**NMA on PTSD**

**Appendix 1**

Network meta-analysis protocol

**COMPARATIVE EFFICACY AND ACCEPTABILITY OF PHARMACOLOGICAL TREATMENTS IN THE ACUTE PHASE TREATMENT OF POSTTRAUMATIC STRESS DISORDER IN ADULTS: A NETWORK META-ANALYSIS**

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**PROTOCOL**

**Version 3.1 (October 2013)**

**Background**

***Description of the condition***

Posttraumatic stress disorder (PTSD) is a mental psychiatric condition that may develop following exposure to a traumatic event. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5),1 the essential feature of PTSD is the development of characteristic symptoms following exposure to a traumatic stressor. PTSD is characterized by three core symptom clusters: (1) re-experiencing, (2) avoidance or numbing (or both), (3) hyper-arousal and (4) negative alterations in cognition and mood. PTSD develops in up to a third of individuals who are exposed to extreme stressors, and symptoms almost always emerge within days of the exposure. Shortly after exposure to trauma, many people experience some of the symptoms of PTSD; in most people, those symptoms resolve spontaneously in the first several weeks after the trauma. However, in approximately 10 to 20% of those exposed to trauma, PTSD symptoms persist and are associated with impairment in social or occupational functioning.2 Although approximately 50% of those diagnosed with PTSD improve without treatment in 1 year, 10 to 20% develop a chronic unremitting course.3

The estimated lifetime prevalence of PTSD among adults is around 6.8% and current (12-month) prevalence about 3.6%.4 Recent surveys of military personnel have yielded estimates ranging from 6.2% for U.S. service members who fought in Afghanistan to 12.6% for those who fought in Iraq.5 People with PTSD suffer decreased role functioning, such as work impairment, and experience many other adverse life-course consequences, including job losses; family discord; and reduced educational attainment, work earnings, marriage attainment, and child rearing.6 PTSD is associated with an increased risk of suicide, high medical costs, high social costs and psychiatric comorbidity (most notably substance use disorders or major depressive disorder).7

***Description of the intervention***

Treatments available for PTSD span a variety of psychological and pharmacological interventions.8 Among psychological interventions, brief eclectic psychotherapy, cognitive behavioural therapies, eye movement desensitization and reprocessing, interpersonal therapy and also psychodynamic therapy have been studied. Psychological therapies are delivered predominantly to individuals, even though some can also be conducted in a group setting. On the other end, many pharmacological therapies have been studied for treatment of patients with PTSD.8 They include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), other second-generation antidepressants, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), alpha-blockers, second-generation antipsychotics, anticonvulsants (mood stabilizers), and benzodiazepines. Currently, only paroxetine and sertraline have been licensed in the US by the Food and Drug Administration for treatment of patients with PTSD.

***Why it is important to do this review***

Numerous organizations have produced guidelines for the treatment of patients with PTSD.9-11 All of these guidelines agree that trauma-focused psychological interventions are empirically supported first-line treatments for adults with PTSD and recognize some benefit of pharmacologic treatments for PTSD. However, various guidelines have arrived at different conclusions and recommendations about broad categories of treatments. Among the various treatment options available, it is clinically very important to know what pharmacological intervention, alone or in combination, is more efficacious and acceptable than others for the acute treatment of PTSD. Notwithstanding some very recent reviews,12 clinical uncertainty still remains about what pharmacological treatment to select among all available compounds.

***Objectives***

To compare the efficacy and acceptability of different pharmacological treatments (either as monotherapy or add-on therapy to other drugs) in the acute phase treatment of PTSD in adults.

**Methods**

***Criteria for considering studies for this review***

**Types of studies**

*Inclusion criteria*

Only double-blind randomized controlled trials (RCTs) comparing any psychotropic agent with placebo, or one another as oral therapy in the acute treatment of PTSD will be included. Psychiatric comorbidity will not be an exclusion criterion.

*Exclusion criteria*

Quasi-randomized controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, will be excluded. We will exclude open-label RCTs and long term studies using a maintenance design (randomising patients without acute symptoms). Medical comorbidity will be an exclusion criterion. We will also exclude crossover studies, in order to rule out the possibility of a "carryover" therapeutic effect.

**Types of participants**

*Inclusion criteria*

Participants aged 18 or older, of both sexes with a primary diagnosis of PTSD, diagnosed according to any of the following operationalized criteria: Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR or ICD-10. Operationalized criteria essentially resembling these official ones will also be eligible. Studies conducted in both in inpatient and outpatient settings will be included.

*Exclusion criteria*

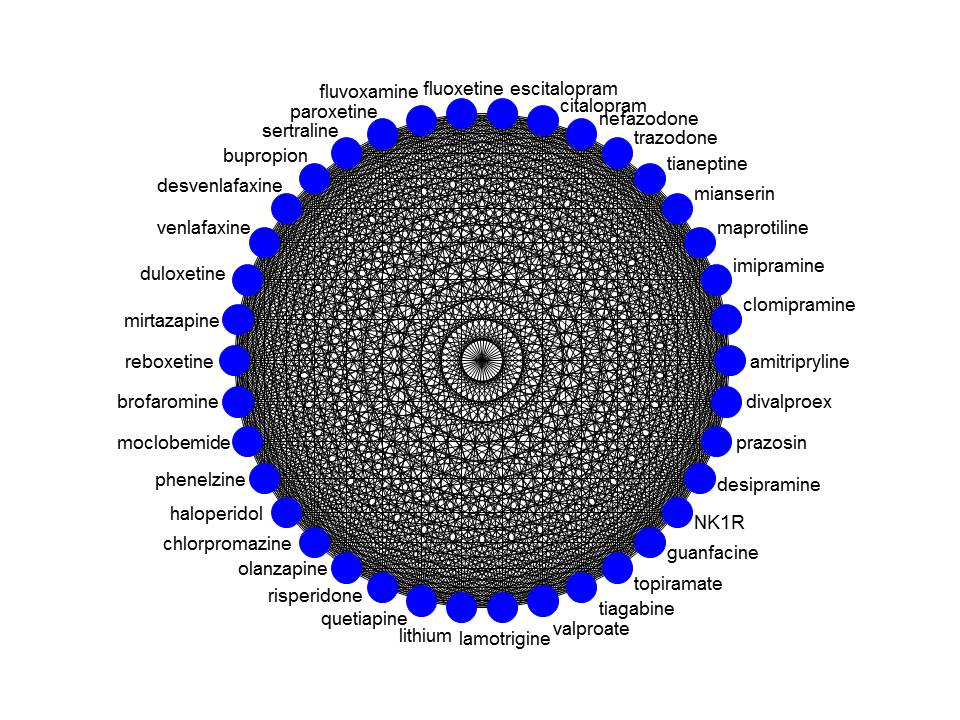
We will exclude studies recruiting children and adolescents.

**Types of interventions**

We will include all pharmacological interventions (even if they are not licensed in any country), only if administered within the therapeutic range. We will exclude all non-pharmacological treatments and the interventions with over-the-counter drugs. We will include RCTs that evaluate one or more of the following pharmacological interventions: antidepressants (amitripryline, clomipramine, imipramine, maprotiline, mianserin, tianeptine, trazodone, nefazodone, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, desvenlafaxine, venlafaxine, duloxetine, mirtazapine, reboxetine, brofaromine, moclobemide, phenelzine), antipsychotics (haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine), lithium and other mood stabilisers/anti-epileptic drugs (lamotrigine, valproate, tiagabine, topiramate) and new drugs with different mechanisms of action (for example guanfacine, selective NK1R antagonists, etc).

We will obtain information about the interventions of interest either from head-to-head or placebo controlled trials. Hence the synthesis comparator set consists of all the interventions listed above, their combinations and placebo.

Figure 1 shows the network of all possible pairwise comparisons between the eligible interventions.



We assume that any patient that meets all inclusion criteria is, in principal, equally likely to be randomized to any of the interventions in the synthesis comparator set.

**Types of outcome measures**

*Primary outcomes*

(1) Efficacy (as continuous outcome), measured by the total score on the CAPS-2 or CGI-I (or any other standardised rating scale, if the previous ones are not available) after 8 weeks (range 6 to 12 weeks).

(2) Acceptability of treatment, defined as the proportion of patients who left the study early by any cause during the first 8 weeks of treatment (range 6 to 12 weeks).

*Secondary outcomes*

(3) Efficacy (as dichotomous outcome), measured by the total number of patients who responded, according to study authors’ definition of response (depression scales are often used in this literature, so could be considered as well).

(4) Acceptability of treatment, defined as the proportion of patients who left the study early due to side effects during the first 8 weeks of treatment (range 6 to 12 weeks).

***Search methods for identification of studies***

The search strategy was designed to detect all RTCs comparing treatments in the decision comparator set against each other or with placebo.

*1. Electronic searches*

We will search MEDLINE, PsycINFO, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). In order to identify randomized trials, we will use the search term of the Cochrane highly sensitive search strategy for identifying randomized trials in each databases with sensitivity-maximizing version (Cochrane handbook). Together with RCT filters, we will search generic terms for PTSD and individual drug names. References to trials will also be sourced from international trials registers via the World Health Organization’s trials portal (http://apps.who.int/trialsearch/); regulatory agencies; drug companies; the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. No language restriction will be applied.

*2. Reference lists*

The references of all selected studies will be searched for more published reports and citations of unpublished studies. Relevant review papers will be checked.

*3. Personal communication*

Subject experts will be contacted to check that all relevant studies, either published or unpublished, have been considered for inclusion.

***Data collection and analysis***

*Selection of studies*

Two review authors (TA, AC) will examine the abstracts of all publications obtained through the search strategy. Full articles of all the studies identified by either of the review authors will then be obtained and inspected by the same two review authors to identify trials meeting the following criteria: (i) double-blind randomized controlled trial; (ii) participants with PTSD diagnosed by operationalized criteria; (iii) pharmacological intervention with prescription drugs. Conflicts of opinion regarding eligibility of a study will be discussed with a third review author (DS or JG), having retrieved the full paper and consulted the authors if necessary, until consensus is reached. External subject or methodological experts will be consulted if necessary.

***Data extraction and management***

*Outcome data*

We will extract from each included study the total score on any standardized scale (e.g. CAPS-2 or CGI-I), the duration of the intervention, the number of participants, the drop-out rates, the authors’ definition of response, the number of patients that responded and the interventions being compared.

*Data on potential effect modifiers*

We will extract from each included study data on the following study, intervention and population characteristics that may act as effect modifiers:

1. Year of publication

2. Baseline severity

3. Sponsorship

4. Mean age at onset

Data from each study will be extracted independently by two review authors (TA, AC). Degree of agreement between the two independent raters will be reported in terms of kappa coefficients and percentage agreements for main outcomes, study and population characteristics and risk of bias items. Any disagreement will be resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information. Information relating to study population, sample size, interventions, comparators, potential biases in the conduct of the trial, and outcomes will be abstracted from the original reports into specially designed paper forms then entered into a spreadsheet.

**Assessment of risk of bias in included studies**

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool, as a model.13 The following 6 domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?

2. Allocation concealment: was allocation adequately concealed?

3. Blinding of participants, personnel and outcome assessors for each main outcome: was knowledge of the allocated treatment adequately prevented during the study?

4. Incomplete outcome data for the primary outcomes: were incomplete outcome data

adequately addressed?[[1]](#footnote-1)

5. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?

6. Sponsorship bias.

A description of what was reported to have happened in each study will be provided, and a judgment on the risk of bias will be made for each domain, based on the following three categories:

* High risk of bias
* Low risk of bias
* Unclear risk of bias.

Two independent review authors (TA, AC) will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreement will be resolved through discussion and in consultation with the principal investigators. Where necessary, the authors of the studies will be contacted for further information.

**Measures of treatment effect**

Continuous outcomes: Where different measures are used to assess the same outcome, data will be pooled with standardized mean difference (SMD) Hedges’s adjusted *g*13. Dichotomous outcomes: these outcomes will be analyzed by calculating the odds ratio (OR).

***Dealing with missing data***

Missing dichotomous outcome data will be managed according to the intention to treat (ITT) principle, and it will be assumed that patients in the full analysis set who dropped out after randomization had a negative outcome. Missing continuous outcome data will either be analyzed on an endpoint basis, including only participants with a final assessment, or analyzed using last observation carried forward to the final assessment (LOCF) if LOCF data were reported by the trial authors.

When p-values, t-values, confidence intervals or standard errors are reported in articles, SD will be calculated from their values.14 Where SDs are missing, attempts will be made to obtain these data through contacting trial authors. Where SDs are not available from trial authors and the vast majority of actual SDs are available and only a minority of SDs are unavailable or unobtainable, a method used for imputing SDs will be used.15 We will check that the original standard deviations are properly distributed, so that the imputed standard deviation represents the average. Where this method is employed, data will be interpreted with caution, taking account of the degree of heterogeneity observed. A sensitivity analysis will also be undertaken to examine the effect of the decision to use imputed data.

***Assessment of clinical and methodological heterogeneity within treatment comparisons***

The studies synthesized in each pairwise comparison should be similar enough in terms of patient characteristics, setting, outcome definitions etc. in order to obtain interpretable and useful results.13 To evaluate the presence of clinical and methodological heterogeneity we will generate descriptive statistics for trial and study population characteristics across all eligible trials. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.13

***Assessment of transitivity across treatment comparisons***

The assumption of transitivity (i.e. one can compare indirectly treatments B and C via treatment A) underlies network meta-analysis and needs careful evaluation. In case that transitivity is not plausible in a network of trials, the indirect and mixed treatment effect estimates are not valid. To infer about the assumption of transitivity:16

1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether antidepressants are administered the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to antipsychotics.
2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons (see ‘Data extraction and management’ for the list of potential effect modifiers). If the distributions are balanced across comparisons we will conclude against evidence of intransitivity.17

***Data synthesis***

**Methods for direct treatment comparisons**

Initially, we will perform standard pairwise meta-analyses using a random effects model18 in STATA19 for every treatment comparison with at least two studies.

**Methods for indirect and mixed comparisons**

We will also perform network meta-analysis (NMA) to synthesize the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will perform NMA using the methodology of multivariate meta-analysis where the different treatment comparisons are treated as different outcomes. This approach is described in detail in White et al.20 For this analysis we will use the STATA (mvmeta command21).

Results from NMA will be presented as summary relative effect sizes (SMD or OR) for each possible pair of treatments. We will also estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA)22 and mean ranks. SUCRA can also be expressed as a percentage interpreted as the percentage of efficacy/safety of a treatment that would be ranked first without uncertainty.

***Assessment of statistical heterogeneity***

**Assumptions when estimating heterogeneity**

In standard pairwise meta-analyses we will estimate a different heterogeneity variances for each pairwise comparisons. In NMA we will assume a common estimate for the heterogeneity variance across the different comparisons.

**Measures for heterogeneity**

We will assess statistically the presence of heterogeneity within each pairwise comparison using the I-squared statistic23 and its 95% confidence interval that measures the percentage of variability that cannot be attributed to random error.

The assessment for the presence of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter (*τ2*) estimated from the NMA models. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner.24 We will also estimate a total I-squared value for heterogeneity in the network as described elsewhere.25

***Assessment of statistical inconsistency***

NMA assumes that there is consistency in the network (i.e. direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (i.e. loops of evidence) of the network26. Therefore, consistency needs to be checked. We will evaluate the presence of inconsistency using the following approaches:

**Local tests**

To evaluate the presence of inconsistency locally we will use the loop-specific approach.27 This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer about the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop.28 We will present the results of this approach graphically in a forest plot using the *ifplot* command in STATA.29

**Global tests**

To check the assumption of consistency in the entire network simultaneously we will use the ‘design-by-treatment’ model as described by Higgins and colleagues.30 This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer about the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in STATA using the *mvmeta* command.21

Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we will employ the I-squared for inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability).25

*Investigation of heterogeneity and inconsistency*

If we find important heterogeneity or/and inconsistency, we will explore the possible sources. If sufficient studies are available, we will perform meta-regression or subgroup analyses by using the following effect modifiers as possible sources of inconsistency and or heterogeneity: (i) year of publication; (ii) study precision; (iii) baseline severity.

*Sensitivity analyses*

In order to examine if the obtained results are preserved when we limit the included studies to those with lower risk of bias, we will examine the following variables.

1. Allocation concealment

Allocation concealment will be used as a marker of trial quality.31 Studies that were rated at high or unclear risk of bias for allocation concealment will be excluded.

2. Imputation

Trials where missing data have been imputed will be excluded.

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1. A difference in the proportion of incomplete outcome data across groups is of concern if the availability of outcome data is determined by the participants’ true outcomes. Studies in which all participants are kept in the intervention groups to which they were randomized, outcome data are measured on all participants and all randomized participants are included in the analysis will be rated as at low risk of bias. Studies in which ‘as treated’ analyses are reported will be rated as at high risk of bias. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear. [↑](#footnote-ref-1)