	19	2.1%	1.24 [0.41, 3.76]
Total (95% CI)		**1698**		**1436**	**100.0%**	**1.07 [0.91, 1.27]**
Total events	455		346			

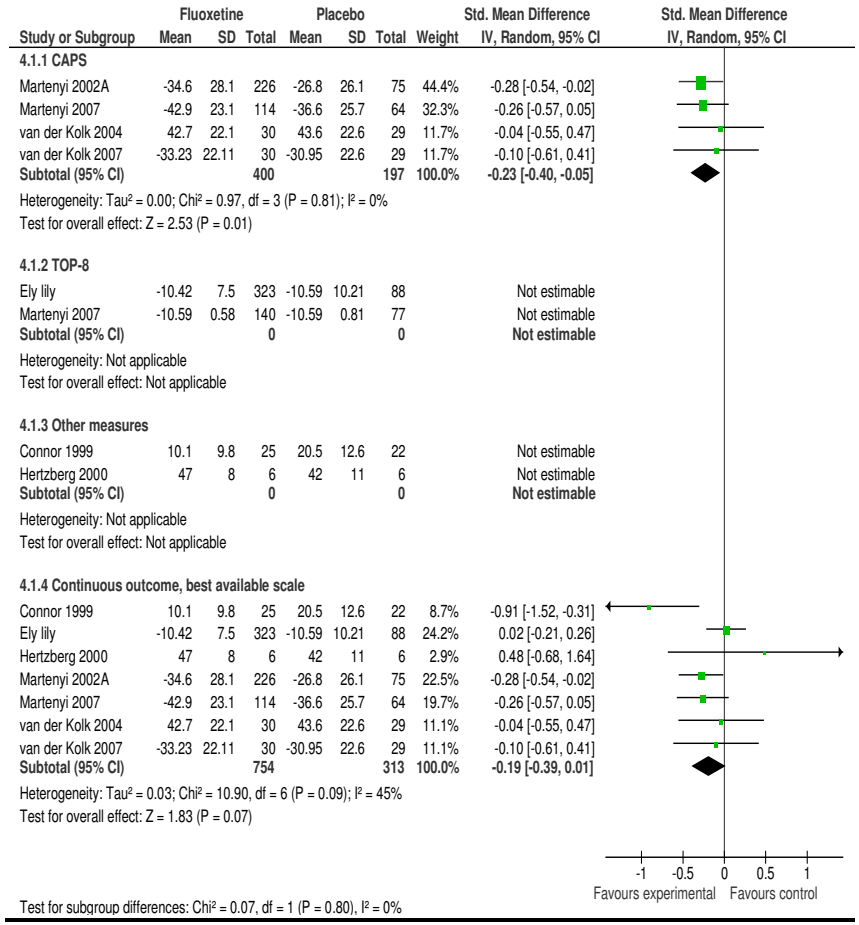
Heterogeneity: Tau² = 0.04; Chi² = 25.44, df = 17 (P = 0.09); I² = 33%

Test for overall effect: Z = 0.83 (P = 0.41)



Fluoxetine versus placebo

Efficacy: PTSD symptom severity

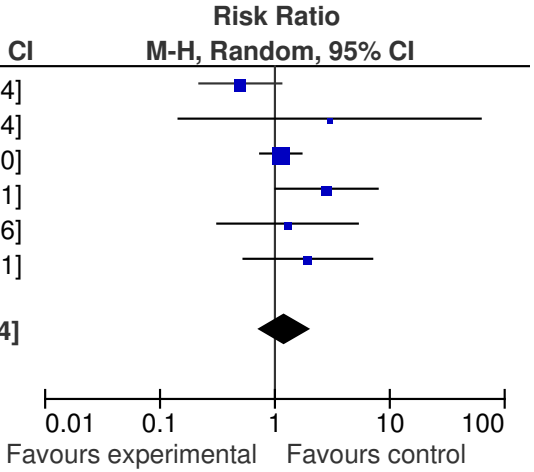


Leaving the study early

Study or Subgroup	Fluoxetine Events	Fluoxetine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Connor 1999	6	27	12	27	21.5%	0.50 [0.22, 1.14]
Hertzberg 2000	1	6	0	6	2.7%	3.00 [0.15, 61.74]
Martenyi 2007	50	163	24	88	36.8%	1.12 [0.75, 1.70]
van der Kolk 1994	12	33	4	31	16.6%	2.82 [1.02, 7.81]
van der Kolk 2004	4	30	3	29	10.4%	1.29 [0.32, 5.26]
van der Kolk 2007	6	30	3	29	11.9%	1.93 [0.53, 7.01]
Total (95% CI)		**289**		**210**	**100.0%**	**1.22 [0.73, 2.04]**
Total events	79		46			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 8.00$, df = 5 (P = 0.16); $I^2 = 38\%$

Test for overall effect: Z = 0.77 (P = 0.44)



GRADE Table

Author(s): Corrado Barbui, Wietse Tol, Jonathan Bisson
Date: 2012-04-19
Question: Should TCAs vs placebo be used in adults with PTSD?
Settings:
Bibliography: Bisson Review

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCAs**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	40	34	-	MD 7.24 lower (12.54 to 1.94 lower)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[5]	none	22/75 (29.3%)	17/66 (25.8%)	RR 1.05 (0.66 to 1.66)	13 more per 1000 (from 88 fewer to 170 more)	□□□□ LOW	IMPORTANT

[1] Bisson Review
[2] Self rated outcome measure
[3] Less than 100 patients in the analysis

[4] Total dropouts are only a proxy measure of adverse effects
[5] Less than 200 patients in the analysis, and the CI ranges from substantial advantage for TCAs to substantial advantage for placebo.

Author(s): Corrado Barbui, Wietse Tol, Jonathan Bisson
Date: 2012-04-19
Question: Should SSRIs vs placebo be used in adults with PTSD?
Settings:
Bibliography: Bisson Review

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRIs**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by lower values)												
22[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	2185	1548	-	SMD 0.20 lower (0.32 to 0.09 lower)	□□□□ MODERATE	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects												
18[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	455/1698 (26.8%)	346/1436 (24.1%)	RR 1.07 (0.91 to 1.27)	17 more per 1000 (from 22 fewer to 65 more)	□□□□ MODERATE	IMPORTANT

[1] Bisson review
[2] Visual inspection of forest plot suggests heterogeneity. this was corroborated by I-squared = 59%
[3] Total dropouts are only a proxy measure of adverse effects

Author(s): Corrado Barbui,, Wietse Tol, Jonathan Bisson
Date: 2012-04-19
Question: Should fluoxetine vs placebo be used in adults with PTSD?
Settings:
Bibliography: Bisson Review

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fluoxetine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by lower values)												
7[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	754	313	-	SMD 0.19 lower (0.39 lower to 0.01 higher)	□□□□ LOW	CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects												
6[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[5]	none	79/289 (27.3%)	46/210 (21.9%)	RR 1.22 (0.73 to 2.04)	48 more per 1000 (from 59 fewer to 228 more)	□□□□ LOW	IMPORTANT

[1] Bisson review
[2] Visual inspection of forest plot suggests some degree of heterogeneity. I-squared =45%
[3] Confidence interval ranges from appreciable benefit associated with fluoxetine treatment to no beneficial effect.

[4] Total dropouts are only a proxy measure of adverse effects
[5] The CI ranges from no difference to substantial advantage for placebo

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	For tricyclic antidepressants, there is no evidence in terms of efficacy as measured with standard clinician-administered rating scales. However, there is evidence in terms of self-rated outcome measures suggesting that tricyclic antidepressants may have a beneficial effect in decreasing symptom severity in adults with PTSD. The confidence in estimate is LOW (less than 100 persons included in the analysis, very wide confidence interval ranging from substantial benefit to very little benefit). There is evidence suggesting that SSRIs as a class are associated with a small but statistically significant beneficial effect in adults with PTSD. The confidence in estimate is MODERATE. For fluoxetine, the evidence suggests there is unlikely to be a clinically important difference between this SSRI and placebo. The confidence in estimate is LOW. In terms of functioning and presence of disorder no evidence is neither available for tricyclic and SSRI antidepressants nor for fluoxetine specifically.
Harms	There is evidence suggesting that acute treatment with tricyclic antidepressants is not associated with more persons leaving the study early, a proxy measure of treatment acceptability. The confidence in estimate is LOW. There is evidence suggesting that acute treatment with SSRIs is not associated with more persons leaving the study early, a proxy measure of treatment acceptability. The confidence in estimate is LOW. Similarly, evidence suggests that treatment with fluoxetine is not associated with more persons leaving the study early, a proxy measure of treatment acceptability. The confidence in estimate is LOW.

	The safety of psychotropics in pregnancy and breastfeeding is not clearly established. For antidepressants, the risks of taking tricyclic antidepressants during pregnancy and when breastfeeding are better established than those of SSRIs and newer drugs. Antidepressants appeared not to be teratogenic, although SSRI exposure in late pregnancy may increase the risk of persistent pulmonary hypertension.

Value and preferences	
In favour	The possibility of lowering PTSD symptoms is an important value.
Against	In situations where people are exposed to potentially traumatic stressors, there is the preference to try to address the stressors before initiating biomedical treatment. This may lead to the preference for a stepped care model that may have a psychologically oriented intervention as a first step and, if still needed, antidepressants in a later step. Among psychologically oriented interventions, CBT and EMDR have shown to have a strong beneficial effect in decreasing symptom severity (see Q14).

Feasibility (including economic consequences)	Training is required to properly diagnose PTSD. In many LAMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge. Both generic tricyclic antidepressants and many generic selective serotonin reuptake inhibitors are associated with low acquisition costs. Amitriptyline (as a representative of the tricyclic antidepressants) and fluoxetine (*not* as a representative of SSRIs) are included in the WHO list of essential medicines for the treatment of depressive disorders.

	Amitriptyline is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	Yes **No X**
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 16:

Selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) should not be offered as the first line of treatment for posttraumatic stress disorder in adults.

SSRIs and TCAs should be considered if:

(a) stress management, CBT with a trauma focus, and EMDR have failed or are not available

or

(b) if there is comorbid moderate-severe depression.

Strength of recommendation: standard
Quality of evidence: low

Remarks

Interactions with other drugs need to be considered and necessary precautions should be taken when prescribing to elderly populations and pregnant or breastfeeding women (see WHO (2010) mhGAP Intervention Guide module on moderate-severe depression).

17. Posttraumatic Stress Disorder (PTSD): Pharmacological Interventions – Children and Adolescents

Q17. For children and adolescents with posttraumatic stress disorder (PTSD), do antidepressants when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Exposure to potentially traumatic stressors is common. Posttraumatic stress disorder (PTSD) is the most studied disorder after exposure to potentially traumatic events and can be associated with significant impairment in functioning.

Pharmacological treatments, especially anti-depressants, are commonly prescribed for people suffering PTSD. However, there is currently no consensus on the effectiveness of pharmacological treatments between different clinical practice guidelines,[48] making this an important scoping question.

The question is limited to those pharmacological treatments that are most likely available now or in the next 5 years in non-specialized health care in low and middle income countries. There is a WHO model list of essential medicines for children and adolescents, and fluoxetine (*not* as a representative of SSRIs) is the only medicine included on this for the treatment of depressive disorders in children older than 8 years.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Children and adolescents with PTSD, after the first month of a potentially traumatic event
- **Interventions:** Antidepressants
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up

[48] Forbes, D., Creamer, M., Bisson, J., Cohen, J.A., Crow, B.E., Foa, E., Friedman, M.J., Keane, T.M., Kudler, H.S., Ursano, R.J. (2010). A guide to guidelines for the treatment of PTSD and related conditions. *Journal of Traumatic Stress*, 23(5), 537-552

- Presence of mental disorder post intervention and at follow-up
- Adverse effects (including tolerability)

Details of commissioned systematic review

NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement, PTSD and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results of studies relevant to children and adolescents with PTSD symptoms are discussed.

Types of studies

All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated psychotherapy with a trauma focus or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

Types of participants

All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions

Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.

The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self

rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy

We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR "pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria

- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, presence of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Narrative description of the studies that went into analysis

One study met the inclusion criteria (Robb 2010). In this study children and adolescents (6–17 years old) meeting DSM-IV criteria for PTSD were randomized to 10 weeks of double-blind treatment with sertraline (50–200 mg/day) or placebo. The primary efficacy measure was the University of California, Los Angeles Post-Traumatic Stress Disorder Index for DSM-IV (UCLA PTSD-I). A total of 131 persons met entry criteria and were randomized to sertraline (n=67; female, 59.7%; mean age, 10.8; mean UCLA PTSD-I score, 43.8) or placebo (n=62; female, 61.3%; mean age, 11.2; mean UCLA PTSD-I score, 42.1).

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Pharmacological interventions	Symptom severity Functioning Presence of disorder Adverse effects	Robb 2010 No data No data Robb 2010	

GRADE table

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-06-26
Question: Shouldanti-depressants vs placebo be used in children and adolescents with PTSD?
Settings:
Bibliography: Bisson Review identified one RCT: Robb 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Placebo	Relative (95% CI)	Absolute		
Symptom severity (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	serious[5]	none	67	61	-	MD 0 higher (0 to 0 higher)		CRITICAL
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Prevention of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects												
1	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[5,6]	none	51/67 (76.1%)	0%	OR 1.02 (0.45 to 2.28)	-	□□□□ VERY LOW	IMPORTANT

[1] Robb 2010: sertraline versus placebo
[2] 131 patients randomized, but only 129 in the Intention to treat population, with 30% dropping out in the sertraline sample. Allocation concealment unclear.

[3] Only one study in the analysis
[4] Children and adolescents (6-17 years) with PTSD
[5] Only one study in the analysis, with less than 200 patients
[6] Confidence interval ranges from appreciable benefit to appreciable harm.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	The systematic review found only one study, which showed that sertraline was not effective when compared with placebo during 10 weeks of treatment. No evidence is available for the outcomes functioning and presence of disorder. It is therefore uncertain if pharmacological treatment may have a beneficial effect in children and adolescents with PTSD in terms of functioning and presence of disorder.
Harms	The systematic review found only one study, which showed that sertraline was a generally safe treatment in children and adolescents with PTSD. However, the evidence base is from one study only, and refers to acute treatment (10 weeks) with no long-term data. It is therefore uncertain how pharmacological treatment compares with placebo in terms of treatment acceptability on the longer term. Evidence collected in children with depression highlighted safety and tolerability concerns associated with antidepressant exposure (see mhGAP evidence reviews conducted in 2009). In adolescents with depression, in terms of suicide ideas/behaviour, the evidence is inconclusive and so it is not possible to determine if there is a clinically important difference between fluoxetine and placebo (see mhGAP evidence reviews conducted in 2009). No data on the long-term consequences of psychotropic drug exposure in children and adolescents are available.

Value and preferences	
In favour	
Against	A widely held preference is that children and adolescents – still in development – should only be exposed to drugs if other effective treatment options have been tried, if the condition is sufficiently severe, if treatment is likely to lead to a substantial improvement in the condition, and if information about long-term consequences is available.

Feasibility (including economic consequences)	Training is required to properly diagnose PTSD in children and adolescents with due attention to any cultural variations that may exist. In many LAMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge. Training is required in the understanding and safe administration of all psychotropic medications Both generic tricyclic antidepressants and many generic selective serotonin reuptake inhibitors are associated with low acquisition costs. Fluoxetine is included in the WHO list of essential medicines for the treatment of depressive disorders in children above 8 years only. Amitriptyline (for adults) is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 17

Anti-depressants should not be used to manage PTSD in children and adolescents

Strength of recommendation: strong
Quality of evidence: very low

Remarks

If there is concurrent moderate-severe depression, also use guidance for helping depressed children and adolescents as included in the WHO (2010) mhGAP Intervention Guide module on depression. There are alternatives to pharmacological treatment (see recommendation 15 on psychological interventions for PTSD in children and adolescents).

18. Bereavement: Universally Applied Structured Psychological Interventions – Adults

Q18. For bereaved adults *without* a mental disorder, do universally applied structured psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Bereavement is referred to here as the event of a loss of a loved one. In this document, *grief* refers to the psychological reactions in response to bereavement. Loss of loved ones is a common occurrence in life, which for most people will not lead to mental disorder. For a small minority, bereavement and grief may be associated with prolonged symptomatology and impairment in functioning. This scoping question focuses on adults that do *not* meet criteria for a mental disorder, i.e. on interventions that are offered to all bereaved individuals independent of whether or not people score above certain threshold levels of symptoms.

Primary care practitioners often encounter bereaved individuals in their practice, with seemingly little consistency in applied interventions.[49] The increased popularity of 'grief work' and bereavement interventions makes this a relevant scoping question.

The scoping question refers to 'structured psychological' interventions, i.e. psychological interventions that go beyond general application of psychological principles that are part of health and social care, such as good communication and mobilizing and providing social support (cf. the mhGAP Intervention Guide (2010; p.6). Examples of structural interventions include psychotherapy or a grief counselling intervention involving a series of sessions that encompass psychoeducation, efforts to improve coping skills, understanding of death and grief, talking about the deceased, and expression of grief-related feelings

The scoping question focuses on 'universally applied' interventions, i.e. interventions applied to all bereaved individuals regardless of the existence of a mental disorder (i.e. delivery without identification).[50]

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[49] Nagraj S, Barclay, S (2011). Bereavement care in primary care: A systematic review and narrative synthesis. *British Journal of General Practice*, DOI: 10.3399/bjgp11X549009

[50] Advice for recently bereaved people meeting criteria for moderate or severe depression can be found in the depression module of mhGAP (page 10), which advises that antidepressants or psychotherapy should not be considered as first line treatment of depression if there is recent bereavement or other major loss in prior 2 months, but to consider discussion and support of culturally appropriate mourning and reactivation of social networks. This is consistent with the raised concerns about medicalization of normal grief responses (see Friedman, R.A. (2012). Grief, depression and the DSM-5. New England Journal of Medicine, 366(20), 1855-7). Also, there has been an on-going discussion on a separate mental disorder category for prolonged grief disorder, traumatic grief disorder, or

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Bereaved adults who do not meet criteria for a mental disorder
- **Interventions:** All universally applied psychological and psychosocial interventions
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity (mainly sub threshold symptoms) post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used ('bereavement' OR 'grief' OR 'mourning') AND 'systematic review'. In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option. We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with adults (>18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Wittouck, C., Van Autreve, S., De Jaegere, E., Portzky, G., van Heeringen, G. (2011). The prevention and treatment of complicated grief: A meta-analysis. *Clinical Psychology Review*, 31, 69-78
COMMENT: This review covers both prevention and treatment studies. The prevention studies are relevant to the PICO question.

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complicated bereavement disorder, etc. The category prolonged grief disorder (disabling grief occurring more than 6 months after the loss) is currently under consideration for inclusion in the ICD-11.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Currier, J.M., Neimeyer, R.A., Berman, J.S. (2008). The effectiveness of psychotherapeutic interventions for bereaved persons: A comprehensive quantitative review. *Psychological Bulletin*, 134(5), 648-661
REASON FOR EXCLUSION: Older than 2 years

Currier JM, Holland JM, Neimeyer RA. (2010) Do CBT-based interventions alleviate distress following bereavement? A review of the current evidence. *International Journal of Cognitive Therapy*, 3(1), 77-93
REASON FOR EXCLUSION: Focused only on CBT interventions

Forte, A.L., Hill, M., Pazder, R., Feudtner, C. (2004). Bereavement care interventions: a systematic review. *BMC Palliative Care*, 3(3), doi:10.1186/1472-684X-3-3
REASON FOR EXCLUSION: Older than 2 years

Harvey, S., Snowdon, C., Elbourne, D. (2008). Effectiveness of bereavement interventions in neonatal intensive care: A review of the evidence. Seminars in Fetal and Neonatal Medicine, 13, 341-356
REASON FOR EXCLUSION: Older than 2 years, and focused on a specific sub-group of parents bereaved of a baby in neonatal care

McDaid, C., Trowman, R., Golder, S., Hawton, K., Sowden, A. (2008). Interventions for people bereaved through suicide: A systematic review. *British Journal of Psychiatry*, 193, 438-443
REASON FOR EXCLUSION: Older than 2 years, and focused on a specific sub-group of people bereaved through suicide

Nagraj, S., Barclay, S. (2011). Bereavement care in primary care: A systematic review and narrative synthesis. British Journal of General Practice, DOI: 10.3399/bjgp11X549009
REASON FOR EXCLUSION: Does not review evaluations of interventions, but UK primary care practices

Rowa-Dewar, N. (2002). Do interventions make a difference to bereaved parents? A systematic review of controlled studies. *International Journal of Palliative Nursing*, 8(9), 452-457
REASON FOR EXCLUSION: Older than 2 years, and methodological limitations in retrieval of evidence

Stroebe, M., Schut, H., Stroebe, W. (2007). Health outcomes of bereavement. *Lancet*, 370, 1960-1973
REASON FOR EXCLUSION: Older than 2 years, and review methodology not systematically described

Szumilas, M., Kutcher, S. (2011). Post-suicide intervention programs: A systematic review. *Canadian Journal of Public Health*, 102(1), 18-29
REASON FOR EXCLUSION: Focused on a specific sub-group of those bereaved through suicide

United Kingdom Department of Health. Bereavement Care Services: A Synthesis of the Literature. London, UK: DoH
REASON FOR EXCLUSION: No formal meta-analysis conducted, wide inclusion criteria (also studies focusing on service need/ provision issues), and databases searched .

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Universal psychological interventions vs. no treatment/ control	Symptom severity (mainly sub-threshold) Functioning Presence of disorder Adverse effects	Wittouck et al, 2011 No data No data No data	Wittouck et al (2011) is a recent thorough review comparing prevention with no intervention

Narrative description of the studies that went into analysis

Wittouck and colleagues' (2011) study identified 14 randomized controlled trials, through searching Web of Science and PsycArticles, focused on (a) prevention ($n_{studies}$=9), and (b) treatment of complicated grief ($n_{studies}$=5). As this scoping question concerns adults *without* a mental disorder, only the studies focused on prevention are discussed here. Treatment studies were defined as studies aimed at lowering symptoms of people *with* pronounced complicated grief.

The 9 prevention studies contained preventive interventions ranging from 1 to 12-sessions. All studies were conducted in high-income countries (5 in the USA, 1 UK, 1 Australia, 1 Netherlands, 1 not reported). These interventions included cognitive behavioral (individual, family and group) interventions (n=4), writing therapy (n=3), information giving and emotional support (n=1), and brief psychotherapy (n=1). All studies used subjective outcome measures to assess complicated grief, which were shown reliable in all but one of the nine studies, and studies were included if they compared a grief intervention with a control condition or non-specific intervention (i.e. non-grief focused). Sample size ranged from 42 to 276 participants.

NOTE: Currier et al's (2008) review was excluded because it was older than 2 years, in accordance with the WHO Handbook on Guidelines Development. This systematic review included a larger amount of studies, and comes to a similar conclusion: "Overall, analyses showed that interventions had a small effect at posttreatment but no statistically significant benefit at follow-up. However, interventions that exclusively targeted grievers displaying marked difficulties adapting to loss had outcomes that compare favorably

with psychotherapies for other difficulties. Other evidence suggested that the discouraging results for studies failing to screen for indications of distress could be attributed to a tendency among controls to improve naturally over time. The findings of the review underscore the importance of attending to the targeted population in the practice and study of psychotherapeutic interventions for bereaved persons." (p. 648).

NOTE: Szumilas & Kutcher, 2011 focuses on interventions with people bereaved through suicide. Given that this review focuses on a specific population sub-group this review was not included in the GRADE table. It is noted, however, that this systematic review leads to similar conclusions as the other systematic reviews. This review identified 3 randomized controlled trials, but only one of these compared treatment to a control group. The latter study evaluated a 10-week broad-spectrum intervention for parents bereaved of children through violent deaths, and found no effects with fathers. Regarding effects found with mothers, it concluded that "The intervention appeared to be the most beneficial for mothers most distressed at baseline."

GRADE Table

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-02-24
Question: Should universal psychological or psychosocial interventions vs treatment as usual or no treatment/waitlist be used for bereaved adults who do not meet criteria for a mental disorder?
Settings:
Bibliography: Wittouck 2011.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Universal psychological or psychosocial interventions	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity: post-intervention (Better indicated by lower values)												
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	442	334	-	SMD 0.0 lower (0.19 lower to 0.19 higher)	□□□□ MODERATE	IMPORTANT

Symptom severity: follow-up (Better indicated by lower values)												
9[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	440	329	-	SMD 0.07 higher (0.08 lower to 0.21 higher)	□□□□ MODERATE	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Prevention of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] A total of nine studies assessed the efficacy of preventive grief interventions (page 71 of Wittouck 2011). Of these, 8 comparisons were included in the analysis of effect immediately after the intervention (Fig 2 of Wittouck 2011).
[2] Dropout rates exceeded 30% in one study (O'Connor 2003); in two other studies dropouts rates were nearly 30% (Kovac and Range 2000; Sikkema 2006). In addition, it is unclear if outcome assessment was performed by masked raters.
[3] A total of nine studies assessed the efficacy at follow-up of preventive grief interventions (page 71 of Wittouck 2011 and Fig 2 of Wittouck 2011).
[4] Dropout rates exceeded 30% in two studies (O'Connor 2003 and range 2000); in two other studies dropouts rates were nearly 30% (Kovac and Range 2000; Sikkema 2006). In addition, it is unclear if outcome assessment was performed by masked raters.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	There is evidence suggesting that universally applied psychological interventions have *no effect* on grief-related symptoms in bereaved adults. The confidence in this estimate is MODERATE. There is no systematic review of evidence on presence of disorder and functioning for universally applied psychological interventions in bereaved adults.
Harms	There is no systematic review of evidence of potential negative consequences from universally applied psychological interventions in bereaved adults.
Benefits outweigh harms?	**NO**

Value and preferences	
In favour	Universally applied psychological interventions that involve the delivery of common-sense strategies in people with psychological symptoms (but no mental disorder) in response to bereavement (e.g. providing (a) emotional support through empathic listening with a respectful and non-judgmental attitude and (b) problem-solving) may be low risk strategies in people who seek help for bereavement-related complaints.
Against	It is inappropriate to offer an intervention that has been subject to study but which lacks a positive evidence base. Interventions may contribute to medicalization.
Uncertainty?	**YES**

Feasibility (including	Most staff in PHC in LAMIC have not received extensive training in communication skills and basic emotional support. Any additional training in more complex psychological interventions would

economic consequences)	require some resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources.
Uncertainty?	**YES**

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	**Yes X** No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes **No X**

Final recommendation by the guideline panel

Recommendation 18:

Structured psychological interventions should *not* be offered universally (to all) bereaved adults who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: moderate

Remarks

General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and the principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

19. Bereavement: Universally Applied Structured Psychological Interventions – Children and Adolescents

Q19. For bereaved children and adolescents *without* a mental disorder, do universally applied structured psychological interventions when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Bereavement is referred to here as the event of a loss of a loved one. In this document, *grief* refers to the psychological reactions in response to bereavement. Loss of loved ones is a common occurrence in life, which for most children and adolescents will not lead to mental disorders. For a small minority, bereavement and grief may be associated with prolonged symptomatology and impairment in functioning. This scoping question focuses on children and adolescents that do *not* meet criteria for a mental disorder, i.e. on interventions that are offered to all bereaved individuals independent of whether or not people score above certain threshold levels of symptoms.

Primary care practitioners often encounter bereaved children and adolescents in their practice, with seemingly little consistency in applied interventions[51]. The increased popularity of 'grief work' and bereavement interventions makes this a relevant scoping question.

The scoping question refers to 'structured psychological' interventions, i.e. interventions that go beyond general application of psychological principles that are part of health and social care, such as good communication and mobilizing and providing social support (cf. the mhGAP Intervention Guide (2010; p.6). Examples of structural interventions include psychotherapy or a grief counselling intervention involving a series of sessions that encompass psychoeducation, efforts to improve coping skills, understanding of death and grief, talking about the deceased, and expression of grief-related feelings (e.g., through talk or drawings). The scoping question focuses on 'universally applied' interventions, i.e. interventions applied with bereaved individuals regardless of the existence of a mental disorder (i.e. delivery without identification).[52]

[51] Nagraj S, Barclay, S (2011). Bereavement care in primary care: A systematic review and narrative synthesis. *British Journal of General Practice*, DOI: 10.3399/bjgp11X549009

[52] Advice for recently bereaved children and adolescents meeting criteria for moderate or severe depression can be found in the depression module of mhGAP (page 10), which advises that psychotherapy should not be considered as first line treatment of depression if there is recent bereavement or other major loss in prior 2 months, but to consider discussion and support of culturally appropriate mourning and reactivation of social networks. This is consistent with the raised concerns about medicalization of normal grief responses (see .Friedman, R.A. (2012). Grief, depression and the DSM-5. New England Journal of Medicine,

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Bereaved children and adolescents who do not meet criteria for a mental disorder
- **Interventions:** All universally applied psychological and psychosocial interventions
- **Comparison:** Treatment as usual or no treatment/ waitlist
- **Outcomes:**
  - Symptom severity (mainly sub threshold symptoms) post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

List of the systematic reviews identified by the search process

The search was conducted in week 28 of 2011 in the following databases: Cochrane Database of Systematic Reviews, PubMed (clinical queries), the Campbell Collaboration, LILACS, psycINFO, EMBASE, and PILOTS. As keywords we used (('bereavement' OR 'grief' OR 'mourning') AND 'systematic review'). In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and EMBASE) we selected this option and used the keywords 'bereavement OR grief or mourning'. We included studies if they were systematic reviews of treatment studies published from 2001 onwards that included studies with children and adolescents (<18 years). In addition, we searched for clinical practice guidelines through Google, the National Guideline Clearinghouse and NICE. Appraisal of quality of systematic reviews was conducted with the use of the Oxford Center for Evidence Based Medicine's checklist.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Currier, J.M., Holland, J.M., Neimeyer, R.A. (2007). The effectiveness of bereavement interventions with children: A meta-analytic review of controlled outcome research. *Journal of Clinical Child and Adolescent Psychology*, 36(2), 253-59

366(20), 1855-7) Also, there is currently no consensus on the inclusion of a separate mental disorder category for prolonged grief disorder, traumatic grief disorder, or complicated bereavement disorder, etc. The category prolonged grief disorder (disabling grief occurring more than 6 months after the loss) is currently under consideration for inclusion in the ICD-11.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

Currier, J.M., Neimeyer, R.A., Berman, J.S. (2008). The effectiveness of psychotherapeutic interventions for bereaved persons: A comprehensive quantitative review. *Psychological Bulletin*, 134(5), 648-661
REASON FOR EXCLUSION: meta-analysis of children, adolescents and adults together

Forte, A.L., Hill, M., Pazder, R., Feudtner, C. (2004). Bereavement care interventions: a systematic review. *BMC Palliative Care*, 3(3), doi:10.1186/1472-684X-3-3
REASON FOR EXCLUSION: meta-analysis of children, adolescents and adults together

McDaid, C., Trowman, R., Golder, S., Hawton, K., Sowden, A. (2008). Interventions for people bereaved through suicide: A systematic review. *British Journal of Psychiatry*, 193, 438-443
REASON FOR EXCLUSION: meta-analysis of children, adolescents and adults together, and focused on a specific sub-group of people bereaved through suicide

Szumilas, M., Kutcher, S. (2011). Post-suicide intervention programs: A systematic review. *Canadian Journal of Public Health*, 102(1), 18-29
REASON FOR EXCLUSION: meta-analysis of children, adolescents and adults together, and focused on a specific sub-group of people bereaved through suicide

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Psychological interventions vs. no treatment/ control	Symptom severity (mainly sub-threshold) Functioning Presence of disorder Adverse effects	Currier, Holland & Niemeyer (2007) No data No data No data	Although older than 2 years, Currier, Niemeyer & Berman (2007) review was the only identified systematic review and meta-analysis including children and adolescents only.

Narrative description of the studies that went into analysis

Currier, Holland & Niemeyer (2007) searched PsycINFO, PsychArticles, Medline, and Dissertation Abstracts and identified 13 studies meeting inclusion criteria (bereavement intervention vs no-treatment, quantitative measures of treatment outcome). The meta-analysis included both randomized and non-randomized controlled studies, with little difference in estimation of effect between these two study types. Six (46%) of the included studies were journal articles and 7 (54%) were unpublished dissertations. 12 out of 13 studies used a group treatment modality (generally 8-9 sessions), and most treatments included psychoeducation, efforts to improve coping skills, understanding of death and grief, talking about the deceased, and expression of grief-related feelings (e.g. through drawing). Children were generally White, on average 10 years of age, and treatment started on average 1.5 years after the bereavement. Only 1 of the included studies screened for children showing adjustment difficulties related to grief. Around a third of the studies included measures specifically related to grief (n=4, 31%; only 1 used a well-established measure), the majority applied general measures of psychiatric symptoms or behavioral disorders. Most studies measured post-intervention, with virtual absence of longer term follow-up.

GRADE Table

Author(s): Corrado Barbui
Date: 2012-02-24
Question: Should universally applied psychological or psychosocial interventions vs treatment as usual or no treatment/waitlist be used for bereaved children and adolescents who do not meet criteria for a mental disorder?
Settings:
Bibliography: Currier 2007

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological or psychosocial interventions	Treatment as usual or no treatment/waitlist	Relative (95% CI)	Absolute		
Symptom severity (Better indicated by higher values)												

13[1]	observational studies[2]	very serious[2, 3]	no serious inconsistency[4]	serious[5]	no serious imprecision	none	0[6]	-	-	Cohen's d 0.14 higher (0 to 0.28 higher)	□□□□ VERY LOW	IMPORTANT
Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Table 1 of Currier 2007
[2] Six of the 13 included studies are not randomized trials.
[3] In 3 studies dropout rates exceeded 40% (Table 1 of Currier 2007). In addition, it is unclear if outcome assessment was performed by masked raters.
[4] Forest plot not available. However, it is reported that the effect sizes "appeared to resemble a homogeneous distribution".
[5] The Currier review included both children with and without a mental disorder.
[6] Unclear

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	There is evidence suggesting that universally applied psychological interventions have *no effect* on symptomatology in a mixed group of children and adolescents with and without specific grief-related distress. The confidence in estimate is VERY LOW. The GRADEd systematic review mentions that interventions that screened for distress and were implemented quickly after the bereavement had better effects than universally applied interventions. There is no systematic review of evidence on the role of universally applied psychological interventions on overall functioning or mental disorder in bereaved children and adolescents.
Harms	There is no systematic review of evidence on potential negative consequences of universally applied psychological interventions in bereaved children and adolescents.
Benefits outweigh harms?	**NO**

Value and preferences	
In favour	Universally applied psychological interventions that involve the delivery of common-sense strategies in people in response to bereavement (e.g. providing (a) emotional support through empathic listening with a respectful and non-judgmental attitude and (b) problem-solving) may be low risk strategies in people who seek help for bereavement-related complaints.
Against	It is inappropriate to offer an intervention that has been subject to study but which lacks a positive evidence base. Interventions may contribute to medicalization.

Uncertainty?	**YES**

Feasibility (including economic consequences)	Most staff in PHC in LAMIC have not received extensive training in communication skills and basic emotional support. Any additional training in specific psychological interventions would require some resources, including supervision. Psychological interventions require time to be delivered, which is important in the context of strained human resources.
Uncertainty?	**YES**

Judgements to inform the decision on the strength of the recommendation

Factor	**Decision**
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No

Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation for the guideline panel

Recommendation 19

Structured psychological interventions should not be offered universally (to all) bereaved children and adolescents who do not meet the criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

In cases where the child has lost a primary caregiver, the issue of protection and continued supportive caregiving, including socio-emotional support, should be addressed.

20. Bereavement: Benzodiazepines – Adults

Q20. For bereaved adults *without* a mental disorder, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Bereavement is referred to here as the event of a loss of a loved one. In this document, *grief* refers to the psychological reactions in response to bereavement. Loss of loved ones is a common occurrence in life, which for most people will not lead to mental disorder. For a small minority, bereavement and grief may be associated with prolonged symptomatology and impairment in functioning.

This scoping question focuses on adults that do *not* meet criteria for a mental disorder.[53] Primary care practitioners often encounter bereaved individuals in their practice, with seemingly little consistency in applied interventions.[54] The popularity of prescribing benzodiazepines in bereaved persons without mental disorder makes this a relevant scoping question.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Bereaved adults who do not meet criteria for a mental disorder
- **Interventions:** Benzodiazepines
- **Comparison:** Placebo/active pharmacological treatment

[53] Advice for recently bereaved people meeting criteria for moderate or severe depression can be found in the depression module of mhGAP (page 10), which advises that antidepressants or psychotherapy should not be considered as first line treatment of depression if there is recent bereavement or other major loss in prior 2 months, but to consider discussion and support of culturally appropriate mourning and reactivation of social networks. This is consistent with the raised concerns about medicalization of normal grief responses (see Friedman, R.A. (2012). Grief, depression and the DSM-5. New England Journal of Medicine, 366(20), 1855-7). Also, there has been an on-going discussion on a separate mental disorder category for prolonged grief disorder, traumatic grief disorder, or complicated bereavement disorder, etc. The category prolonged grief disorder (disabling grief occurring more than 6 months after the loss) is currently under consideration for inclusion in the ICD-11.

[54] Nagraj S, Barclay, S (2011). Bereavement care in primary care: A systematic review and narrative synthesis. *British Journal of General Practice*, DOI: 10.3399/bjgp11X549009

- **Outcomes:**
  - Symptom severity (mainly sub threshold symptoms) post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

Details of commissioned systematic reviews

Two systematic reviews were commissioned to identify studies of benzodiazepines for bereaved adults:

(1) Pharmacotherapy for bereaved adults who do not meet criteria for a mental disorder (Bisson systematic review).
NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement, PTSD and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results of studies relevant to bereaved adults are discussed. Note that this review goes beyond benzodiazepines

Types of studies
All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTMH PTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated trauma focused psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

Types of participants
All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions

Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.

The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy

We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR "pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria
- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Results
No RCTs of pharmacotherapy for grief reactions were identified.

(2) Benzodiazepines for bereaved adults who do not meet criteria for a mental disorder (Lindsay Glynn systematic search).
This review was commissioned to supplement the Bisson et al review, as the Bisson et al review only covered studies from 2005

Literature Search Strategies
Databases searched include MEDLINE, CINAHL, EMBASE, PsycInfo, Cochrane, and Scopus. Relevant articles from all search results were selected to ensure specificity. The reference lists from all relevant articles were hand-searched to locate additional articles, which were added to the final citation list. Supplemental searches in Google Scholar and practice guideline collections yielded no further results.

Terms such as bereavement related depression, complicated grief, traumatic grief, and prolonged grief disorder were noted as relevant topical terms in the literature in addition to the database-specific subject headings. These terms were not searched separately as they were automatically addressed in searches using the keywords grief and bereavement. Both subject heading searches and keyword searches were utilized to ensure exhaustive results.

Given the limited research in this subject area, no limits (i.e. study type, language, publication year) were applied to any database or article index search. While RCTs and systematic reviews are the preferred publication type, utilizing such limits would have eliminated relevant articles that outlined specific research in commentaries and letters that was not ultimately translated to a full research publication.

MEDLINE (PubMed)
Bereavement [MeSH] exp AND Benzodiazepines [MeSH] exp
benzodiazepines AND (grief OR grieving OR bereavement OR personal loss)
The *Related Articles* feature was utilized to locate additional articles.

CINAHL
MH Antianxiety Agents, Benzodiazepine+ AND (MH Bereavement+ OR MH Grief+)
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

EMBASE
Benzodiazepine Derivative/exp AND (bereavement/exp OR grief/exp)

benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

PsycInfo
DE Benzodiazepine/exp AND (DE Bereavement OR DE Grief)
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

Cochrane
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss) in Title, Abstract, and keywords

Scopus
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)
Cited By feature was utilized to locate additional articles.

Results

The search identified one study:

Warner, J., Metcalfe, C., & King, M. (2001). Evaluating the use of benzodiazepines following recent bereavement. British Journal of Psychiatry, 178(1), 36-41.

INCLUDED IN GRADE TABLES OR FOOTNOTES

Warner, J., Metcalfe, C., & King, M. (2001). Evaluating the use of benzodiazepines following recent bereavement. British Journal of Psychiatry, 178(1), 36-41.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Benzodiazepines vs. placebo	Symptom severity	Warner 2001	

		Functioning Presence of disorder Adverse effects	No data No data Warner 2001	

Narrative description of the studies that went into analysis

Warner (2001) is a randomized double-blind, placebo-controlled evaluation of diazepam after recent bereavement. Participants were randomized to either 6-week supply of 2 mg diazepam – prescribed within 2 weeks of bereavement of a spouse or partner - or identically packaged placebo up to three times daily. Thirty subjects were randomized. No evidence was found of an effect of benzodiazepines on the course of the first 6 months of bereavement.

GRADE Table

Author(s): Corrado Barbui, Wietse Tol
Date: 2012-05-08
Question: Should benzodiazepines vs placebo be used in bereaved adults who do not meet criteria for a mental disorder?
Settings:
Bibliography: Bisson Review; Lindsay Glynn systematic search

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benzodiazepines**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Symptom severity (Better indicated by higher values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	16	14	-	MD 0.3 higher (6.2 lower to 6.7 higher)	□□□□ LOW	IMPORTANT

Functioning (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Presence of disorder (Better indicated by lower values)												
0	no evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Adverse effects												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	serious[4]	very serious[3]	none	4/20 (20%)	1/15 (6.7%)	OR 3.5 (0.28 to 184)	133 more per 1000 (from 47 fewer to 863 more)	□□□□ VERY LOW	IMPORTANT

[1] Warner 2001
[2] Only one study contributed to this analysis.
[3] Only one trial with less than 50 patients. Wide confidence interval.
[4] Total dropouts are only a proxy measure of adverse effects.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	The evidence is inconclusive, and therefore it is not possible to determine if benzodiazepines are effective in bereaved adults who do not meet criteria for a mental disorder. There is no evidence on the effect of benzodiazepines on functioning and presence of disorder.
Harms	The evidence is inconclusive, and therefore it is not possible to determine if benzodiazepines are harmful in bereaved adults who do not meet criteria for a mental disorder. In addition to the evidence from randomized trials, data from observational and epidemiological

	studies highlighted a risk of tolerance and dependence. According to NICE UK, one of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (10–30% of chronic benzodiazepines users are physically dependent on them), and suffer a withdrawal syndrome when they stop taking them (50% of all users suffer withdrawal symptoms). The withdrawal syndrome includes anxiety, depression, nausea and perceptual changes. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects. The safety of psychotropic drugs in pregnancy and breastfeeding is not clearly established. In particular, exposure to benzodiazepines during the first trimester is associated with an increased risk of oral clefts, and exposure during the third trimester is associated with neonatal difficulties.

Value and preferences	
In favour	The possibility of decreasing acute symptomatology that prevents functioning at certain important times (e.g. in flight, organizing a funeral, etc.) and overall psychological distress is an important value.
Against	Providing medication for bereavement may contribute to the medicalization of normal psychological reactions and may contribute to dependence.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. To avoid the risks of harm referred to above, training of primary care practitioners would be necessary on responsible use of benzodiazepines. In many LAMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge.

	Benzodiazepines are associated with low acquisition costs. Diazepam (as a representative of the benzodiazepines) is included in the WHO list of essential medicines for the treatment of anxiety disorders. Diazepam is included in the Interagency Emergency Health Kit (IEHK), a box with medicines and medical supplies designed to meet the expected primary health care needs of people exposed to major humanitarian emergencies.

Judgements to inform the decision on the strength of the recommendation

Factor	**Decision**
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 20

Benzodiazepines should not be offered to bereaved adults who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Quality of evidence: very low

Remarks

As mentioned in the remarks for recommendation 18 on psychological interventions for bereaved adults: General principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and the principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

21. Bereavement: Benzodiazepines – Children and Adolescents

Q21. For bereaved children and adolescents *without* a mental disorder, do benzodiazepines when compared to treatment as usual, waiting list or no treatment result in reduction of symptoms, improved functioning/ quality of life, presence of disorder, or adverse effects?

Background on the scoping question

Bereavement is referred to here as the event of a loss of a loved one. In this document, *grief* refers to the psychological reactions in response to bereavement. Loss of loved ones is a common occurrence in life, which for most people will not lead to mental disorder. For a small minority, bereavement and grief may be associated with prolonged symptomatology and impairment in functioning.

This scoping question focuses on children and adolescents that do *not* meet criteria for a mental disorder.[55] Primary care practitioners often encounter bereaved individuals in their practice, with seemingly little consistency in applied interventions[56]. The popularity of prescribing benzodiazepines in bereaved persons without mental disorder makes this a relevant scoping question.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome

- **Population:** Bereaved children and adolescents who do not meet criteria for a mental disorder
- **Interventions:** Benzodiazepines
- **Comparison:** Placebo/active pharmacological intervention

[55] Advice for recently bereaved children and adolescents meeting criteria for moderate or severe depression can be found in the depression module of mhGAP, which advises that psychotherapy should not be considered as first line treatment of depression if there is recent bereavement or other major loss in prior 2 months, but to consider discussion and support of culturally appropriate mourning and reactivation of social networks. This is consistent with the raised concerns about medicalization of normal grief responses (see Friedman, R.A. (2012). Grief, depression and the DSM-5. New England Journal of Medicine, 366(20), 1855-7). Also, there is currently no consensus on the inclusion of a separate mental disorder category for prolonged grief disorder, traumatic grief disorder, or complicated bereavement disorder, etc. The category prolonged grief disorder (disabling grief occurring more than 6 months after the loss) is currently under consideration for inclusion in the ICD-11.

[56] Nagraj S, Barclay, S (2011). Bereavement care in primary care: A systematic review and narrative synthesis. *British Journal of General Practice*, DOI: 10.3399/bjgp11X549009

- **Outcomes:**
  - Symptom severity (mainly sub threshold symptoms) post intervention and at follow-up
  - Functioning/ quality of life post intervention and at follow-up
  - Presence of mental disorder post intervention and at follow-up
  - Adverse effects (including tolerability)

Details of commissioned systematic review:

Two systematic reviews were commissioned to identify studies of benzodiazepines:

(1) Pharmacotherapy for bereaved children and adolescents who do not meet criteria for a mental disorder (Bisson systematic review).

NOTE: this systematic review was commissioned for a broader set of scoping questions, including pharmacological interventions for people with bereavement, PTSD and ASD. For this scoping question, the methodology of the review is presented for all studies, but only the results of studies relevant to bereaved children and adolescents are discussed. Note that this review goes beyond benzodiazepines

Types of studies

All double-blind, randomised, placebo controlled and comparative trials completed from October 2005 until October 2011 were considered in our primary and additional searches, covering 13 separate databases. Trials included in the NICE, Cochrane and ANCPTMH PTSD reviews were also considered.

Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Trials in which there was ongoing or newly initiated trauma focussed psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Trials in which there was ongoing supportive psychotherapy were allowed, provided it was not initiated during the course of the treatment. Open label trials were not considered.

Types of participants

All studies of subjects with PTSD, ASD or grief reactions. There was no restriction on the basis of different diagnostic criteria for PTSD, duration or severity of PTSD symptoms. There was no restriction on the basis of co-morbid disorders, age or gender of participants.

Types of interventions

Pharmacological treatments for children and adults with PTSD, ASD or a grief reaction, in which the comparator was a placebo (active or non-active) or other medication.

Types of outcome measures.

The primary outcomes of interest were clinician administered PTSD symptom severity measures such as the Clinician Administered PTSD Scale (CAPS) and the Treatment Outcome PTSD Scale (TOP-8). Secondary outcomes of interest were remission rates, self rated PTSD symptom scales such as the Impact of Event Scale (IES) and Davidson Trauma Scale (DTS), and measures of treatment response to co-morbid symptoms such as depression and anxiety (e.g. the Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), the Hamilton Anxiety Scale (HAM-A) and the Covi Anxiety Scale (COV)). Measures of quality of life and functional disability such as the Sheehan Disability Scale (SDS) were also considered. Total number of participants who left the trial early due to any reason was used as a measure of treatment tolerability.

Search strategy

We conducted a primary bibliographic database search of Medline, Medline In Process, Embase, HMIC, PsycINFO, ASSIA and CINAHL using the Ovid interface. This initial broad search was intended to identify not only the RCTs of interest but other study methodologies and journal reviews of pharmacotherapy for PTSD.

The comprehensive search term used (see appendix 1) was created by amalgamating the previous search strategies from the NICE, Stein and Australian Guideline reviews with an updated list of medications.

Specific additional searches were carried out to identify international studies in Japanese, Chinese, Spanish and Portuguese (no additional studies identified) In addition, we searched The National PTSD Centre's PILOTS Database, The Cochrane Library, The Controlled Trials Register, Web Of Knowledge, Open Sigle, and Google Scholar using the term: ("post traumatic stress disorder" OR "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder") AND ("treatment" OR "medication" OR "pharmacotherapy") AND "controlled". Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs.

Study selection

One reviewer transferred the initial search hits into EndNoteX4 software and duplicates were removed. Two reviewers then independently screened the titles and abstracts of RCTs identified from the search. Those that were clearly irrelevant were excluded and potentially relevant studies were then assessed for inclusion as full texts. Any discrepancies between reviewers' decisions were resolved by discussion and guidance from a third senior reviewer.

Data extraction and risk of bias assessment

One reviewer extracted the details of the studies into a standardised table which was then checked by another reviewer. Details from each study were collected on:

- Study citation, year of publication, location, setting, number of centres, design, sample size, duration and length of follow up, diagnostic criteria, inclusion and exclusion criteria
- Characteristics of study participants including gender distribution, mean and range of age, disease severity, duration of PTSD symptoms, presence of co-morbid depression, proportion with combat related trauma, number randomised into each group, number of dropouts
- Characteristics of interventions including mean and maximum doses
- Outcome measures reported including whether the data represented an intention-to-treat (ITT) or completers only sample. For ITT samples, the method of imputation was noted.

One reviewer inputted outcome data into the Cochrane Collaboration's Review Manager 5 software, which was then checked by another reviewer. Data from studies included in previous systematic reviews were extracted by one reviewer and independently cross checked by a second reviewer for accuracy. Risk of bias was independently assessed for each trial by two reviewers using the domain-based evaluation method recommended by the Cochrane Collaboration (appendix). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Discrepancies between the two raters were resolved by discussion and arbitrated by a third senior rater. Masked study assessment (hiding details of publishing journal, author etc) was not undertaken, since it is unclear whether this reduces bias.

Data analysis

Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals (CI) of 95% were used for all analyses.

Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used.

The degree of heterogeneity between studies was calculated using the I2 statistic. Where the statistic was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used. A random effects model was used when the statistic was greater than 30%.

Data was analysed from the ITT sample in the "once randomised always analysed" fashion where possible to avoid effect of bias from completers only analyses.

Results

No RCTs of pharmacotherapy for grief reactions were identified.

(2) Benzodiazepines for bereaved children and adolescents who do not meet criteria for a mental disorder (Lindsay Glynn systematic search).

This review was commissioned to supplement the Bisson et al review, as the Bisson et al review only covered studies from 2005

Literature Search Strategies

Databases searched include MEDLINE, CINAHL, EMBASE, PsycInfo, Cochrane, and Scopus. Relevant articles from all search results were selected to ensure specificity. The reference lists from all relevant articles were hand-searched to locate additional articles, which were added to the final citation list. Supplemental searches in Google Scholar and practice guideline collections yielded no further results.

Terms such as bereavement related depression, complicated grief, traumatic grief, and prolonged grief disorder were noted as relevant topical terms in the literature in addition to the database-specific subject headings. These terms were not searched separately as they were automatically addressed in searches using the keywords grief and bereavement. Both subject heading searches and keyword searches were utilized to ensure exhaustive results.

Given the limited research in this subject area, no limits (i.e. study type, language, publication year) were applied to any database or article index search. While RCTs and systematic reviews are the preferred publication type, utilizing such limits would have eliminated relevant articles that outlined specific research in commentaries and letters that was not ultimately translated to a full research publication.

MEDLINE (PubMed)
Bereavement [MeSH] exp AND Benzodiazepines [MeSH] exp
benzodiazepines AND (grief OR grieving OR bereavement OR personal loss)
The *Related Articles* feature was utilized to locate additional articles.

CINAHL
MH Antianxiety Agents, Benzodiazepine+ AND (MH Bereavement+ OR MH Grief+)
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

EMBASE
Benzodiazepine Derivative/exp AND (bereavement/exp OR grief/exp)

benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

PsycInfo
DE Benzodiazepine/exp AND (DE Bereavement OR DE Grief)
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)

Cochrane
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss) in Title, Abstract, and keywords

Scopus
benzodiazepine* AND (grief OR griev* OR bereavement OR personal loss)
Cited By feature was utilized to locate additional articles.

Results

No RCTs of pharmacotherapy for grief reactions were identified.

PICO Table

Serial no.	Intervention/ Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Benzodiazepines vs. no treatment/ control	Symptom severity Functioning Presence of disorder Adverse effects	No data No data No data No data	

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	There is no evidence on the benefit of benzodiazepines for bereaved children and adolescents who do not meet criteria for a mental disorder with regard to symptom severity, presence of disorder or functioning.
Harms	There is no evidence on the harms of benzodiazepines for bereaved children and adolescents who do not meet criteria for a mental disorder. In addition to the evidence from randomized trials, data from observational and epidemiological studies – mostly with adult populations - highlighted a risk of tolerance and dependence. According to NICE UK, one of the key concerns about the use of benzodiazepines is that many people develop tolerance to their effects, gain little therapeutic benefit from chronic consumption, become dependent on them (10–30% of chronic benzodiazepines users are physically dependent on them), and suffer a withdrawal syndrome when they stop taking them (50% of all users suffer withdrawal symptoms). With regard to children and adolescents, very few rigorous studies have been conducted but dependency risks have been similarly reported (Witek et al, 2005, Psychiatric Quarterly, 76). The withdrawal syndrome includes anxiety, depression, nausea and perceptual changes. There are also problems of abuse with benzodiazepines as they enhance and often prolong the 'high' obtained from other drugs and alleviate their withdrawal effects.

Value and preferences	
In favour	
Against	Children and adolescents – still in development – should only be exposed to drugs if other effective treatment options have been tried, if the condition is sufficiently severe and treatment is likely to lead to a substantial improvement and if information about long-term consequences is available.

	Providing medication for bereavement may contribute to the medicalization of normal psychological reactions and may contribute to dependence.

Feasibility (including economic consequences)	Training is required in the understanding and safe administration of all psychotropic medications. To avoid the risks of harm referred to above, training of primary care practitioners may be necessary on responsible use of benzodiazepines. In many LAMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge.

Judgements to inform the decision on the strength of the recommendation

Factor	Decision
Is there high or moderate quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	Yes **No X**
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	**Yes X** No
Are the expected values and preferences clearly in favour of the recommendation?	**Yes X** No
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	**Yes X** No

Final recommendation by the guideline panel

Recommendation 21

Benzodiazepines should not be offered to bereaved children and adolescents who do not meet criteria for a mental disorder.

Strength of recommendation: strong
Q*uality of evidence: very low*

Remarks

As mentioned in the remarks for recommendation 19 on psychological interventions for bereaved children and adolescents: general principles of care, as reported in the WHO (2010) mhGAP Intervention Guide (particularly principles on communication, mobilizing and providing social support, and attention to overall well-being) and principles of psychological first aid should be considered. Encourage participation in culturally appropriate mourning.

In cases where the child has lost a primary caregiver, the issue of protection and continued supportive caregiving, including socio-emotional support, should be addressed.