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1 **Psychological treatments for post-traumatic stress disorder in adults: a network**
2 **meta-analysis**

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16

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18

1 **Abstract**

2 **Background:** Post-traumatic stress disorder (PTSD) is a potentially chronic and disabling
3 disorder affecting a significant minority of people exposed to trauma. Various psychological
4 treatments have been shown to be effective, but their relative effects are not well
5 established.

6 **Methods:** We undertook a systematic review and network meta-analyses of psychological
7 interventions for adults with PTSD. Outcomes included PTSD symptom change scores post-
8 treatment and at 1-4-month follow-up, and remission post-treatment.

9 **Results:** We included 90 trials, 6560 individuals and 22 interventions. Evidence was of
10 moderate-to-low quality. Eye movement desensitisation and reprocessing [EMDR] (SMD -
11 2.07; 95%CrI -2.70 to -1.44), combined somatic/cognitive therapies (SMD -1.69; 95%CrI -
12 2.66 to -0.73), trauma-focused cognitive behavioural therapy [TF-CBT] (SMD -1.46; 95%CrI -
13 1.87 to -1.05) and self-help with support (SMD -1.46; 95%CrI -2.33 to -0.59) appeared to be
14 most effective in reducing PTSD symptoms post-treatment versus waitlist, followed by non-
15 TF-CBT, TF-CBT combined with a selective serotonin reuptake inhibitor [SSRI], SSRIs, self-
16 help without support, and counselling. EMDR and TF-CBT showed sustained effects at 1-4-
17 month follow-up. EMDR, TF-CBT, self-help with support and counselling improved remission
18 rates post-treatment. Results for other interventions were either inconclusive or based on
19 limited evidence.

20 **Conclusions:** EMDR and TF-CBT appear to be most effective in reducing symptoms and
21 improving remission rates in adults with PTSD. They are also effective in sustaining
22 symptom improvements beyond treatment endpoint. Further research needs to explore the
23 long-term comparative effectiveness of psychological therapies for adults with PTSD and
24 also the impact of severity and complexity of PTSD on treatment outcomes.

1 **INTRODUCTION**

2 Worldwide, post-traumatic stress disorder (PTSD) has a lifetime prevalence of 3.9% in the
3 general population, and 5.6% among those exposed to trauma (Koenen *et al.*, 2017). PTSD
4 is associated with substantial levels of disability, poor quality of life and functional
5 impairment (Alonso *et al.*, 2004). It is often comorbid with other mental disorders such as
6 depression, anxiety, substance abuse (Kessler *et al.*, 1995), and has been associated with
7 numerous physical health difficulties, including cardiovascular and metabolic disease
8 (Ahmadi *et al.*, 2011).

9

10 Several psychological treatments are available for the management of PTSD in adults.
11 Trauma-focused cognitive behavioural therapy (TF-CBT) is a broad class of psychological
12 interventions that predominantly use trauma-focused cognitive, behavioural or cognitive-
13 behavioural techniques and exposure approaches to treatment. Although some interventions
14 place their main emphasis on exposure and others on cognitive techniques, most use a
15 combination. There is considerable overlap in the proposed mechanisms underlying the
16 effectiveness of the various versions of TF-CBT. TF-CBT includes therapies such as
17 cognitive therapy (CT), cognitive processing therapy (CPT), exposure therapy/prolonged
18 exposure, virtual reality exposure therapy, mindfulness-based CT and narrative exposure
19 therapy. Other available treatments for PTSD include eye movement desensitisation and
20 reprocessing (EMDR), interpersonal psychotherapy, present-centered therapy, self-help
21 therapies such as internet-based TF-CBT and expressive writing, counselling, non-TF-CBT,
22 which focuses on current symptoms of PTSD without re-visiting the trauma experience, and
23 combined somatic/cognitive therapies such as emotional freedom techniques and thought
24 field therapy; these are exposure-based therapies with both cognitive and somatic
25 components that utilise the tapping of points on the body (Church *et al.*, 2013; Robson *et al.*,
26 2016).

27

1 A number of systematic reviews and meta-analyses have evaluated the effectiveness of
2 psychological treatments for adults with PTSD (Bisson *et al.*, 2013; Cusack *et al.*, 2016;
3 Forman-Hoffman *et al.*, 2018; Frost *et al.*, 2014; Gerger *et al.*, 2014; Khan *et al.*, 2018;
4 Kuester *et al.*, 2016; Seidler and Wagner, 2006; Sijbrandij *et al.*, 2016; van Emmerik *et al.*,
5 2013). Commonly they find most robust evidence for the efficacy of individual TF-CBT and
6 EMDR, and some evidence for non-TF-CBT, present-centered therapy and self-help. For
7 other interventions (such as combined somatic/cognitive therapies) there has been more
8 limited high quality research that did not always meet the inclusion criteria for these reviews,
9 and therefore no robust conclusions on their effectiveness could be drawn. One review
10 suggested that individual TF-CBT, EMDR and non-TF-CBT are more effective than other
11 therapies for PTSD (Bisson *et al.*, 2013). Moreover, there was evidence to suggest
12 superiority of EMDR over TF-CBT (Khan *et al.*, 2018). However, these findings were not
13 confirmed in another review (Gerger *et al.*, 2014). With the exception of one review (Gerger
14 *et al.*, 2014), these analyses have made limited comparisons across a narrow range of
15 treatments using standard pairwise meta-analysis to synthesise evidence from randomised
16 controlled trials (RCTs). This approach does not allow for the relative effectiveness across all
17 treatments to be assessed, unless all possible comparisons have been evaluated in head-to-
18 head trials.

19

20 Network meta-analysis (NMA) is a generalisation of pairwise meta-analysis to data
21 structures that include, for example, A versus B, B versus C, and A versus C trials (Lu and
22 Ades, 2004). NMA strengthens inferences concerning the relative effect of two treatments by
23 including both direct and indirect treatment comparisons. This means that NMA allows
24 estimation of the relative effects of treatments that may not have been directly compared in
25 RCTs. Simultaneous estimation of all relative effects for any number of treatments is
26 possible provided that treatments are connected in a single 'network of evidence' - that is,
27 every treatment is linked to at least one of the other treatments under assessment through
28 direct comparisons (Caldwell *et al.*, 2005; Mavridis *et al.*, 2015).

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The objective of this study was to examine the relative effectiveness of psychological treatments for PTSD in adults using NMA techniques. The analyses presented here supported the updating of national guidance for PTSD in England (National Institute for Health and Care Excellence, 2018a). The guideline was developed by a guideline committee, an independent multi-disciplinary group of clinical academics, health professionals and service user and carer representatives with expertise and experience in the field of PTSD.

METHODS

Search strategy

A search for RCTs of treatments for people with clinically important post-traumatic stress symptoms was conducted in the following databases: MEDLINE, Embase, PsycINFO, CINAHL and The Cochrane Library. Databases were searched using relevant medical subject headings, free-text terms and a study design filter. The aim of the search was to update the evidence included in the previous National Institute for Health and Care Excellence (NICE) PTSD guideline, published in 2005. The search was undertaken in January/February 2017 with re-runs performed in January 2018. Online Supplementary Appendix 1 provides full details of the databases and search terms used. The reference lists of all relevant systematic reviews were hand-searched for any additional eligible studies. Clinical trial registries (ISRCTN and ClinicalTrials.gov) were also hand-searched to identify any relevant unpublished trials and authors were contacted to request study reports (where these were not available online). Primary authors of published included studies were also contacted to request outcome data where these could not be extracted.

Selection criteria for the systematic review and the network meta-analysis

A systematic review of psychological, psychosocial and other non-pharmacological interventions targeted at clinically important post-traumatic stress symptoms in adults more

1 than one month after a traumatic event was carried out in accordance with the Preferred
2 Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher *et*
3 *al.*, 2009). Eligible populations included adults with either a diagnosis of PTSD according to
4 the Diagnostic and Statistical Manual of Mental Disorders (DSM), the World Health
5 Organization (WHO) International Classification of Diseases (ICD) or similar criteria, or with
6 the presence of clinically significant PTSD symptoms, as indicated by baseline scores above
7 a pre-defined threshold on a validated PTSD symptom scale. If some, but not all, of a study's
8 participants had clinically important PTSD symptoms, the study would be included if at least
9 80% of participants had clinically important PTSD symptoms or if disaggregated data only for
10 those with PTSD could be extracted from the paper. If less than 80% of the participants had
11 clinically important PTSD symptoms, or if disaggregated data only for those with PTSD were
12 not available, then the mean baseline PTSD symptom score was used and a study was
13 included in the review if this mean was above a pre-defined clinical threshold. Primary
14 outcomes for the review included PTSD symptom endpoint or change scores on a validated
15 PTSD scale; response to treatment; and recovery or remission defined either as the number
16 of people no longer meeting diagnostic criteria for PTSD, or with PTSD symptom scores
17 below the threshold on a validated scale.

18

19 For quality assurance of study identification, and in accordance with NICE guidance
20 (National Institute for Health and Care Excellence, 2014), the titles and abstracts of identified
21 studies were screened by two reviewers against inclusion criteria specified in the guideline
22 review protocols until a good inter-rater reliability was observed (percentage agreement \geq
23 90%). Initially, a random 10% of references were double-screened and inter-rater agreement
24 was good; therefore, the remaining references were screened by one reviewer. All primary-
25 level studies included after the first citation scan were acquired in full and re-evaluated for
26 eligibility at the time of being entered into a study database (standardised template created
27 in Microsoft Excel). At least 10% of data extraction (including data informing the risk of bias
28 assessment) was double-coded. Discrepancies or difficulties with coding were resolved

1 through discussion between reviewers or the opinion of a third reviewer was sought. Data
2 were extracted on study characteristics, intervention details, outcome data, and risk of bias.

3
4 For the NMA, we considered only first-line psychological treatments offered to adults with a
5 diagnosis of PTSD or clinically important post-traumatic stress symptoms more than three
6 months after trauma. Pharmacological and combined psychological and pharmacological
7 treatments that were linked in the treatment network were also considered. Hypnotherapy,
8 psychosocial interventions (meditation, mindfulness-based stress reduction, supported
9 employment, peer and practical support) and physical interventions (exercise, yoga,
10 acupuncture, bio-neuro-feedback and repetitive transcranial magnetic stimulation) were not
11 included in the analysis as they were not considered to be alternative, first-line treatments for
12 the management of PTSD in adults. Relaxation was included as a control intervention that
13 provided additional indirect comparisons across interventions of interest.

14
15 Interventions in the TF-CBT class were not considered separately according to their type.
16 Although the specific interventions that make up a class do not include exactly the same
17 content or follow the same manual, they use the same broad approach and there is
18 considerable overlap in the proposed mechanisms; the efficacy of interventions within the
19 class was therefore considered to be equivalent. Hence, in the analyses presented here, TF-
20 CBT is considered as an umbrella term and forms one node in the network. For the analyses
21 that informed the NICE clinical guideline on PTSD, we divided the TF-CBT class by number
22 of sessions and format of delivery and created different nodes in the network according to
23 the intensity of TF-CBT, as these differences in resource use comprised practical
24 considerations that informed the guideline economic analysis, and, subsequently, practice
25 recommendations.

26
27 The guideline systematic review included two categories of RCTs: those that compared
28 interventions or their combinations delivered as the sole treatment in a trial arm versus

1 waitlist or another inactive control or active intervention; and those comparing interventions
2 added to treatment as usual (TAU) versus TAU alone or versus an inactive control added to
3 TAU or versus another active intervention added to TAU. The definition of TAU varied widely
4 across studies, including minimum contact comparison, a mixture of psychoeducation and
5 supportive counselling, medication, substance misuse treatment, any treatment outside the
6 research setting or any treatment except the intervention assessed in the study. To reduce
7 heterogeneity attributable to the diversity of TAU across RCTs, comparisons involving TAU
8 alone or combined with a control or with an intervention of interest were not included in the
9 NMA even if they provided links in the network.

10

11 The NMA considered two outcomes: PTSD symptom change scores and remission. Data on
12 these outcomes were mostly reported at treatment endpoint. Moreover, a number of studies
13 reported data on one or both of these outcomes at 1-4-month follow-up. PTSD symptom
14 change scores between baseline and 1-4-month follow-up were adequate to inform a NMA;
15 in contrast, remission data at 1-4-month follow-up were very sparse (the network only
16 included 10 studies, 7 interventions and 572 participants; the only active intervention that
17 had been tested on more than 100 participants was TF-CBT). Beyond 1-4 months of follow-
18 up, available data were very sparse for both outcomes. Based on the availability of data for
19 the two outcomes of interest, three separate NMAs were conducted on the following
20 outcomes and time points:

- 21 • PTSD symptom change scores between baseline and treatment endpoint
- 22 • PTSD symptom change scores between baseline and 1-4-month follow-up
- 23 • Remission at treatment endpoint

24

25 If both were available in the same study, PTSD symptom change scores derived from self-
26 rated symptom scales were prioritised over those derived from clinician-rated symptom
27 scales, because the former were deemed to better capture symptoms experienced by adults

1 with PTSD, according to the NICE guideline committee. Similarly, intention-to-treat (ITT)
2 data, obtained after imputation of missing data, were prioritised over completer data, if both
3 were available in the same study.

4

5 The guideline study protocol was published on the NICE website during consultation of the
6 draft guidance with registered stakeholders

7 (<https://www.nice.org.uk/guidance/ng116/history>). The systematic review protocol and the
8 additional inclusion criteria applied for the NMA are provided in online Supplementary
9 Appendix 2.

10

11 **Statistical analysis**

12 NMAs were conducted within a Bayesian framework using a generalised linear model (GLM)
13 approach (Dias *et al.*, 2013a), estimated using Markov Chain Monte Carlo simulation
14 techniques implemented in WinBUGS 1.4.3 (Lunn *et al.*, 2000; Spiegelhalter *et al.*, 2003). An
15 overview of the approach and methods adopted is provided below. Details of the statistical
16 analysis and WinBUGS codes used to synthesise changes in PTSD symptom scores and
17 dichotomous remission data are reported in online Supplementary Appendix 3.

18

19 For the synthesis of continuous data (changes in PTSD symptom scores), a linear model
20 with a normal likelihood and identity link was used (Dias *et al.*, 2018). Because the RCTs
21 included in the NMAs used different continuous scales to report change in PTSD symptoms,
22 relative effects were expressed in the form of the Standardised Mean Difference (SMD)
23 between pairs of interventions. For the synthesis of dichotomous data (remission), a linear
24 model with binomial likelihood and logit link was used (Dias *et al.*, 2013a; Dias *et al.*, 2018).
25 The output of this analysis was the set of log-odds ratios (LORs) between pairs of
26 interventions. The suitability of fixed and random effects models in terms of model fit was
27 assessed and compared, and the most suitable model (fixed or random effects) was then
28 selected for the analysis of each outcome.

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For each analysis we report posterior mean relative effects (either SMD or LOR) with 95% credible intervals (CrI). We also report posterior mean ranks with 95%CrI for every treatment tested on at least 100 individuals in each analysis, where a rank of 1 indicates highest effectiveness. We only included interventions tested on at least 100 people in the ranking, as this was deemed the minimum adequate evidence to draw conclusions on effectiveness. Results were interpreted in terms of ‘evidence of effect’, rather than ‘statistical significance’ (Pike, 2019), and this was determined based on whether the 95%CrI crossed the line of no effect. Although no cut-off points were used in order to judge the magnitude of effect, in general a SMD value of 0.2 to 0.3 was deemed to indicate a small effect, a value around 0.5 a medium effect, and a value of 0.8 and above a large effect (Cohen, 1969).

Inconsistency checks

A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. In other words, it is assumed that there is agreement between the direct and indirect evidence informing the treatment contrasts (this has also been termed the similarity or transitivity assumption (Mavridis *et al.*, 2015)). Inconsistency arises when there is a conflict between direct evidence (from an A versus B trial) and indirect evidence (gained from A versus C and B versus C trials) and can only be statistically assessed when there are closed loops of evidence on 3 treatments that are informed by at least 3 distinct trials (van Valkenhoef *et al.*, 2016). The assumption of consistency between indirect and direct evidence was explored by undertaking global inconsistency tests (Dias *et al.*, 2010; Dias *et al.*, 2013b) and local tests through node-splitting (Dias *et al.*, 2013b; van Valkenhoef and Kuiper, 2016). When evidence of inconsistency was found, studies contributing to loops of evidence where there might be inconsistency were checked for data accuracy. Analyses were repeated if corrections in the data extraction were made. If evidence of inconsistency

1 was still present following data corrections, no studies were excluded from the analysis, as
2 their results could not be considered to be less valid than those of other studies solely
3 because of the inconsistency findings; nevertheless, the presence of inconsistency in the
4 NMA was highlighted and results were interpreted accordingly.

5

6 Details of the methods used to test inconsistency and the WinBUGS codes of the
7 inconsistency models are provided in online Supplementary Appendix 4.

8

9 ***Pairwise sub-analyses***

10 For the purposes of the NICE clinical guideline, a number of sub-analyses of the pairwise
11 meta-analyses were considered, including sub-analysis by specific intervention type for the
12 TF-CBT comparisons, and sub-analyses by trauma type and multiplicity of index trauma for
13 all interventions. It is beyond the scope of this paper to explore all sub-analyses but for
14 illustrative purposes, exploratory sub-analyses have been conducted by specific TF-CBT
15 intervention, method of analysis (ITT versus modified ITT versus completer) and multiplicity
16 of index trauma (single or multiple) for the TF-CBT versus waitlist comparison for the PTSD
17 symptom change scores between baseline and treatment endpoint outcome. This
18 comparison and outcome were selected as it was the only pairwise meta-analysis with
19 sufficient studies to enable meaningful comparison between subgroups. A sub-analysis by
20 trauma type was not included because there were almost as many trauma types as studies
21 and as such the analysis was not interpretable.

22

23 **RESULTS**

24 **Studies and treatments**

25 The systematic literature search identified 715 studies potentially eligible for the systematic
26 review, 529 of which were excluded. Ninety-six more studies were excluded as they did not
27 meet criteria for the NMA, leaving 90 eligible studies on 22 interventions (including two

1 inactive controls) that reported one or more outcomes of interest (Figure 1). In 64% of the
2 included studies, the study population comprised adults with a diagnosis of PTSD; in the
3 remaining 36% of the included studies, the study population consisted of adults with clinically
4 significant PTSD symptoms, as indicated by baseline scores above a pre-defined threshold
5 on a validated PTSD symptom scale. The characteristics of included studies are reported in
6 online Supplementary Appendix 5. A list of excluded studies, with reasons for exclusion, is
7 provided in online Supplementary Appendix 6. Online Supplementary Appendix 7 shows the
8 full data included in each NMA.

9

10 ***Risk of bias assessment***

11 All 90 included trials were assessed for risk of bias using the Cochrane risk of bias tool
12 (Higgins and Green, 2011). Sequence generation and allocation concealment were
13 adequately described in 36 and 29 trials, respectively. All trials were regarded as at high risk
14 of bias for lack of participant and provider masking. In 20 studies, a clinician-rated scale was
15 used, with assessors being unaware of treatment assignment. In seven trials it was unclear if
16 the assessors were blinded, and in 63 studies a self-rated scale was used meaning that
17 raters were non-blind but were less likely to have a conflict of interest in terms of detection
18 bias. Attrition was high in 11 trials and unclear in 35 studies. However, we favoured ITT
19 analysis and, for the remission outcome, we conservatively treated drop-outs as failing to
20 remit. Of the studies that reported PTSD symptom change scores, approximately 60%
21 reported ITT data, or ITT data were possible to estimate, with the remaining providing
22 completer data only. Included trials reported a variety of outcomes. Only nine trials were
23 registered on a trials database and reported all listed outcomes. Consequently, most studies
24 were judged as being at high or unclear risk of reporting bias. Other potential biases were
25 identified in seven studies; these included high risk of bias due to potential conflicts of
26 interest or due to methodological limitations not otherwise captured. An overview of the trials'
27 risk of bias assessment is provided in online Supplementary Appendix 8.

28

1 ***NMA model fit statistics***

2 In all NMAs, the random effects model provided a better fit over the fixed effect model and fit
3 the data well. However, the between-trial standard deviation (SD), which measures the
4 heterogeneity of treatment effects estimated by trials within contrasts, was high when
5 compared with the size of the intervention effect estimates across all three analyses
6 (posterior median SD: 0.93 in the NMA of PTSD changes between baseline and treatment
7 endpoint; 0.59 in the NMA of changes in PTSD symptom scores between baseline and 1-4-
8 month follow-up; 1.05 in the NMA of remission at treatment endpoint).

9

10 Details of model fit statistics are provided in online Supplementary Appendix 9.

11

12 ***Inconsistency checks***

13 No evidence of inconsistency between direct and indirect evidence was found in the NMAs
14 of changes in PTSD symptom scores at treatment endpoint and at follow-up. The NMA of
15 remission at endpoint showed evidence of inconsistency between pooled direct and indirect
16 estimates comparing TF-CBT, EMDR, and self-help without support. Direct effects in these
17 comparisons were implausibly large and with very wide 95%CrI (e.g. mean LOR of EMDR
18 versus TF-CBT -2.01, 95%CrI -4.01 to -0.01), a finding likely attributable to the small number
19 and size of RCTs involved in these comparisons; indirect/NMA estimates for these
20 comparisons are therefore likely to be more trustworthy.

21

22 Results of inconsistency checks are provided in online Supplementary Appendix 10.

23

24 ***Treatment outcomes***

25 Results of the three analyses are presented in Tables 1-3, as posterior mean effects with
26 95%CrI of each intervention versus waitlist, which served as the reference. In each analysis,
27 interventions have been ordered from the most to the least effective, according to their
28 posterior mean effect versus waitlist. The tables also show the number of participants

1 randomised to each intervention across RCTs included in each analysis, and the number of
2 RCTs that assessed each intervention in each NMA. In each analysis, ranking is provided for
3 all interventions tested on at least 100 individuals.

4

5 Changes in PTSD symptom scores between baseline and treatment endpoint

6 The network of changes in PTSD symptom scores between baseline and treatment endpoint
7 was formed by 71 RCTs with 151 arms that assessed 19 interventions tested on a total of
8 4,700 participants (Figure 2a). The majority of the evidence was on TF-CBT (N=903 in 29
9 trials), followed by self-help without support (N=335 in 11 trials) and EMDR (N=260 in 11
10 trials). There was also good- or moderately good-sized evidence on counselling (N=278 in 9
11 trials), non-TF-CBT (N=209 in 7 trials), self-help with support (N=198 in 5 trials), combined
12 somatic/cognitive therapies (N=237 in 4 trials), selective serotonin reuptake inhibitors
13 [SSRIs] (N=166 in 5 trials), psychoeducation (N=152 in 2 trials) and TF-CBT combined with
14 SSRIs (N=115 in 3 trials). All other interventions were tested on fewer than 100 participants
15 each. Of the 71 trials, 26 recruited participants with a single trauma and 38 recruited
16 participants with multiple traumas; the remaining 7 studies did not report this kind of
17 information.

18

19 For interventions tested on $N \geq 100$ each with evidence of effect versus waitlist (i.e. 95%CrI
20 that did not cross the line of no effect), the ranking (from the most to the least effective) was
21 as follows: EMDR (mean SMD versus waitlist -2.07, 95%CrI -2.70 to -1.44), combined
22 somatic/cognitive therapies (mean SMD versus waitlist -1.69, 95%CrI -2.66 to -0.73), TF-
23 CBT (mean SMD versus waitlist -1.46, 95%CrI -1.87 to -1.05), self-help with support (mean
24 SMD versus waitlist -1.46, 95%CrI -2.33 to -0.59), non-TF-CBT (mean SMD versus waitlist -
25 1.22, 95%CrI -1.95 to -0.49), TF-CBT combined with a SSRI (mean SMD versus waitlist -
26 1.21, 95%CrI -2.35 to -0.07), SSRIs (mean SMD versus waitlist -1.14, 95%CrI -2.09 to -
27 0.19), self-help without support (mean SMD versus waitlist -0.91, 95%CrI -1.67 to -0.15) and
28 counselling (mean SMD versus waitlist -0.73, 95%CrI -1.41 to -0.05) (Table 1).

1 Psychoeducation was the only intervention with an adequate evidence base (N=152) and
2 inconclusive effect versus waitlist. Although results suggest a trend towards the superiority of
3 EMDR over other active interventions, no evidence of differential effects between EMDR and
4 other treatments with a large evidence base was found. Comparisons between active
5 treatments suggested differences in effect only between EMDR and counselling (mean SMD
6 -1.34, 95%CrI -2.19 to -0.49) and between TF-CBT and counselling (mean SMD -0.73,
7 95%CrI -1.37 to -0.09).

8

9 Metacognitive therapy (mean SMD -3.04, 95%CrI -5.09 to -0.98) and present-centered
10 therapy (mean SMD -1.42, 95%CrI -2.45 to -0.40) also showed large effects versus waitlist
11 with 95%CrI that did not cross the zero line; however, these effects were based on a more
12 limited evidence base (N=10 and 99, respectively).

13

14 Overall, results were characterised by relatively wide 95%CrI around mean effects and
15 ranks; for example, TF-CBT mostly ranked between the 2nd and 8th place in different
16 iterations of the NMA model. High between-study heterogeneity may have contributed to the
17 uncertainty around mean effects.

18

19 Changes in PTSD symptom scores between baseline and 1-4-month follow-up

20 The network of changes in PTSD symptom scores between baseline and 1-4-month follow-
21 up included 28 RCTs, 2,315 participants and 15 interventions (Figure 2b). TF-CBT was
22 again the intervention with the largest evidence base (N=753 in 13 trials); other interventions
23 with moderately good-sized evidence base were counselling (N=205 in 4 trials), non-TF-CBT
24 (N=123 in 4 trials), EMDR (N=121 in 4 trials) and psychoeducation (N=183 in 3 trials). All
25 other interventions were tested on fewer than 100 participants each. Of the 28 trials, 10 and
26 15 recruited participants with a single and multiple trauma, respectively; 3 studies did not
27 provide any information on participants' number of previous traumas.

28

1 Of the interventions tested on $N \geq 100$ each, only two showed evidence of effect versus
2 waitlist: EMDR (mean SMD -1.12, 95%CrI -1.94 to -0.27) and TF-CBT (mean SMD -0.73,
3 95%CrI -1.23 to -0.25) (Table 2). Comparison between the two showed no evidence of
4 difference in effect (mean SMD -0.39 favouring EMDR, 95%CrI -1.30 to 0.54). Interventions
5 with $N \geq 100$ but inconclusive effects versus waitlist included psychoeducation, non-TF-CBT
6 and counselling.

7

8 Of interventions with a limited evidence base (each tested on $N < 100$), couple intervention,
9 self-help with support and behavioural therapy also showed evidence of effectiveness
10 against waitlist.

11

12 This analysis was also characterised by high between-study heterogeneity and uncertainty
13 that was reflected in wide 95%CrI around mean effects and rankings across interventions.

14

15 Remission at treatment endpoint

16 The NMA of remission at treatment endpoint consisted of 34 studies, 2,249 participants and
17 16 interventions (Figure 2c). TF-CBT was tested on $N=601$ participants in 21 trials; other
18 interventions with a moderately good-sized evidence base were counselling ($N=150$ in 6
19 trials); EMDR ($N=132$ in 5 trials); and self-help with support ($N=105$ in two trials). All other
20 interventions were tested on fewer than 100 participants each. Of the 34 trials, 15 and 16
21 recruited participants with a single and multiple trauma, respectively; 3 studies did not
22 provide any information on participants' number of previous traumas.

23

24 All interventions with an adequate evidence base ($N \geq 100$) showed evidence of large effects
25 versus waitlist. Their order, from the most to least effective was: EMDR (mean LOR versus
26 waitlist 3.38, 95%CrI 2.04 to 4.84), TF-CBT (mean LOR versus waitlist 2.46, 95%CrI 1.79 to
27 3.19), self-help with support (mean LOR versus waitlist 1.76, 95%CrI 0.03 to 3.49), and
28 counselling (mean LOR versus waitlist 1.34, 95%CrI 0.20 to 2.51). Comparisons between

1 active treatments suggested differences in effect only between EMDR and counselling
2 (mean LOR 2.04, 95%CrI 0.37 to 3.79) and between TF-CBT and counselling (mean LOR
3 1.12, 95%CrI 0.12 to 2.15).

4
5 Several interventions with limited evidence (each tested on N<100) showed large effects
6 versus waitlist on the remission outcome; these included psychodynamic therapy, non-TF-
7 CBT, relaxation, IPT and present-centered therapy.

8
9 As with previous outcomes, there was uncertainty in the results as suggested by very wide
10 95%CrI around mean effects and rankings across all interventions (Table 3). There was also
11 very high between-study heterogeneity.

12
13 Results between all pairs of treatments examined in the NMAs and also results from indirect
14 and, where available, direct (head-to-head) comparisons are reported in online
15 Supplementary Appendix 11. For information, results of the NICE guideline analyses are
16 shown in online Supplementary Appendix 12.

17

18 ***Pairwise sub-analyses***

19 Exploratory sub-analyses of the pairwise meta-analysis comparing trauma-focused CBT and
20 waitlist for PTSD symptom change scores between baseline and endpoint suggests no
21 significant subgroup differences for different specific TF-CBT interventions (including CPT,
22 cognitive therapy, prolonged exposure, narrative exposure therapy, brief eclectic
23 psychotherapy, and non-branded individual and group CBT). There were also no significant
24 subgroup differences between ITT, modified ITT and completer analysis, or for single
25 compared to multiple incident index trauma. See online Supplementary Appendix 13 for
26 forest plots of these sub-analyses.

27

1 **DISCUSSION**

2 **Overview of findings**

3 This study aimed to identify the relative treatment effects of various psychological treatments
4 for PTSD. EMDR, combined somatic/cognitive therapies, TF-CBT and self-help with support
5 appeared to have the greatest effects in reducing PTSD symptoms post-treatment, followed
6 by non-TF-CBT, combined TF-CBT/SSRIs, SSRIs, self-help without support and counselling.
7 No evidence of difference in effect post-treatment was identified between interventions, with
8 the exception of EMDR and TF-CBT, both of which were found to be superior to counselling.
9 Analysis of follow-up data suggested that EMDR and TF-CBT sustained this effect at 1-4
10 months. EMDR, TF-CBT, self-help with support, and counselling were also effective in
11 achieving remission from PTSD at treatment endpoint. Results for other interventions were
12 either inconclusive or based on limited evidence.

13
14 Commonalities across effective psychotherapies for PTSD include psychoeducation,
15 imaginal exposure, and cognitive processing, restructuring and/or meaning making
16 (Schnyder *et al.*, 2015). Moreover, all treatments found to be effective comprised structured
17 therapies, delivered by healthcare professionals who have completed specialist training and
18 who have access to regular supervision and undertake appropriate continuing professional
19 development (CPD) accreditation. Combined somatic/cognitive therapies are exposure-
20 based therapies with cognitive and somatic components, thus they share some
21 characteristics with the TF-CBT class. All except one of the RCTs on self-help with support
22 included in the NMA focused on computerised TF-CBT, consistent with TF-CBT delivered by
23 a therapist. On the other hand, of the 13 trials on self-help without support, only 4 focused on
24 computerised TF-CBT. Further to the presence or absence of the TF-CBT element in self-
25 help interventions for PTSD, which may have been the driver of their effectiveness, there is
26 evidence that facilitated self-help is more effective than self-help without support in the
27 treatment of anxiety disorders and depression (National Institute for Health and Care
28 Excellence, 2011).

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Counselling was found to be amongst the least effective interventions. This can be attributed to counselling’s non-directive person-centred approach, which is less likely to help the person overcome avoidance (which is one of the criteria for PTSD), and thus less likely to reduce PTSD symptoms. However, in 10 out of the 11 RCTs examining counselling across the 3 NMAs, counselling served as a control treatment to other active interventions, primarily TF-CBT, and therefore it is possible that counselling’s effectiveness has been underestimated to some extent, due to researcher allegiance.

Comparison with findings of other reviews

The results of our analysis are consistent with those of other published reviews, according to which TF-CBT interventions and EMDR have the strongest evidence of effectiveness post-treatment and at short follow-up, both showing highest effects versus inactive controls compared with other psychological interventions (Bisson *et al.*, 2013; Cusack *et al.*, 2016; Forman-Hoffman *et al.*, 2018). This finding is also in line with five recently published PTSD clinical practice guidelines (as compared in Hamblen *et al.*, 2019). Four of these five guidelines, including the NICE clinical guideline (International Society for Traumatic Stress Studies, 2019; National Institute for Health and Care Excellence, 2018a; Phoenix Australia Centre for Posttraumatic Mental Health, 2013; Departments of Veterans Affairs and Defense, 2017), make recommendations of equal strength for TF-CBT and EMDR for adults, whereas in one guideline (American Psychological Association, 2017) TF-CBT interventions are favoured with a strong recommendation while EMDR has been given a moderate rating. Conversely, Khan *et al.* (2018) suggests that EMDR may be more effective than TF-CBT, however this finding was not supported by another publication that employed NMA techniques (Gerger *et al.*, 2014). The latter review is in agreement with our findings, which show no evidence of difference between EMDR and TF-CBT. Further research is needed to establish any reliable difference between the efficacy of TF-CBT and EMDR.

1 There is some published evidence suggesting that non-TF-CBT (Bisson *et al.*, 2013),
2 present-centered therapy (Frost *et al.*, 2014) and self-help (mainly internet-based TF-CBT
3 and expressive writing therapy) (Kuester *et al.*, 2016; Sijbrandij *et al.*, 2016; van Emmerik *et*
4 *al.*, 2013) are also effective options in the treatment of PTSD in adults. There are also
5 recommendations for other psychotherapies in recently published clinical PTSD guidelines,
6 although there was less consistency than for TF-CBT and EMDR (Hamblen *et al.*, 2019). For
7 instance, three of the guidelines included recommendations for non-trauma focused
8 psychotherapies (International Society for Traumatic Stress Studies, 2019; Phoenix Australia
9 Centre for Posttraumatic Mental Health, 2013; Departments of Veterans Affairs and
10 Defense, 2017). This evidence, from both published reviews and clinical guidelines, is in line
11 with our findings that suggest that non-TF-CBT, present-centered therapy and self-help (with
12 or without support) are effective relative to waitlist for improving PTSD symptoms.

13

14 Our findings on the effectiveness of combined somatic/cognitive therapies are consistent
15 with results reported in the systematic review by Forman-Hoffman *et al.* (2014), who carried
16 out separate evaluations of the emotional freedom technique and thought field therapy
17 (defined in the review as ‘imagery rehearsal therapy’) and found very limited evidence on
18 both interventions which, nevertheless, indicated that these might be effective in the
19 treatment of PTSD symptoms.

20

21 Another published NMA of treatments for adults with PTSD suggested that several
22 interventions are effective in the management of PTSD (Gerger *et al.*, 2014). That study
23 considered a more limited number of interventions than our analysis, including three types of
24 TF-CBT (CBT, CT, exposure therapy) that were assessed separately but also as a TF-CBT
25 class, EMDR, stress management (relaxation or biofeedback), supportive therapies
26 (comprising psychotherapy placebos and counselling), and other psychological therapies
27 (including psychodynamic, client-centered, gestalt and other forms). The authors reported
28 that all assessed interventions were more effective than waitlist; TF-CBT interventions and

1 EMDR were more effective than stress management and supportive therapies, but no
2 difference was observed between TF-CBT and EMDR. The robustness of evidence varied
3 considerably between different interventions and between-trial heterogeneity was high.
4 These findings are in line with our results. The study considered only PTSD symptom
5 severity at end of treatment or at maximum of 1 month post-treatment, whereas our NMAs
6 considered PTSD change scores at treatment endpoint and at 1-4-month follow-up and also
7 remission at end of treatment. Therefore, our conclusions cover a wider range of
8 interventions and outcomes and longer-term effects, where available.

9

10 Our findings are also broadly consistent with the results of a NMA of psychological
11 interventions in children and young people with PTSD, which suggested that TF-CBT, in
12 particular individual forms, was most effective in the management of PTSD in youth,
13 whereas EMDR was effective but to a lesser extent; counselling did not appear to be
14 effective compared with waitlist. Results in young populations also suggested a large
15 positive effect for emotional freedom technique (a form of combined somatic/cognitive
16 therapy), but this finding was based on very limited evidence (Mavranouzouli *et al.*, 2020).

17

18 Overall, our results and conclusions are in agreement with previously published meta-
19 analyses in this area. Small differences between our study results and those of other studies
20 (which, nevertheless, led to very similar conclusions) have potentially arisen from differences
21 in inclusion criteria relating to the population (e.g. we included only adult populations while
22 some other studies did not apply any age restrictions or considered only children and young
23 people with PTSD; we did not restrict to people with a formal diagnosis of PTSD while some
24 other studies did), interventions (we used a wider range of interventions compared with other
25 reviews and it is also possible that our categorisation into classes is different from that used
26 in other studies), comparators (we excluded studies that used TAU as a comparator or as a
27 component of an active arm), outcomes (we included continuous PTSD symptom change
28 scores at endpoint and 1-4 month follow-up as well as dichotomous remission, whereas

1 some of the other studies included only continuous data and/or only treatment endpoint
2 data) and study characteristics (we included studies with a sample size of at least 10 per
3 arm, a criterion not applied in most, if not all, the other reviews), as well as differences in the
4 method of analysis (we used NMA techniques whereas the vast majority of the other reviews
5 in the area relied on pairwise meta-analysis of head-to-head comparisons).

6

7 **Strengths and limitations of the analysis**

8 To our knowledge, this is the first NMA of psychological treatments for adults with PTSD that
9 was designed to inform a clinical guideline. The results of our NMAs further informed an
10 economic analysis that assessed the cost-effectiveness of psychological interventions for
11 adults with PTSD (Mavranouzouli *et al.*, *under review*). NMA techniques enabled evidence
12 synthesis from both direct and indirect comparisons between interventions, and allowed
13 simultaneous inference on all treatments examined in pairwise trial comparisons while
14 respecting randomisation (Caldwell *et al.*, 2005; Lu and Ades, 2004). Inconsistency checks
15 found no evidence of inconsistency between direct and indirect estimates in the NMAs of
16 changes in PTSD symptoms post-treatment and at follow-up. This finding provides
17 reassurance that the included studies were comparable across interventions, although it is
18 acknowledged that, in agreement with the findings of other reviews, between-trial
19 heterogeneity was high. On the other hand, we detected evidence of inconsistency in the
20 NMA of remission post-treatment. However, we found that direct effects in this NMA were
21 implausibly large and with very wide 95%CrI due to limitations in the direct evidence;
22 therefore indirect/NMA evidence may be more trustworthy for the remission outcome. This
23 means that results on this outcome (remission at treatment endpoint) should be treated with
24 caution.

25

26 Between-trial heterogeneity was high across all analyses. This finding, which is consistent
27 with previous reviews (Bisson *et al.*, 2013; Forman-Hoffman *et al.*, 2018; Gerger *et al.*,
28 2014), is likely to have been caused by heterogeneity across populations included in the

1 trials considered in our analysis, for example, in terms of the presence of a formal PTSD
2 diagnosis, the baseline severity and complexity of PTSD symptoms, the type, extent and
3 multiplicity of trauma exposure, the chronicity of symptoms and the presence of comorbidity.
4 Moreover, the vast majority of the included studies did not distinguish between PTSD and
5 complex PTSD, which ICD-11 (unlike DSM-5) now conceptualises as distinct diagnoses.
6 This distinction is supported by evidence (Brewin *et al.*, 2017) but some disagreement about
7 the validity of the construct amongst experts remains, as suggested by the discrepancy
8 between the two classification systems (ICD-11 and DSM-5). We note that our review was
9 undertaken before ICD-11 (and the distinction between PTSD and complex PTSD) was
10 released (June 2018). Trials are likely to have varied widely in the proportion of participants
11 with complex PTSD; this may have had an impact on the effectiveness of assessed
12 interventions in each study and the heterogeneity across studies. Another factor potentially
13 contributing to the high between-trial heterogeneity of our NMAs is the variability of
14 interventions within each treatment node of the analysis (including different levels of
15 intensity), and the difference across study settings, e.g. inpatient versus outpatient. This high
16 between-trial heterogeneity may have contributed to the uncertainty in the mean relative
17 effects, as reflected in the wide CrI for some comparisons in our analyses, and has limited
18 our ability to draw firm conclusions on the relative effectiveness between interventions.
19 However it is worth noting that, although exploratory in nature and limited to a single
20 pairwise comparison, our sub-group analyses suggest that between-study heterogeneity
21 cannot be accounted for solely by differences between specific TF-CBT interventions, based
22 on the method of analysis (ITT versus completer), or by the multiplicity of index trauma
23 (single versus multiple incident index trauma). This suggests that this heterogeneity is
24 complex and further studies employing meta-regression techniques, ideally with access to
25 individual patient data, are required to fully explore differences in effect estimates between
26 studies.

27

1 We decided to analyse all TF-CBT interventions together, as a class, because, although they
2 do not include exactly the same content or follow the same manual, they use the same
3 broad approach; in grouping the interventions into a TF-CBT class we took the view that it is
4 the core components of the treatments (e.g. exposure and cognitive restructuring) that make
5 them effective. We also took into account that 'breaking' the solid evidence base for the TF-
6 CBT class into smaller, separate pieces of evidence for specific interventions would
7 unavoidably thin the evidence base and incur the risk of reducing the robustness of our
8 conclusions on the effectiveness of interventions within the TF-CBT class relative to other
9 types of treatment. Some reviews (for example Bisson *et al.*, 2013; Khan *et al.*, 2018) have
10 followed our approach and have evaluated the overall effects of the TF-CBT class, rather
11 than looking at the effects of specific interventions within the TF-CBT class separately. The
12 Departments of Veterans Affairs and Defense (2017) guideline also grouped TF-CBT
13 interventions together but chose to list the specific treatments for which there was the
14 strongest support, which is a similar approach to the one taken by the NICE clinical guideline
15 (Hamblen *et al.* 2019). There is now an emerging number of reviews that have attempted to
16 evaluate the effects of distinct interventions within the TF-CBT class (e.g. American
17 Psychological Association, 2017; Cusack *et al.*, 2016; Forman-Hoffman *et al.* 2018), with
18 another review assessing the overall effect of the TF-CBT class, and also effects of
19 individual forms within TF-CBT class where evidence was adequate to allow sub-group
20 analysis (International Society for Traumatic Stress Studies, 2019). These reviews have
21 carried out separate evaluations of various TF-CBT interventions such as CPT, CT,
22 prolonged exposure and mixed TF-CBT which has elements of different types of CBT. The
23 majority of these studies have found evidence on the effectiveness of all interventions within
24 the TF-CBT class but none of the studies reported any evidence on differential effects
25 between different types of TF-CBT. A previously published NMA in the area (Gerger *et al.*,
26 2014), which evaluated CBT, exposure and CT separately and made indirect comparisons
27 between them, identified no differences in relative effects. The authors then merged CBT
28 and CT into one category of CBT with a focus on cognitions and reanalysed the data; no

1 difference was found between CBT with focus on cognitions and exposure. These results
2 suggest that there may be no difference in the effectiveness of different interventions within
3 the TF-CBT class, and supports our decision to consider TF-CBT interventions together, as
4 one class, in our analysis. It is worth noting here that our exploratory post-hoc sub-analysis
5 by specific TF-CBT intervention for all studies including a waitlist control (see Appendix 13A)
6 also suggests no significant sub-group difference between specific TF-CBT intervention
7 types.

8

9 In our analyses we prioritised self-reported over clinician-rated scale data, where possible,
10 as self-reported outcomes were deemed to better capture symptoms experienced by adults
11 with PTSD, based on the NICE guideline committee's expert opinion. This approach is in line
12 with a previously published NMA in the same area (Gerger *et al.*, 2014), although other
13 reviews have conducted separate analyses for clinician-rated and self-reported outcome
14 data (Bisson *et al.*, 2013; Forman-Hoffman *et al.*, 2018), or even prioritised clinician-rated
15 outcomes over self-reported ones, where both were available, in the primary analysis
16 (International Society for Traumatic Stress Studies, 2019). It is acknowledged that in other
17 mental health areas, such as depression, it is recommended that both clinician-rated and
18 self-reported outcomes be assessed as they have been shown to capture different aspects
19 of treatment outcome (Cuijpers *et al.*, 2010; Uher *et al.*, 2012). A sub-group analysis
20 conducted by Gerger *et al.* (2014) showed that the differences between effect sizes in trials
21 reporting self-reported outcomes versus those reporting clinician-rated ones were small and
22 non-significant ($p=0.58$) and within-trial heterogeneity was not affected by inclusion of only
23 one type of outcome in the analysis. Therefore, we are confident that our choice of
24 prioritising self-reported over clinician-rated outcomes has not had a negative impact on
25 results.

26

27 In our NMA we did not include TAU, either alone or combined with a control or with an
28 intervention of interest; this is because the definition of TAU varied considerably across

1 trials, so that inclusion of TAU in the networks was expected to considerably increase
2 heterogeneity and reduce robustness of the results. Omission of studies that assessed
3 interventions alone or combined with TAU versus TAU has limited the evidence base of our
4 analyses. However, the number of included studies (which did not include TAU) was higher
5 than the number of excluded studies that included TAU; included 'non-TAU' studies also
6 considered a higher number of participants than the excluded 'TAU' studies. Therefore, our
7 analyses have considered a significant amount of evidence without introducing
8 heterogeneity attributable to the diversity of TAU.

9

10 The studies included in the NMAs were subject to risk of bias, in particular selection and
11 reporting bias. In none of the studies were participants blinded, which was unavoidable due
12 to the nature of the interventions. In most trials assessors were not blinded either. As
13 described earlier, self-rated PTSD symptom scores were preferred to clinician-rated ones if
14 both were reported in a study, as they were deemed to better capture symptoms
15 experienced by people with PTSD. However, self-rated assessment cannot be blinded in
16 trials of psychological interventions; on the other hand, raters were less likely to have a
17 conflict of interest in terms of detection bias. The quality and limitations of RCTs included in
18 the analyses need to be considered when interpreting the results.

19

20 For the change in PTSD symptom score outcome we prioritised ITT over completer data
21 where possible, nevertheless, for approximately 40% of the studies we used completer data
22 as only these were available. An exploratory sub-group analysis of the TF-CBT versus
23 waitlist comparison for PTSD symptom change scores between baseline and treatment
24 endpoint suggests no statistically significant subgroup difference between the results of
25 studies using ITT, modified ITT and completer analysis (see Appendix 13B). This is also
26 consistent with a sub-group analysis conducted in the context of a NMA of treatments for
27 PTSD by Gerger *et al.* (2014) that showed that the differences between effect sizes in trials
28 reporting ITT data versus those reporting completer data were small and non-significant

1 (p=0.47), although within-trial heterogeneity was somewhat reduced by inclusion of ITT data
2 only (from $\tau^2=0.30$ when both ITT and completer data were included in the analysis it fell at
3 $\tau^2=0.21$ when only ITT data were analysed). Our ITT approach for the dichotomous
4 remission analysis meant that all participants were analysed in the group to which they had
5 been randomised and that study non-completers were assumed to have failed to remit. This
6 strategy provides a conservative estimate of treatment effects compared with completer
7 analysis (Nüesch *et al.*, 2009), assuming that active interventions have a higher risk of drop-
8 out compared with control conditions (this higher risk could be attributable to side effects,
9 unacceptability of the active intervention, or to people discontinuing treatment early if their
10 symptoms improve).

11

12 Evidence on the longer-term effectiveness of treatments for PTSD is limited, as follow-up
13 data are sparse. Adequate evidence on remission rates at 1-4-month follow-up was only
14 available for TF-CBT; for this reason we were not able to conduct any meaningful NMA of
15 remission follow-up data. Available evidence suggests that TF-CBT and EMDR are effective
16 in sustaining improvements in PTSD symptoms at 1-4-month follow-up. Evidence for other
17 interventions was limited or inconclusive.

18

19 **Implications for practice and need for further research**

20 Results support current clinical practice within which TF-CBT and EMDR are the mainstream
21 options offered to adults with PTSD. Our findings suggest that other treatments, such as
22 supported self-help, combined somatic/cognitive therapies and non-TF-CBT are also
23 effective and could be potential alternative treatment options, although amongst them only
24 supported self-help has some limited evidence for sustained effects beyond treatment. This
25 might have implications for clinical practice as services currently focus on provision of TF-
26 CBT and EMDR. In contrast, although effective versus waitlist, counselling appears to be
27 less effective than other treatment options and therefore should not be routinely offered if
28 more effective options are available. In our review, we were not able to focus on complex

1 PTSD, which is currently less likely to be identified and managed effectively in routine
2 practice. Further research is therefore needed to identify appropriate interventions specific to
3 populations with complex PTSD.

4

5 Based on the results of the NMAs and the primary economic analysis (Mavranezouli *et al.*,
6 **under review**; National Institute for Health and Care Excellence, 2018b), the NICE guideline
7 on PTSD recommended EMDR and individual TF-CBT for the treatment of adults with PTSD
8 presenting more than three months after trauma (National Institute for Health and Care
9 Excellence, 2018a). Both interventions were effective in reducing PTSD symptoms post-
10 treatment and demonstrated sufficient evidence to suggest sustainment of effect beyond
11 treatment. The recommendation for EMDR was restricted to people with non-combat-related
12 trauma, as evidence from sub-group pairwise meta-analysis suggested a non-significant
13 effect on people with combat-related trauma, a finding that was confirmed by a recent
14 systematic review and meta-analysis (Kitchiner *et al.*, 2019).

15

16 In addition, based on the available evidence and after taking account of the narrower
17 evidence base, a weaker ('consider') recommendation was made for self-help with support
18 and SSRIs for people who expressed a preference for these interventions, and, in the case
19 of self-help, did not have severe PTSD symptoms and were not at risk of harm to
20 themselves or others. A 'consider' recommendation was also made for non-TF-CBT targeted
21 at specific symptoms, for people who are unable or unwilling to engage in a trauma-focused
22 intervention or have residual symptoms after treatment. Finally, the guideline committee
23 noted the positive evidence for combined somatic/cognitive therapies, but also considered
24 their particularly limited evidence base beyond treatment endpoint and the lack of specific
25 indications for these interventions, and decided not to recommend them but instead to make
26 a recommendation for further research.

27

1 TF-CBT was the treatment with the largest evidence base on PTSD symptom severity and
2 remission, both at the end of treatment and at 1-4-month follow-up. Further research is
3 needed to establish the results for EMDR more firmly, in particular in relation to TF-CBT, as
4 conclusions on its effectiveness are based on a more limited evidence base compared with
5 TF-CBT and its relative effects versus TF-CBT were characterised by uncertainty. Similarly,
6 research should further explore the effectiveness of other interventions, especially combined
7 somatic/cognitive therapies, which demonstrated high effects at treatment endpoint, but also
8 non-TF-CBT and self-help with support regarding remission and effectiveness beyond end of
9 treatment, as relevant evidence is limited or lacking. Future research should also establish
10 the effects of different types of TF-CBT relative to other types of treatment, but also relative
11 to other types of TF-CBT, as evidence on comparative effectiveness is limited for some
12 types of TF-CBT. In particular, evidence on sustainability of effects beyond treatment
13 endpoint is sparse and only available for a few treatments; this lack of evidence is most
14 evident for remission rates beyond treatment endpoint. This gap in evidence needs to be
15 addressed by future trials, which should ideally include at least 12 months of follow-up, to
16 explore the longer-term effectiveness of psychological therapies for PTSD.

17

18 **CONCLUSION**

19 EMDR and TF-CBT appear to be most effective in reducing symptoms and improving
20 remission rates in adults with PTSD. They also appear to be effective in sustaining the
21 reduction of PTSD symptoms beyond treatment endpoint. Other interventions, such as
22 combined somatic/cognitive therapies, self-help, non-TF-CBT, SSRIs and counselling
23 appear to be effective in reducing PTSD symptoms post-treatment; self-help with support
24 and counselling appear to improve remission rates post-treatment, too. Counselling is likely
25 to be less effective than EMDR and TF-CBT. Further research is needed to establish these
26 findings for EMDR, as its evidence base is more limited compared with TF-CBT, and to
27 better assess the relative effectiveness of interventions such as different types of TF-CBT,
28 combined somatic/cognitive therapies, self-help with support and non-TF-CBT, in particular

1 regarding remission rates and effectiveness beyond end of treatment. Overall, there is a
2 need for well-conducted RCTs to explore the long-term comparative effectiveness of
3 psychological therapies for adults with PTSD.

4

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9 Cornelius Katona, Jonathan Leach, Richard Meiser-Stedman, Rebecca Regler, Vikki Touzel,
10 and David Trickey.

11

12 **CONFLICTS OF INTEREST:**

13 SD and NW were co-applicants on a grant (unrelated to this work) from the MRC
14 Methodology Research Programme which included an MRC Industry Collaboration
15 Agreement with Pfizer Ltd, who part-funded a researcher to work on statistical methodology.
16 GB is a co-investigator on a NIHR RfPB grant, Eye Movement Desensitization and
17 Reprocessing Therapy in Early Psychosis (EYES): A feasibility randomised controlled trial.
18 NGreenberg is the Royal College of Psychiatrists Lead for Military and Veterans' Health and
19 is a trustee of two military charities. He is also a senior researcher with King's College
20 London working on a number of military mental health studies. NGrey is a member of the
21 Wellcome Trust Anxiety Disorders Group developing, testing and disseminating Cognitive
22 Therapy for PTSD (CT-PTSD), a trauma-focused cognitive behavioural therapy (TF-CBT).
23 He has published papers and book chapters on CT-PTSD, and facilitates teaching
24 workshops for which payment is received. As editor, he receives royalties from sales of a
25 trauma book, A Casebook of Cognitive Therapy for Traumatic Stress Reactions. CK is
26 Medical Director of the Helen Bamber Foundation (a human rights charity) and refugee and
27 asylum mental health lead for the Royal College of Psychiatrists. He writes expert psychiatric
28 reports in the context of asylum mental health. JL is NHS England Medical Director for

1 Military and Veterans Health. SP receives funding from NICE for the development of clinical
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3

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Table 1. Network meta-analysis of psychological treatments for PTSD in adults, changes in PTSD symptom scores between baseline and treatment endpoint: interventions, magnitude of evidence base and results

Changes in PTSD symptom scores between baseline and treatment endpoint				
N total = 4700; k total = 71; 151 study arms				
Intervention	N	k	Mean SMD (95%CrI) vs waitlist	Mean rank (95%CrI)
Metacognitive therapy	10	1	-3.04 (-5.09 to -0.98)	
Couple intervention	22	1	-2.67 (-5.41 to 0.06)	
EMDR	260	11	-2.07 (-2.70 to -1.44)	1.78 (1 to 5)
Combined somatic/cognitive therapies	237	4	-1.69 (-2.66 to -0.73)	3.64 (1 to 9)
Resilience-oriented treatment	20	1	-1.63 (-3.59 to 0.32)	
TF-CBT	903	29	-1.46 (-1.87 to -1.05)	4.51 (2 to 8)
Self-help with support	198	5	-1.46 (-2.33 to -0.59)	4.72 (1 to 10)
Present-centered therapy	99	3	-1.42 (-2.45 to -0.40)	
non-TF-CBT	209	7	-1.22 (-1.95 to -0.49)	6.07 (2 to 10)
TF-CBT + SSRI	115	3	-1.21 (-2.35 to -0.07)	6.14 (1 to 11)
Psychoeducation	152	2	-1.21 (-3.13 to 0.71)	6.19 (1 to 12)
IPT	55	2	-1.19 (-2.54 to 0.15)	
SSRI	166	5	-1.14 (-2.09 to -0.19)	6.55 (2 to 11)
Self-help without support	335	11	-0.91 (-1.67 to -0.15)	7.77 (3 to 11)
Relaxation	25	2	-0.73 (-2.15 to 0.70)	
Counselling	278	9	-0.73 (-1.41 to -0.05)	
Attention placebo	221	9	-0.39 (-1.42 to 0.63)	10.12 (5 to 12)
Waitlist	1312	43	Reference	11.61 (10 to 12)
Attention bias modification	83	3	2.14 (0.63 to 3.65)	

CrI: credible intervals; EMDR: eye movement desensitisation reprocessing; IPT: interpersonal psychotherapy; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor; TF-CBT: trauma-focused cognitive behavioural therapy
k: number of randomised controlled trials (RCTs) that assessed each intervention; N: number randomised to each treatment across RCTs

Negative values indicate a better effect for the intervention compared with the reference treatment (waitlist).

Only interventions tested on at least 100 people were considered in ranking

In bold effects where the 95%CrI do not cross the line of no effect (SMD=0)

Table 2. Network meta-analysis of psychological treatments for PTSD in adults, changes in PTSD symptom scores between baseline and 1-4-month follow-up: interventions, magnitude of evidence base and results

Changes in PTSD symptom scores between baseline and 1-4-month follow-up				
N total = 2,315; k total = 28; 57 study arms				
Intervention	N	K	Mean SMD (95%CrI) vs waitlist	Mean rank (95%CrI)
Couple intervention	21	1	-2.04 (-3.72 to -0.36)	
Self-help with support	85	3	-1.27 (-2.12 to -0.42)	
Self-help without support	40	2	-1.19 (-2.52 to 0.13)	
Behavioural therapy	47	2	-1.19 (-2.16 to -0.21)	
Combined somatic/cognitive therapies	23	1	-1.17 (-2.75 to 0.43)	
EMDR	121	4	-1.12 (-1.94 to -0.27)	1.50 (1 to 4)
TF-CBT	753	13	-0.73 (-1.23 to -0.25)	2.47 (1 to 4)
Psychoeducation	183	3	-0.51 (-1.47 to 0.44)	3.46 (1 to 6)
non-TF-CBT	123	4	-0.43 (-1.35 to 0.53)	3.80 (1 to 6)
IPT	32	1	-0.39 (-1.76 to 0.97)	
Counselling	205	4	-0.30 (-1.12 to 0.53)	4.31 (2 to 6)
Present-centered therapy	70	2	-0.15 (-1.29 to 1.01)	
Attention placebo	44	2	-0.02 (-1.35 to 1.33)	
Waitlist	496	14	Reference	5.46 (4 to 6)
Family therapy	72	1	0.15 (-1.13 to 1.43)	

CrI: credible intervals; EMDR: eye movement desensitisation reprocessing; IPT: interpersonal psychotherapy; SMD: standardised mean difference; TF-CBT: trauma-focused cognitive behavioural therapy

k: number of randomised controlled trials (RCTs) that assessed each intervention; N: number randomised to each treatment across RCTs

Negative values indicate a better effect for the intervention compared with the reference treatment (waitlist).

Only interventions tested on at least 100 people were considered in ranking.

In bold effects where the 95%CrI do not cross the line of no effect (SMD=0)

Table 3. Network meta-analysis of psychological treatments for PTSD in adults, remission at treatment endpoint: interventions, magnitude of evidence base and results

Remission at treatment endpoint				
N total = 2,249; k total = 34; 76 study arms				
Intervention	N	k	Mean LOR (95%CrI) vs waitlist	Mean rank (95%CrI)
Psychodynamic therapy	49	1	4.61 (1.87 to 7.57)	
EMDR	132	5	3.38 (2.04 to 4.84)	1.17 (1 to 3)
non-TF-CBT	65	2	3.30 (1.48 to 5.29)	
Relaxation	57	2	2.65 (0.77 to 4.59)	
IPT	72	2	2.53 (0.71 to 4.40)	
Present-centered therapy	75	2	2.50 (0.75 to 4.36)	
TF-CBT	601	21	2.46 (1.79 to 3.19)	2.15 (1 to 3)
Couple intervention	49	2	2.14 (-0.51 to 4.83)	
Self-help with support	105	2	1.76 (0.03 to 3.49)	3.07 (1 to 4)
TF-CBT + SSRI	57	1	1.65 (-0.61 to 4.00)	
Self-help without support	74	3	1.52 (-0.16 to 3.32)	
SSRI	87	2	1.42 (-0.45 to 3.42)	
Counselling	150	6	1.34 (0.20 to 2.51)	3.66 (3 to 4)
Attention placebo	23	1	1.09 (-1.97 to 4.24)	
Psychoeducation	28	1	-0.75 (-4.66 to 3.07)	
Waitlist	625	23	Reference	4.97 (4 to 5)

CrI: credible intervals; EMDR: eye movement desensitisation reprocessing; IPT: interpersonal psychotherapy; LOR: log-odds ratio; SSRI: selective serotonin reuptake inhibitor; TF-CBT: trauma-focused cognitive behavioural therapy
k: number of randomised controlled trials (RCTs) that assessed each intervention; N: number randomised to each treatment across RCTs
Positive values indicate a better effect for the intervention compared with the reference treatment (waitlist).
Only interventions tested on at least 100 people were considered in ranking.
In bold effects where the 95%CrI do not cross the line of no effect (LOR=0)





