Abstract

Currently there is a lack of evidence on whether women and men respond differently to trauma-focused ~~evidence-based~~ psychological treatments for PTSD. This study was a systematic review and meta-analysis to examine whether gender is associated with response to trauma-focused psychological interventions for PTSD~~gender modifies the effect of trauma-focused psychological interventions for PTSD~~. Randomized controlled trials comparing trauma-focused interventions for PTSD with comparison conditions were identified in a literature review. Fifty-six randomized controlled trials were included in the meta-analysis: 31 had a mixed gender sample, 19 were female only and six were male only. There was evidence that gender modified the effect of trauma-focused interventions, with larger effects for females compared with any condition based on the primary outcome of clinician-rated PTSD symptoms at post-intervention and short-term follow-up. This finding was supported by direct effects meta-analyses of studies that provided data on both females and males. There was also a larger effect for females in an analysis restricted to trials that evaluated an intervention likely to be provided in routine clinical practice. These findings support a gender difference in outcomes following trauma-focused psychological interventions for PTSD. Future research should seek to identify specific factors related to gender that facilitate or inhibit response to these interventions.

Key words: gender, systematic review, meta-analysis, posttraumatic stress disorder, treatment, trauma-focused, outcomes

According to DSM-5 (American Psychiatric Association, 2013), Posttraumatic Stress Disorder (PTSD) is a mental disorder characterized by severe and persistent stress reactions -following exposure to a potentially traumatic event (PTE), including re-experiencing of the event, avoidance of memories and reminders of the event, negative cognitions and mood, and increased arousal symptoms. Gender differences in both exposure to PTEs and the development of PTSD following exposure have been well-documented. Women are more likely to report partner abuse, sexual assault, rape and childhood sexual abuse, whereas men are more likely to experience non-sexual physical assault, combat, accidental injury and witnessing someone being badly injured or killed (Mills et al., 2011; Tolin & Foa, 2006). Epidemiological studies from several countries have shown ~~indicated~~ that, while women are less likely than men to be exposed to traumatic events, the- prevalence of PTSD within the community is significantly higher among women (Breslau et al., 1998; Chapman et al., 2012; de Vries & Olff, 2009; R. Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; R. C. Kessler, Sonnega, Hughes, & Nelson, 1995; Norris et al., 2003; Pietrzak, Goldstein, Southwick, & Grant, 2011; Stein, Walker, Hazen, & Forde, 1997). For example, Chapman and colleagues (2012) found that Australian women had a higher lifetime (9.7% versus 4.7%) and 12-month (5.9% versus 2.8%) rate of PTSD compared with men. PTEs involving interpersonal violence (that are more likely to be experienced by women) are associated with a high probability of PTSD (R. Kessler et al., 1995), although t~~T~~he higher prevalence of PTSD in women may not simply be the result of increased exposure to certain types of trauma (Tolin & Foa, 2006). Other factors to consider include gender differences in severity of trauma, type and severity of symptoms, comorbid mental and physical disorders, appraisal and processing of trauma, emotional expression, social support, and physiological reactivity (Cason, Grubaugh, & Resick, 2002; Christiansen & Elklit, 2013; Chung & Breslau, 2008; R. Kessler et al., 1995).

Comment [DJW1]: Reference repeated for some reason

Currently, there is a lack of evidence to determine whether there is a gender difference in response to psychological and other interventions for PTSD. If firm evidence is found, then this would necessitate efforts to identify gender-related factors that influence this differential

response in order to develop optimal treatment for both women and men with PTSD. Previous systematic reviews and meta-analyses have found that the effects of different types of psychotherapies were larger in studies with a higher proportion of women (Watts et al., 2013), and that the effects of trauma-focused cognitive-behavioural therapies were larger in women-only studies (all sexual assault or assault survivors) compared with all studies (Bisson et al., 2007). However, both studies used 'indirect' analyses (based on female only, male only and mixed gender studies) to assess for a gender difference in outcomes, that is, regression analysis or sub-group analysis to assess whether gender predicted ~~or modified~~ the effect size. In contrast, direct effects analyses include only studies that have data from both women and men and calculate the difference between the treatment response for each in each study, then pools these differences across studies. This has the benefit of limiting clinical and methodological heterogeneity and potential confounders in included studies.

Comment [DJW2]: Need this reference

Comment [DJW3]: Change this to Cochrane 2013 reference

The aim of the current systematic review and meta-analysis was to undertake indirect and direct effects analyses to examine whether gender is associated with response to ~~gender modifies the effect of evidence-based~~ trauma-focused psychological interventions for PTSD~~, that is, interventions that involve confronting trauma-related memories and situations and addressing unhelpful beliefs about the traumatic experience (Australian Centre for Posttraumatic Mental Health, 2013)~~.

Method

The Cochrane Collaboration systematic review methodology (Higgins & Green, 2011) was used as a guide for this study.

Search Strategy

Relevant randomized controlled trials (RCTs) that were published up until July 11, 2012, were identified via MEDLINE, PsychINFO, Embase and Cochrane Central Register of Controlled Studies (CENTRAL). The keywords or equivalent terms used to search the databases were: 'posttraumatic stress disorder', 'post-traumatic stress disorder', 'stress disorder' and 'traumatic stress'. In addition, hand-searches were undertaken of the abstracts of the International Society for Traumatic Stress Studies (ISTSS) conferences for the years

2008 – 2012, as well as the reference list of the revised Australian PTSD guidelines (Australian Centre for Posttraumatic Mental Health, 2013).

Study selection

Any published or unpublished English language RCT that tested the efficacy of a trauma-focused psychological intervention for PTSD was considered for inclusion. A trauma-focused intervention was defined as one that encourages the person to confront their traumatic memory or situations avoided since the traumatic event, or that challenged the person's unhelpful thoughts or beliefs about their traumatic experience (Australian Centre for Posttraumatic Mental Health, 2013). There were no restrictions in terms of the mode of delivering the intervention, such that individual, group, face-to-face, self-help, internet and virtual reality interventions were all eligible for inclusion. Both single (i.e. female only or male only) and mixed (i.e. both females and males) gender studies were eligible. Studies with multiple intervention arms (e.g., psychological and pharmacotherapy) were included if at least one intervention arm was a trauma-focused intervention. Studies that compared two trauma-focused interventions only (without any other comparison group) were excluded.

For participants, the following inclusion criteria applied: mean age at least 15 years old; at least 70% had a primary diagnosis of PTSD or subclinical PTSD as defined as having at least one symptom in each of recognized ~~three~~ PTSD symptom clusters (e.g. re-experiencing, avoidance and arousal), or any acceptable and equivalent definition adopted by the authors; the diagnosis was based on a structured diagnostic or clinical interview using DSM or ICD criteria, or a self-rated measure of PTSD using a cut-off score pre-defined by the authors; and the duration of PTSD symptoms was at least one month.

Comparison conditions were categorized as follows: wait list or no intervention, usual care, attention control, pharmacotherapy, and non-trauma-focused psychological interventions. Individual comparison conditions were combined into 'any comparison' which was the primary comparison condition. Wait list or no intervention included placement on a wait list for intervention or no intervention at all. Usual care included interventions or services that would normally be offered in the absence of the study. Attention control included non-

directive interventions such as non-specific supportive counselling that was judged to primarily provide an equivalent period of contact time as the trauma-focussed intervention. Non-trauma-focused interventions included skills-based interventions that did not explicitly encourage the individual to confront their traumatic memory or situations, or challenge the person's unhelpful thoughts or beliefs about their traumatic experience, such as non-trauma-focussed cognitive and/or behavioural therapy, problem solving therapy and relaxation training.

~~Non-trauma-focused interventions included skills-based interventions that did not explicitly encourage the individual to confront their traumatic memory or situations, or challenge the person's unhelpful thoughts or beliefs about their traumatic experience.~~

The primary outcome measure was severity of PTSD symptoms using a standardized clinician-rated measure. The secondary outcome measure was severity of PTSD symptoms using a standardized self-rated measure.

Where a full-text publication was not available for a study which passed the screening stage, authors were contacted directly to request a manuscript. Two reviewers (D.K. and T.V.) independently assessed all potentially relevant articles for inclusion. Any disagreements about inclusion or exclusion of studies were resolved by discussion with other authors (S.H. and D.W.).

Assessment of risk of bias

Studies were assessed for risk of bias with regard to random sequence generation, allocation concealment, and blinded assessment of outcomes, respectively (Higgins & Green, 2011). Studies were further rated with regard to missing data (≥15% missing data, and methods of imputation). Two reviewers (D.K. and D.W.) independently carried out the assessment of risk of bias, with any disagreement resolved by discussion.

Data extraction

Data were extracted from all included studies following the full-text assessment. One reviewer (D.K.) extracted the data and two others (T.V. and D.W.) checked the data, with any disagreement resolved by discussion.

Statistical analysis

Common assessment time-points for RCTs include post-treatment, and 3 months and 6 months following intervention. For this reason, we sought outcome data for the following time-points: post-intervention, short-term follow-up (i.e. one to five months following intervention), and long-term follow-up (i.e. six or more months following intervention).

~~Outcome data were sought for the following time-points: post-intervention, short-term follow-up (i.e. one to five months following intervention), and long-term follow-up (i.e. six or more months following intervention).~~ When a study provided two sets of outcome data for a single follow-up time-point, preference was given to the earlier ~~the data~~ collected data~~at the earlier time-point~~.

When necessary, study authors were contacted directly to request gender-specific outcome data including the number of participants and the means and standard deviations of PTSD outcome measures.

For studies that included two trauma-focused interventions, the data from each arm were combined. For studies with more than one comparison condition, data from only one condition was included as 'any comparison' selected according to the following prioritization: wait list or no intervention, usual care, attention control, pharmacotherapy, and non-trauma-focused psychological intervention.

The Review Manager statistical software program (Review Manager (RevMan), 2011) was used for all analyses. The outcome measures were continuous and were analyzed as standardized mean differences (SMDs) with 95% confidence intervals to allow for ease of comparison across studies that used different measures of the same outcomes. For all meta-analyses, intention to treat (ITT) data were combined with completer data and the random effects model was used.

Statistical heterogeneity was assessed based on Cochrane recommendations: I^2 values of 0-40% may not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% represents considerable heterogeneity (Higgins & Green, 2011).

Planned subgroup analyses were undertaken to investigate the impact of the comparison group on the treatment outcome. In order to examine whether gender modified intervention effects, subgroup analyses were undertaken on females versus males.

Direct effects meta-analyses were performed using studies that included and reported data on both females and males. This enabled us to investigate the impact of indirect effects from female only and male only studies on treatment outcome. The mean difference between the intervention effect of females and males and the standard error of this difference were calculated. The pooled mean difference was calculated using inverse variance weighting. DerSimonian and Laird's method of moments estimator was used to estimate between-study variance (Der Simonian & Laird, 1986). A second direct effects meta-analysis included only those mixed gender studies where participants experienced the same trauma type to avoid the potential confound of trauma type.

Sensitivity analyses were undertaken based on the primary comparison and outcome at the post-intervention time-point. Firstly, we investigated the impact of restricting the analysis to only those trials that tested an intervention most likely to be provided in routine practice, that is, the intervention was not exclusively group-based, self-help or delivered online, and the prescribed number of sessions was between 5 and 20. Secondly, we investigated the impact of excluding trials judged to be at high risk of bias due to the following not clearly stated to have been undertaken: random sequence generation, allocation concealment, and blinded assessment of outcomes. Additional analyses also examined the impact of excluding those trials with more than 15% of data unavailable for analysis, and those with only completer data available.

Results

Description of studies

We were unable to obtain data for 30 (34.9%) of the 86 primary studies that met the inclusion criteria (see flowchart of the search for studies in Figure 1). As a result, 56 studies provided data for inclusion in the meta-analysis: 31 mixed gender, 19 female only, and six male only. Usable data were obtained for females only in two mixed gender studies (Asukai

et al., 2010; Başoğlu et al., 2005), and males only in five mixed gender studies (Difede et al., 2007; Forbes et al., 2012; Litz et al., 2007; McLay et al., 2011; Nacasch et al., 2011). Details of studies included in the meta-analysis are shown in Table 1 in the online supplement.

The majority of trauma-focused interventions evaluated in these studies were cognitive and/or behavioral interventions. There were nine studies that evaluated two trauma-focused interventions (in addition to a comparison condition) for which the data were combined. The duration of interventions lasted between one day and 30 weeks.

Twenty-three studies included a wait list or no intervention comparison condition, nine included usual care, four included attention control, one included pharmacotherapy, and eight studies included a non-trauma-focused intervention.

Study participants experienced a wide range of trauma types, often within a single sample of participants.~~Study participants experienced a wide range of trauma types, often within a single study.~~ Of note, participants experienced military-related combat or other trauma in nine studies, rape or sexual assault in nine studies, and child sexual or physical abuse in seven studies. Four studies did not report trauma type.

Risk of bias

For included studies, a high or unclear rating of bias was made for 28 (50.0%) studies regarding random sequence generation, 42 (75.0%) studies regarding allocation concealment, and 7 (12.5%) studies regarding blinded assessment of outcomes (see Table 2 in the online supplement). Forty studies (71.0%) provided only completer data, while 16 (29.0%) studies provided ITT data or reported no missing data. Twenty (35.7%) studies had more than 15% of data unavailable for analysis.

Gender differences in treatment effects of trauma-focused psychological interventions for PTSD

There were medium to large statistically significant reductions in clinician- and self-rated PTSD symptoms favoring trauma-focused interventions for females and males combined at all available time-points (see Table 3 in the online supplement). Heterogeneity was substantial for most of these analyses.

For the ‘any comparison’ condition based on clinician-rated PTSD symptoms, there was evidence that gender modified the intervention effect, with a larger effect for females compared with males at post-intervention (Standard Mean Difference (95% CI): -1.02 (-1.27, -0.76) versus -0.60 (-0.86,-0.33)) and short-term follow-up (-0.54 (-0.81, -0.26) versus -0.18 (-0.35, -0.00)). The forest plot of clinician-rated PTSD symptoms at post-intervention is shown in Figure 2. There was no evidence that gender modified the intervention effect at long-term follow-up, although it should be noted there were relatively few data for males. For self-rated PTSD symptoms, there was some evidence for a larger intervention effect for females at post-intervention (SMD (95% CI): -0.93 (-1.17, -0.69) for females versus -0.62 (-0.90, -0.34) for males), and for males at long-term follow-up (-0.50 (-0.81, -0.20) for females versus -1.02 (-1.46, -0.59) for males), although both results did not reach statistical significance and there were relatively few data available for males in the latter comparison. There was no evidence that gender modified the intervention effect at short-term follow-up.

Further analyses were conducted to examine whether gender modified the intervention effect for trauma-focused interventions compared with wait list or no intervention, usual care, attention control, pharmacotherapy, and non-trauma-focused interventions separately (detailed results provided in online supplement Table 3). For comparisons with wait list or no intervention, there was some evidence for a non-significant larger effect for females on clinician-rated PTSD symptoms at post-intervention (SMD (95% CI): -1.26 (-1.53, -0.98) versus -0.78 (-1.21, -0.35)), and evidence for a larger effect for females on self-rated PTSD symptoms at post-intervention (SMD (95% CI): -1.22 (-1.45, -0.99) vs -0.76 (-1.14, -0.38)). For comparisons with usual care, there was some evidence for a non-significant larger effect for females on clinician-rated PTSD symptoms at short-term follow-up (SMD (95% CI): -0.77 (-1.16, -0.38) vs -0.15 (-0.63, 0.33)). For comparisons with attention control there was some evidence for a non-significant larger effect for females compared with males on self-rated PTSD symptoms at post-intervention (-0.43 (-0.68, -0.17) vs -0.12 (-0.34, 0.09)). There were few data available for comparisons with pharmacotherapy and non-trauma-focused interventions, particularly for males in the latter analyses.

Direct effects meta-analyses

A direct effects meta-analysis that included only those studies that provided data on both females and males (Beck et al., 2009; Ehlers et al., 2003; Ehlers et al., 2005; T. Jensen et al., 2014; Monson et al., 2012; Monson et al., 2006; Mueser et al., 2008; Pacella et al., 2012; Schnyder et al., 2011; Shalev et al., 2012) demonstrated a larger effect for females compared with males (mean difference (95% CI): 10.00 (1.21, 18.79)). Heterogeneity appeared to be relatively unimportant (chi-square = 12.18, df=9, p=0.20; I^2 = 26%). A second direct effects analysis was restricted to those studies that recruited participants with the same type of trauma, namely, two studies of motor vehicle accident survivors (Beck et al., 2009; Ehlers et al., 2003). The findings showed a non-significant larger effect for females compared with males (mean difference (mean difference (95% CI): 5.89 (-17.42, 29.21) with heterogeneity unlikely to be important (I^2 = 0%).

Sensitivity analyses

Seven of 38 studies (Başoğlu et al., 2005; Beck et al., 2009; Bohus et al., 2013; J. A. Jensen, 1994; Litz et al., 2007; Rothbaum, 1997; Schnurr et al., 2003) were excluded from an analysis restricted to trials that evaluated an intervention likely to be provided in routine practice. For two studies that tested two trauma-focused interventions, we used the 'unmerged' data for the intervention that did not include a non-trauma component; that is, prolonged exposure (and not prolonged exposure plus stress inoculation) in the Foa and colleagues (1999) study, and affect and interpersonal regulation plus prolonged exposure (and not supportive counselling plus prolonged exposure) in the Cloitre and colleagues (2010) study. The results showed that gender modified the intervention effect, with a larger effect for females compared with males (chi-square=4.33, df =1, p=0.04; heterogeneity for females and males combined: I^2 = 78%).

Further analyses showed a smaller intervention effect for studies with low ratings of bias for random sequence generation (chi-square =7.36, df=1, p=0.007) and randomization allocation concealment (chi-square =6.54, df=1, p=0.01). There was also some evidence for a smaller intervention effect for studies with ITT data compared with completer data,

although this finding was not significant (chi-square =3.01, df = 1, p=0.08). The intervention effect was not modified by blinding of outcome assessors (chi-square =0.27, df=1, p=0.60) or the percentage of participants with more than 15% missing data (chi-square =0.45, df=1, p=0.50).

Discussion

The current study identified 56 randomized controlled trials that were included in the meta-analysis. The current study supports the available research evidence and practice guidelines that trauma-focused interventions are effective for both women and men with PTSD (Australian Centre for Posttraumatic Mental Health, 2013). The main finding was that women had greater reductions than men in the primary outcome measure of clinician-rated PTSD symptoms when trauma-focused psychological interventions were compared with 'any comparison' at both post-intervention and short-term follow-up. Women were also found to have greater reductions in self-rated PTSD symptoms at post-intervention when trauma-focused interventions were compared with wait list or no intervention. The main finding was supported by a direct effects meta-analysis of data from studies that included both women and men. Finally, there was a larger effect for women in an analysis restricted to trials that evaluated an intervention likely to be provided in routine clinical practice.

Methodological factors that are largely unrelated to gender, such as treatment quality and fidelity, the type of control condition, and the level of general functioning of patients, may help to explain the finding that women appear to respond better to psychological treatments for PTSD ~~Some researchers have suggested that methodological factors that are largely independent of gender, such as treatment quality and fidelity, the type of control condition, and the level of general functioning of patients, may help to explain the finding that women appear to respond better to psychological treatments for PTSD~~ (Cason et al., 2002). For example, it may be the case that there are substantive differences in methodology and quality between studies of (female) rape victims and (male) military veterans. In the current study, the results of the direct effects meta-analysis of data from studies that recruited both women and men suggests that the larger intervention effect for women is unlikely to be

related to such factors. Moreover, the current study provides some preliminary evidence of a gender difference in treatment response irrespective of trauma type. While not statistically significant, the results of the direct effects analysis of data from two treatment studies where participants were included on the basis of a single trauma type (motor vehicle accident) suggest that women had greater reductions in PTSD symptoms compared with men. It should be noted, however, that controlling for trauma type does not exclude the possibility that a difference between women and men in the *severity* of trauma exposure is related to a gender difference in treatment response. It is also possible that such a difference in treatment response may be related to other gender-related differences, including expression of emotions, coping strategies, interpersonal and social support, civilian versus military status, and the chronicity and severity of PTSD and comorbid mental health conditions (Cason et al., 2002). The present study was unable to determine whether such variables were implicated in gender differences in PTSD outcomes.

Some caution should be taken when interpreting the current findings. ~~First,~~ First, one third of eligible studies were not included due to a lack of gender-specific data~~approximately one third of the studies deemed eligible for inclusion were not able to be included because of a lack of available or usable gender-specific data~~. Most of the studies that were not included were mixed gender studies that could have contributed data to both indirect and direct effects meta-analyses, and the inclusion of these additional studies could potentially have changed the current findings. Second and relatedly, for some comparisons there were relatively few studies and data which resulted in inadequate power to assess whether gender modified the intervention effect. Third, there was significant statistical heterogeneity in many of the analyses undertaken. There was considerable clinical diversity within the trauma-focused interventions, which included cognitive and/or behavioral therapies, EMDR, narrative exposure therapy, and other types of interventions, and they varied considerably in terms of duration and planned number of sessions. The planned use of random effects models that take statistical heterogeneity into account was appropriate, and in particular the direct effects meta-analyses had low heterogeneity. Overall, however, it is unclear whether

heterogeneity may have influenced gender-related effects. Fourth, there was often inadequate reporting of aspects of the conduct of studies known to introduce risk of bias and potentially inflate intervention effects. For example, the risk of bias was assessed to be unclear for random sequence generation in almost half of the included studies, and unclear for randomization allocation concealment in three-quarters of the studies. Sensitivity analyses undertaken showed that studies with lower ratings of bias regarding some, but not all, aspects of the conduct of studies tended to have smaller intervention effects. Again, however, it is not clear if the quality of studies had a differential impact on the outcomes of females versus males.

The current study has a number of strengths. First, to our knowledge, this is the first study to undertake a systematic review and meta-analysis that included direct effects analyses to examine a potential gender difference in outcomes following psychological interventions for PTSD. Second, the current review was conducted using explicit and systematic methods that adhered closely to the Cochrane guidelines to minimize bias in the review process. Third, we attempted to find unpublished studies by hand-searching conference proceedings of the ISTSS, as well as searching the Cochrane Central Register of Controlled Studies which is a database that includes the results of grey literature searches undertaken by different review groups internationally.

The current findings highlight the need to more closely investigate potential gender differences in treatment response to psychological interventions for PTSD. Further well-designed controlled trials are required that report on outcomes for women and men separately. Trials that recruit both women and men who have been exposed to the same discrete trauma type would be particularly useful to assess the influence of gender on treatment outcomes. More broadly, f~~F~~uture research efforts should seek to identify specific gender-related factors that facilitate or inhibit response to trauma-focused psychological interventions to inform enhancements or adaptations of those interventions for women and men with PTSD.

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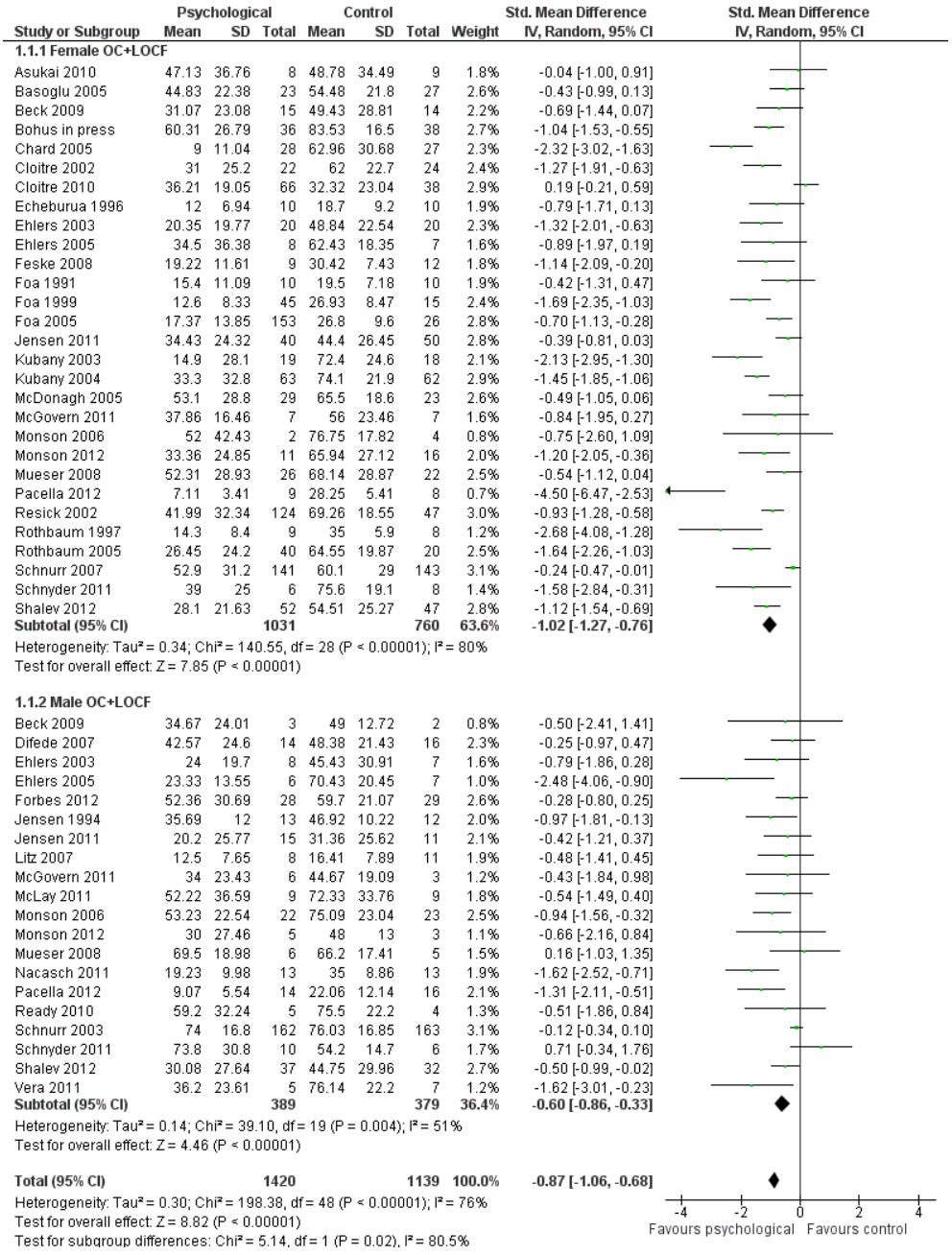

Figure 2. Forest plot of clinician-rated PTSD symptoms post-intervention for trauma-focused interventions versus any comparison condition

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