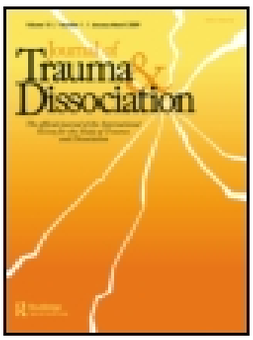

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Meta-Analysis of the Efficacy and Safety of Prazosin versus Placebo for the Treatment of Nightmares and Sleep Disturbances in Adults with Post-Traumatic Stress Disorder

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Meta-analysis of the efficacy and safety of prazosin versus placebo for the treatment of nightmares and sleep disturbances in adults with post-traumatic stress disorder

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Abstract

<B>Context: </B>Although sleep disturbances occur commonly in patients with post-traumatic stress disorder (PTSD) and are associated with adverse outcomes and increased suicidality, they are often inadequately addressed by antidepressant medications. <B>Objective: </B>This review aims to assess whether prazosin reduces nightmares, sleep disturbances, and illness severity in adults with PTSD. <B>Methods: </B>Electronic databases (PubMed, PsycINFO) were searched in September 2014 for randomized controlled trials (RCT) in adults. Search terms included "post-traumatic stress disorder" (PTSD), " prazosin," "nightmares," and "sleep disturbance." Included studies used prazosin and provided objective outcome data related to nightmares and/or sleep quality. <B>Results: </B>Six studies (191 participants) met criteria for inclusion. Prazosin was more effective than placebo in improving nightmares (SMD of 1.022, 95% CI 0.41, 1.62, p = 0.001), sleep quality (SMD of 0.93, 95% CI -0.02, 1.88, p = 0.054 and SMD of 1.14,

95% CI of 0.24, 2.03, p = 0.01), and illness severity (SMD of 1.20, 95% CI 0.79, 1.61, p = < 0.001) with no significant effect on systolic (SMD of -0.01, 95% CI -0.40, 0.37, p =0.94) or diastolic blood pressure (SMD of 0.30, 95% CI -0.09, 0.68, p = 0.154). <B>Conclusion: </B>PTSD-related nightmares, sleep disturbances and overall illness severity showed a significant response to treatment with prazosin. With careful dose titration, prazosin was well tolerated and had no significant sustained effect on blood pressure.

Key Words: Prazosin, Posttraumatic Stress Disorder, Nightmares, Sleep Disturbance

Meta-analysis of the efficacy and safety of prazosin versus placebo for the treatment of nightmares and sleep disturbances in adults with post-traumatic stress disorder

PTSD is a debilitating mental health condition that is difficult to treat and is associated with numerous adverse health outcomes. The lifetime prevalence of PTSD is 6 to 9% among Americans and higher, 10 to 40%, among high risk populations, including disaster survivors, rape victims, and military personnel with combat exposure (Sareen, 2014). Trauma-related nightmares have been referred to as the "hallmark" symptom of PTSD (Writer, Meyer, & Schillerstrom, 2014). At least 83% of PTSD sufferers report recurrent distressing dreams (Green, 2014).

Sleep disturbances in patients with PTSD consist of subjective measures, such as nightmares, re-awakenings, and difficulty falling and staying asleep, as well as objective changes, including alterations in REM sleep, sleep-disordered breathing, and periodic limb movement disorder (Maher, Rego, & Asnis, 2006). The nighttime symptoms of PTSD have been predictive of increased anxiety burden and higher frequency of back pain, headaches, gastrointestinal

symptoms, and other somatic complaints (Maher et al., 2006). As nightmares in the context of mental illness have been strongly associated with increased suicidality, they may be the most important target symptom to address (Sjostrom, Hetta, & Waern, 2009).

The first-line pharmacologic treatments for PTSD are antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs) (Mellman, Clark, & Peacock, 2003). When treated with SSRIs, however, only 20 to 30% of PTSD sufferers achieve remission (Berger et al., 2009).Further, PTSD-related sleep disturbances can be resistant to treatment with SSRIs. Since first-line treatments often fail, other antidepressants and adjunctive agents, such as atypical antipsychotics, anticonvulsants, benzodiazepines, and adrenergic-inhibiting agents, have been tried with varying levels of success (Berger et al., 2009). Of these agents, prazosin has consistently resulted in positive effects in treating symptoms of PTSD, particularly those that are more often treatment-resistant, such as nightmares and difficulty falling and staying asleep (Green, 2014).

Prazosin is an alpha-1-receptor antagonist that has been used off-label to treat PTSD and has been shown to improve sleep disturbances and mitigate alterations in arousal and reactivity (Taylor & Raskind, 2002). The symptomatology of PTSD is thought to arise from increased adrenergic activity in the CNS with elevated secretion of norepinephrine (NE), as well as heightened responsiveness of receptors to NE. In addition to contributing to symptoms of increased arousal, nightmares, and frequent nighttime awakenings, increased CNS activation may impair fear extinction learning, as a result of REM sleep fragmentation (Ahmadpanah et al., 2014; Spoormaker et al., 2010).Through blockade of alpha-1 adrenergic receptors, prazosin reduces CNS activation and in turn may reduce REM sleep fragmentation thereby

improving sleep, ameliorating nightmares, and attenuating maladaptive fear conditioning. (Spoormaker et al., 2010).

Dizziness and orthostasis are two of the more concerning side effects associated with prazosin use and accordingly clinicians may be hesitant with dose titrations (Koola, Sajoy, Fawcett, & Fawcett, 2014). Although never previously assessed by a meta-analysis, a few prior RCTs utilizing prazosin for the treatment of PTSD-related nightmares demonstrated that with graduated dose titrations, prazosin had little effect on blood pressure (Raskind et al., 2007; Raskind et al., 2013; Taylor et al., 2008). In one case study, prazosin was successfully titrated to 30 and 45 mg in two patients without any significant lasting effect on blood pressure (Koola et al., 2014).

In recent years, evidence supporting the use of the prazosin for the treatment of PTSD-related nightmares and sleep disturbances has been accumulating. In the meta-analysis by Seda and colleagues, prazosin was compared to Image Rehearsal Therapy, a cognitive behavioral psychotherapy; both treatments significantly improved nightmares and sleep quality with comparable moderate effect sizes (Seda, Sanchez-Ortuno, Welsh, Halbower, & Edinger, 2015). In a more recently published meta-analysis by De Berardis and colleagues, prazosin significantly improved distressing dreams and global functioning in subjects with PTSD, but its effect did not reach statistical significance on the broader sleep disturbance measure (De Berardis et al., 2015). Our meta-analysis serves to assess the safety and efficacy of prazosin for the treatment of PTSD-related nightmares and sleep disturbances by (1) updating the literature with the inclusion of an additional, larger RCT, (2) correcting for discrepancies in the data extraction of the prior two meta-analyses, and (3) including additional safety data by assessing blood pressure changes

secondary to prazosin, as concerns for hypotension continue to be a significant barrier to its use and optimal dose titration

Methods

Eligibility Criteria

This review collected randomized controlled trials assessing the effect of prazosin as compared to placebo on nightmares, sleep quality, and illness severity in patients with PTSD and post-traumatic stress symptoms. Criteria for inclusion required for studies to be written in the English language, involve adult participants over the age of 18, and to use prazosin as the study medication. Studies that included participants with unstable medical conditions or active substance abuse disorders were excluded. All studies provided objective outcome data related to nightmares or sleep quality.

Information Sources

Studies were identified using a search of electronic databases. The search was conducted in September 2014 and was applied to the PubMed and PsycINFO databases, which include articles published since 1966 and since 1960, respectively. The literature search was repeated in August 2015 and no additional studies meeting criteria for inclusion were identified.

Search

An electronic search of the PubMed and PsycINFO databases was conducted using the following search terms: [(Trauma) OR (PTSD) OR (Post Traumatic Stress Disorder) OR (Traumatic Stress Disorder) OR (Post Traumatic Stress)] AND [(Prazosin) OR (Minipress) OR (Alpha-1 Antagonist)] AND [(Nightmares) OR (Sleep) OR (Sleep Disturbance)]. Search filters were used to restrict studies to randomized controlled trials published in English and with human subjects.

Study Selection

Duplicate studies were removed and the remaining unique search results were screened independently in a standardized manner by two reviewers (K.G. and L.K.) for assessment of eligibility according to the above inclusion criteria. Articles were screened by title and abstract, with full-text review conducted for studies in which adherence to inclusion criteria was unclear by title and abstract alone. Any disagreement between the two reviewers after full-text review was resolved by consensus and a third reviewer (L.R.). Chance-corrected agreement between the two reviewers was assessed using the Cohen Kappa statistic. The Kappa for interrator agreement was 0.915, representing excellent agreement.

Data Collection Process

Outcome data was measured differently among studies, with scales including the 17-item Clinician-Administered PTSD Scale for DSM-IV (CAPS), Pittsburgh Sleep Quality Inventory (PSQI), Clinical Global Impressions Scale (CGI), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Insomnia Severity Index (ISI), PTSD Dream Rating Scale (PDRS), and Sheehan Disability Scale (SDS). Reviewers decided by consensus which of the above scales to include in the review based on pertinence to study objective and use across adequate number of studies. Data was extracted separately by instrument from each relevant study. Reviewers extracted data independently and data was checked by all reviewers for any discrepancies.

Data Items

Data items collected from each study included study duration, profile of participants (number, age, and gender), psychiatric diagnosis, comparator group, intervention group, study measure, and outcome. Nightmare outcome data was measured using Item #2 of the CAPS instrument, which assesses frequency of nightmares and intensity of distress related to nightmares. CAPS Item #2 was scored using the "1, 2 rule" where the severity score for each symptom cluster is determined by summing the frequency score (1) with the intensity score (2). Sleep outcome data was measured by Item #13 of the CAPS instrument and by the PSQI instrument. CAPS Item #13 assesses difficulty falling or staying asleep by rating frequency on a scale of 0 to 4 (0 = never and 4 = difficulty falling asleep almost daily) and intensity on a scale of 0 to 4 (0 = no sleep problems and 4 = extreme or profound difficulty staying asleep with more than 3 hours of sleep loss). These component scores are then summed to give a total severity score which ranges from

0 to 8. Illness severity was measured using the CGI instrument. Blood pressure change was assessed by comparing end-of-study to baseline measurements. When blood pressure measurements were taken as orthostatic readings in the supine and standing positions, as in the studies by Raskind et al. (2003) and Raskind et al. (2007), only measurements from the standing position were included in the analysis. Data for these outcome measures was extracted from the relevant studies and included the following: final number of participants for both control and intervention groups, end of study mean for each group, and standard deviation for each mean value.

Risk of Bias in Individual Studies

Each included study was reviewed, using the Cochrane approach, for risk of bias in each of the following categories: adequate sequence generation, allocation concealment of intervention, blinding, completeness of outcome data, selective outcome reporting, and presence of other bias. Studies were reviewed independently by each of the reviewers in all of the above areas with any discrepancies resolved by consensus.

Synthesis of Results

Outcomes from the above measures of nightmares, sleep quality, illness severity, and change in blood pressure were aligned across studies, with standardized mean differences used to create a forest plot for each individual scale or measure. Study results were not combined and data processing was not performed.

[Insert Figure 1]

Results

Study Characteristics

Six randomized, placebo-controlled studies were included in the meta-analysis with study selection detailed in Figure 1 (Ahmadpanah et al., 2014; Germain et al, 2012; Raskind et al., 2003; Raskind et al., 2007; Raskind et al, 2013; Taylor et al., 2008). Among the six included studies, there were a total of 241 subjects, 191 of which were included in the statistical analysis. The duration of the studies ranged from seven to 20 weeks. Characteristics for each study are detailed in Table 1. The intervention medication for all studies was prazosin. The Ahmadpanah et al.<I> </I>study included a hydroxyzine group; data from this arm was excluded from our study. Two studies (Raskind et al., 2003; Taylor et al., 2008) utilized a crossover design.

Subjects included in all studies met DSM-IV criteria for PTSD, with the exception of 21 subjects in the Germain et al. study who endorsed sub-threshold symptoms. Four of the six studies required participants to have had prior combat experience (Germain et al., 2012; Raskind et al., 2003; Raskind et al., 2007; Raskind et al., 2013), whereas the Ahmadpanah et al. and Taylor et al. studies included participants who had other forms of past trauma. Each study permitted subjects to continue on previously prescribed psychotropic medications.

In all included studies, the dose of prazosin was initiated at 1 mg nightly for a minimum of three nights, followed by titration to effect at different intervals and doses per study design. Moreover, the Raskind et al. (2013) study included mid-morning dosing. Final nightly mean dose of

prazosin varied from 3.1 mg in the Taylor et al study, to 15.6 mg in the Raskind et al.<I> </I>(2013) study.

[Insert Table 1]

Risk of Bias Within Studies

The Taylor et al. and Raskind et al. (2003) studies did not include details of randomization method<I> </I>and the adequacy of their sequence generation and allocation concealment was unclear. All studies except for the Taylor et al. study blinded both participants and study personnel; in this study, only participants were blinded. The Germain et al. study provided a detailed description of excluded subjects, whereas the other five studies did not directly address incomplete outcome data.

Risk of Bias Across Studies

Aggregate outcome determined from six studies demonstrated low to moderate risk of bias.

Synthesis of Results

This meta-analysis revealed that prazosin produced greater improvement than placebo in all three primary outcome measures: nightmare frequency and intensity, as measured by CAPS Item # 2; sleep quality, as measured by CAPS Item # 13 and PSQI; and overall illness severity, as measured by CGI. Forest plots showing the aggregate outcomes are pictured in Figures 2, 3, 4, and 5. Pooled mean effect sizes for blood pressure demonstrate that prazosin compared with placebo had no significant effect on systolic or diastolic blood pressures (Figures 6 and 7).

Heterogeneity was evaluated for primary and secondary outcome measures through statistical analysis. Heterogeneity was found in one of the three primary outcome measures, the PSQI (I² = 85.7%; χ^2 = 20.99, d.f. = 3, p = < 0.001), and was absent in all other outcomes measures. Publication bias was determined through use of funnel plots. Of the primary and secondary outcome measures assessed, only three of the measures included four or more studies (CAPS Item #13, PSQI, and CGI) and thus were evaluated via funnel plot. The funnel plots suggest that there was no significant publication bias for CAPS Item #13 (p = 0.835) or PSQI (p = 0.498), but the CGI outcome was significant for possible publication bias (p = 0.001); of note, this outcome was also significant for bias attributed to the small number of studies included in the meta-analysis. Figures 2, 3, 4, and 5 show the Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) for all primary outcome measures. Figures 6 and 7 show the SMD and 95% CI for the secondary outcomes measures of systolic and diastolic blood pressure.

There was a large treatment effect size found in all three primary outcome measures. For the CAPS Item # 2 “distressing dreams” item, there was a large treatment effect size with an overall SMD of 1.02 (95% CI 0.41, 1.63, p = 0.001). For PSQI, there was also a large effect size with an overall SMD of 1.14 (95% CI 0.24, 2.03, p = 0.01). Subjects who received prazosin had a greater improvement in sleep latency and duration as measured by the CAPS Item # 13. On this outcome measure, there was a large effect size with an overall SMD of 0.93 (95% CI -0.02, 1.88, p = 0.05), but it was not statistically significant. Of all outcome measures, the largest effect size was seen with CGI, with prazosin treated subjects demonstrating a greater improvement in illness severity (overall SMD of 1.20, 95% CI 0.79, 1.61). Prazosin had no significant effect on systolic

(SMD -0.01, CI -0.40, 0.37, p =0.94) or diastolic blood pressure (SMD 0.30, CI -0.09, 0.68, p = 0.154). There was no significant heterogeneity between studies on either measure (SBP, I² = 0 χ² =1.32, d.f. = 2, p = 0.52 DBP, I² = 0; χ² = 1.48, d.f. = 2, p = 0.48).

[Insert Figure 2] [Insert Figure 3]

[Insert Figure 4] [Insert Figure 5]

[Insert Figure 6] [Insert Figure 7]

<B><U>Discussion </U></B>

Primary Outcome Measures

Based on the results of six RCTs and inclusive of a total of 191 subjects, this meta-analysis demonstrates that prazosin results in a clear reduction in nightmares, sleep disturbances, and overall illness severity in patients with PTSD, with high magnitude effect sizes on all three measures. The results of the present study are comparable to those of two recently published meta-analyses, with some important differences. In the meta-analysis by Seda and colleagues, prazosin also reduced the severity of the same outcome measures of nightmares, sleep disturbances, and illness severity, but with moderate, rather than high magnitude effect sizes. The differences between the magnitudes of the effect sizes found in this study as compared to those by Seda and colleagues can be explained by a number of factors, for example the inclusion of additional metrics, such as the PTSD Checklist (PCL) and the Impact of Event Scale – Revised (IES-R), which were excluded from the present analysis in an effort to minimize variability in comparators made across trials, the inclusion of a more recently published RCT in

this analysis, and discrepancies in the data extraction process. The most prominent discrepancy in the data extraction involved the nightmares outcome SMD from the Raskind and colleagues (2007) study. In the present analysis, the value extracted for this item was 0.83, whereas Seda and colleagues reported it as 0.21. This difference contributed in part to the lower overall effect size for the nightmares outcome in their study. For the sleep quality outcome as measured by PSQI, the Ahmadpanah and colleagues study, which was not included in the meta-analysis by Seda and colleagues had a very large effect size of 2.44, which contributed significantly to the larger overall effect size for sleep quality found in the present study.

In the more recently published meta-analysis by De Berardis and colleagues, the results for two of the three outcome measures were similar to the findings in our study: prazosin significantly reduced nightmares and illness severity with high magnitude effect sizes (De Berardis et al., 2015). The findings from the study by De Berardis and colleagues, however, differ from those in our study in that the effect of prazosin on sleep quality, as measured by PSQI, failed to reach statistical significance in their study. This can be explained by a difference in data extraction for the sleep quality measure: the effect size of 4.46 reported by De Berardis and colleagues for the study by Raskind (2013) differed greatly from the same data point reported in our study, which was found to be 0.93. This difference led to higher variance in their analysis. The higher variance in their analysis along with the additional RCT by Ahmadpanah and colleagues included in our study likely account for the difference in statistical significance on this measure.

Optimal Duration of Treatment

Most RCTs included in this analysis were only eight or fewer weeks in duration. Little is known about what constitutes an adequate trial of prazosin for the treatment of PTSD symptoms and at what time-point the maximal benefit of the medication would be expected to be achieved. In the RCTs included in this analysis, eight weeks was sufficient time to demonstrate a significant separation between prazosin and placebo on all three primary outcome measures. Of note, when outcome measures were assessed at three- and four-week time intervals, as in the RCTs by Taylor and colleagues and Raskind and colleagues (2007), results were not as strong for the nightmares and sleep quality measures. In the RCT by Raskind and colleagues (2007), at week four, there was no significant difference between the prazosin and placebo groups on nightmares or sleep quality. By the end of the study (week eight), however, the prazosin group improved significantly on all measures. In the RCT by Taylor and colleagues subjects were treated with either prazosin or placebo for a three-week time period, separated by a one-week washout in a crossover design. When subjects were given prazosin for three weeks, although there were significant improvements in nightmares and sleep quality (as measured by CAPS Item #13), the effect sizes for either of these measures were not as large as those of the longer-duration RCTs included in the nightmares and sleep quality analyses (Figures 2 and 3). While more studies are needed to draw any firm conclusions, these results suggest that prazosin is more effective for nightmares and sleep quality at week eight as compared to earlier time-points.

Blood Pressure and Tolerability

To our knowledge, the present study is the first meta-analysis to assess the effect of prazosin on blood pressure when used in the context of treating PTSD. Data from three of six RCTS were included in our blood pressure (BP) analysis and demonstrate that prazosin has no significant effect on systolic or diastolic blood pressure (Raskind et al., 2007; Raskind et al., 2013; Taylor et al., 2008). We did not perform a separate sub-analysis on orthostatic BP as this data was only gathered in 2 RCTs (Taylor et al., 2007; Taylor et al., 2013). In both studies, however, orthostatic values and associated adverse events were noted to be comparable in both the prazosin and placebo groups.

Given that prazosin is FDA-approved for the treatment of hypertension, it is surprising that significant changes in blood pressure were not observed. There are several possible explanations for this. First, prazosin may only have a significant effect on blood pressure in patients with pre-existing hypertension (HTN). In the RCTs included in our study, subjects with untreated medical conditions, such as HTN, were excluded and thus all patients were normotensive at the start of the study. In a study comparing prazosin to other alpha-1 antagonists for benign prostatic hyperplasia, prazosin did not have an effect on blood pressure in normotensive patients, but significantly reduced blood pressure in hypertensive patients (Tsujii, 2000). Additionally, in two of the three RCTs included in our blood pressure analysis, prazosin was administered as a single daily dose at bedtime. Prazosin is a short-acting medication, with a half-life of only two to three hours and thus it is typically dosed at least three times daily when used for the treatment of HTN. Although the timing of blood pressure readings was not specified in the three RCTs included in

our BP analysis, it is possible that BP measurements were taken many hours after prazosin administration, in which case the effect on blood pressure may no longer have been apparent.

The results of our blood pressure analysis should be interpreted with caution because perhaps the most concerning side effect associated with prazosin use is the "first dose phenomenon," which involves severe postural hypotension and associated pre-syncope and syncope occurring shortly after the first dose has been absorbed into the bloodstream (Graham et al., 1976). The only blood pressure numbers reported in the RCTs included in this analysis were those taken at baseline and at the end of the study; thus, transient changes related to the administration of the first dose were not taken into account. All three studies took care in titrating the dose of the study drug slowly so as to avoid any sudden changes in blood pressure. In the study by Raskind and colleagues (2007), two participants with subjective orthostatic dizziness during prazosin titration elected to discontinue the study due to distress from blood pressure-related side effects and one participant in the study by Raskind and colleagues (2013) had a brief syncopal episode in the context of dehydration during physical exercise while on a maintenance dose of prazosin. Aside from these occurrences, however, prazosin rarely caused symptoms attributable to BP reductions. Larger follow-up studies ought to be conducted to address the "first dose phenomenon," as well as the effect of prazosin on BP in patients with low resting BP. However, the evidence that prazosin was generally very well tolerated and without a sustained effect on BP in this analysis is promising and may ease practitioner concerns about blood pressure-related side effects.

Limitations and Future Directions

The limitations in the current analysis involve the small number of RCTs included and the use of multiple RCTs written by the same author, which limits the generalizability of the results as the patient populations were relatively homogenous. In all of the three RCTs in which Raskind was first author, all subjects were United States military veterans or soldiers with a combat history and most subjects were men (90%). Across the six RCTs included in the study, only 56 (23%) of the original 241 subjects were women. In the United States, almost three times as many women as men are diagnosed with PTSD (Gradus, 2014-2015) and a recent study suggests that while women with PTSD are more likely than men to be medicated, men are more likely than women to receive prazosin (Bernardy et al., 2013).Further studies devoted to prazosin use in women are warranted.

In future studies, it would be advantageous to address other logistical concerns regarding the optimal dosing and treatment duration of prazosin. As the average maximum dose of prazosin varied widely in the RCTs included in this analysis (from 3 mg to 15 mg), it would be useful to have comparison studies assessing the efficacy and safety of various dose ranges. Further, the sustainability of the treatment effect is unknown. Studies with longer treatment periods and long-term follow up assessments could help direct practice patterns.

Conclusion

The results of this study are in agreement with those of prior meta-analyses in demonstrating that prazosin is superior to placebo for the treatment of nighttime symptoms of PTSD. An

outstanding concern is that of safety. While more studies are needed to ascertain dosing guidelines and establish optimal duration of treatment, in our study, prazosin, when carefully titrated, was well tolerated and had no significant effect on blood pressure. Therefore, the results of this study provide strong evidence for the efficacy and tolerability of prazosin in the treatment of PTSD-related nightmares and sleep disturbances.

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<B>Table 1: </B>Description of Study Characteristics

<B>Reference</B>	<B>Study design</B>	<B>Duration</B> <B>(weeks)</B>	<B>Subjects</B>	<B>Diagnoses</B>	<B> Relevant Outcome Measures</B>	<B>Comparator Group</B>	<B>Dose</B> <B>(mg/d)</B>	<B>Adverse effects</B>	<B
<B>Ahmadpanah et al, 2014</B>	RCT	8	100 subjects (72 men) Age (y)	PTSD	PSQI	Placebo, Hydroxyzine	15	Nausea, dry mouth, GI complaints more common in prazosin and hydroxyzine groups	S i F i g

			35.5						
<B>Germa in et al, 2012</B>	RCT	8	50 veterans (45 men) Age (y) 41 ± 13.2	PTSD (n=29) and subsyndromal PTSD (n=21)	CGI-I,PSQI	Placebo, CBT	8.9 ± 5.7	Mild orthostatic symptoms reported by participants in both groups	Si in PS si ch
<B>Raskind et al, 2003</B>	RCT with crossover	20 wk crossover at wk 10	10 male veterans Age (y) 53	PTSD	CAPS, CGI-C	Placebo	9.5	2 patients with transient decreased BP and dizziness	Si in C 13 C

<B>Raskind et al, 2007</B>	RCT	8	40 PTSD veterans (38 men) Age (y) 56± 9	CAPS, CGI-C, PSQI	Placebo	13± 3	15 patients reported transient dizziness (9 prazosin, 6 placebo)	S i C C
<B>Raskind et al,</B> <B>2013</B>	RCT	15	67 PTSD soldiers/ army veterans <B>(57 </B>male <B>) </B>Age (y) 30	CAPS, PSQI, CGI,	Placebo	Men: 4.0/15.6* Women 1.7/7.0*	1 patient in prazosin group with brief syncope	S i C C
<B>Taylor et al,	RCT with crossover	7 wks, with 1 wk	13 civilians (2 men)	PTSD	CAPS,	Placebo	3.1 ±3	Dizziness occurred 3

2008</B>	washout at wk 3	Age (y) 49 ± 1	CGI-I	times in both prazosin and placebo groups

CAPS #2= Clinician-Administered PTSD Scale item #2 (nightmare frequency and intensity), CAPS #13 = Clinician-Administered PTSD Scale item #13 (difficulty falling or staying asleep), CGI-C = Clinical Global Impression of Change, CGI-C = Clinical Global Impression of Improvement, PSQI = Pittsburgh Quality Sleep Index, PTSD = Post-traumatic stress disorder

*midmorning/bedtime doses of prazosin (mg)

<B>Table 1 (cont.)</B>

Figure 1</B>: PRISMA flow diagram depicting sequence of exclusions yielding final studies included in meta-analysis

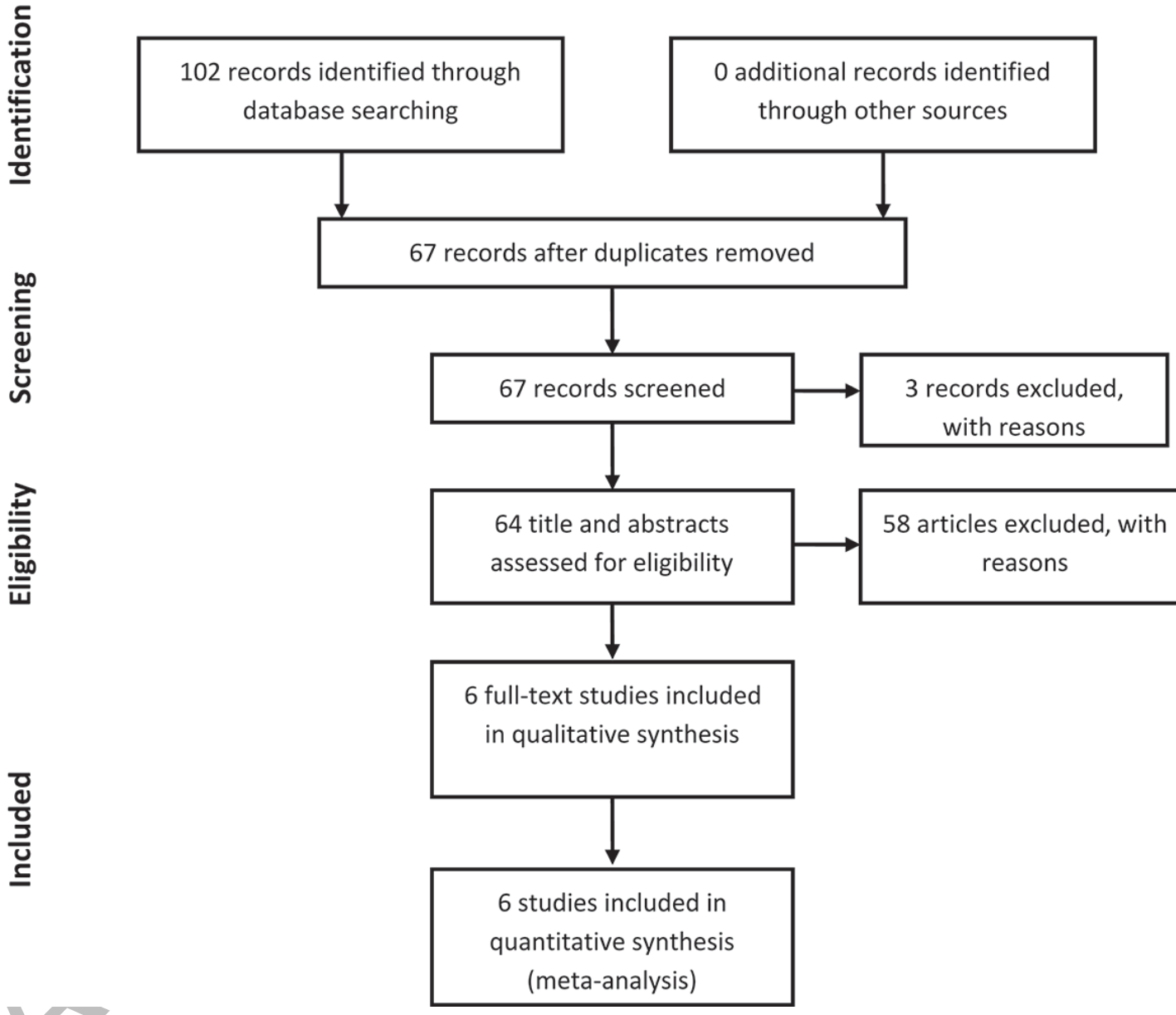

Figure 2: Forest plot of nightmares outcome (CAPS Item #2).

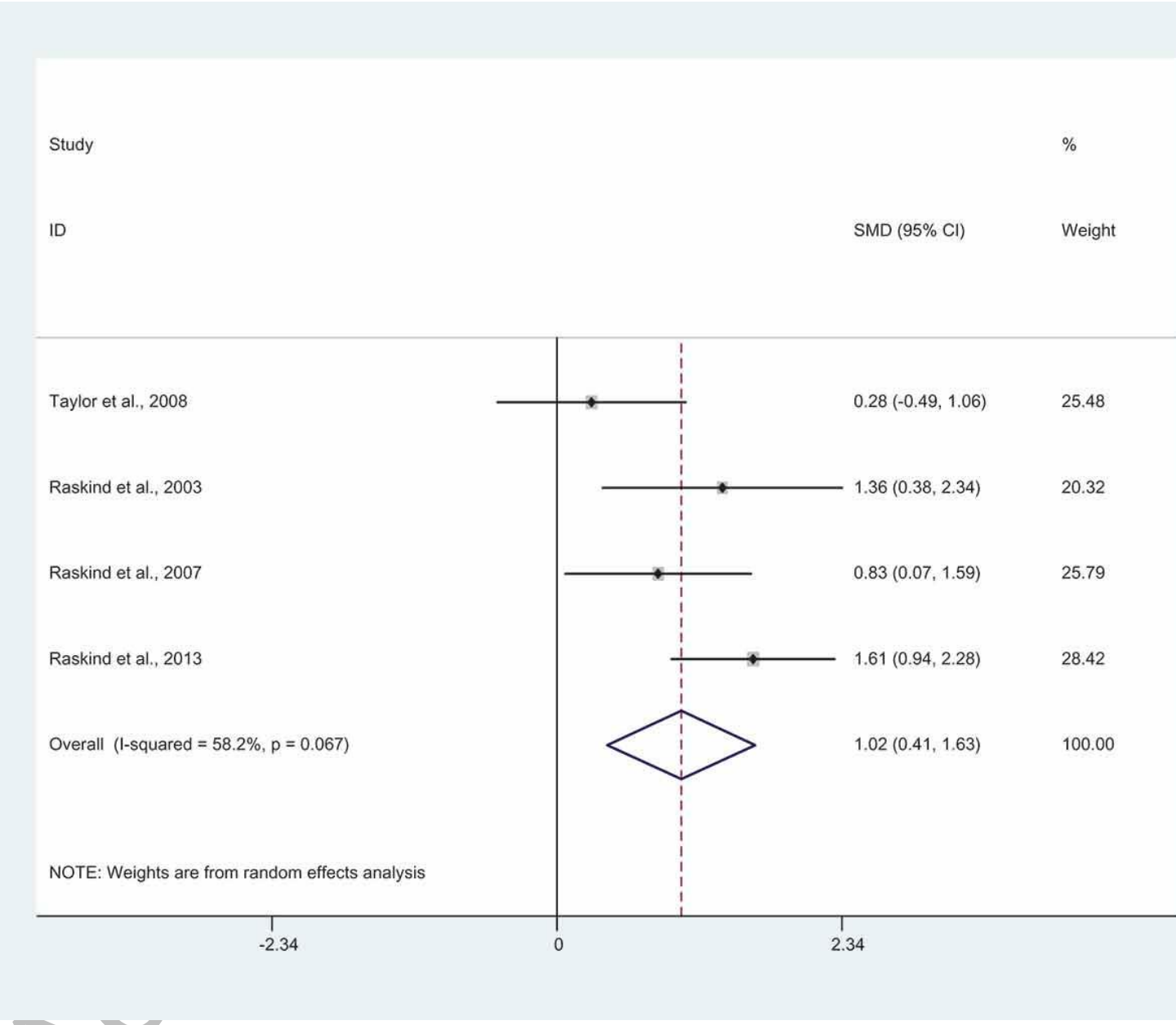

Figure 3: Forest plot of sleep quality outcome (CAPS Item #13).

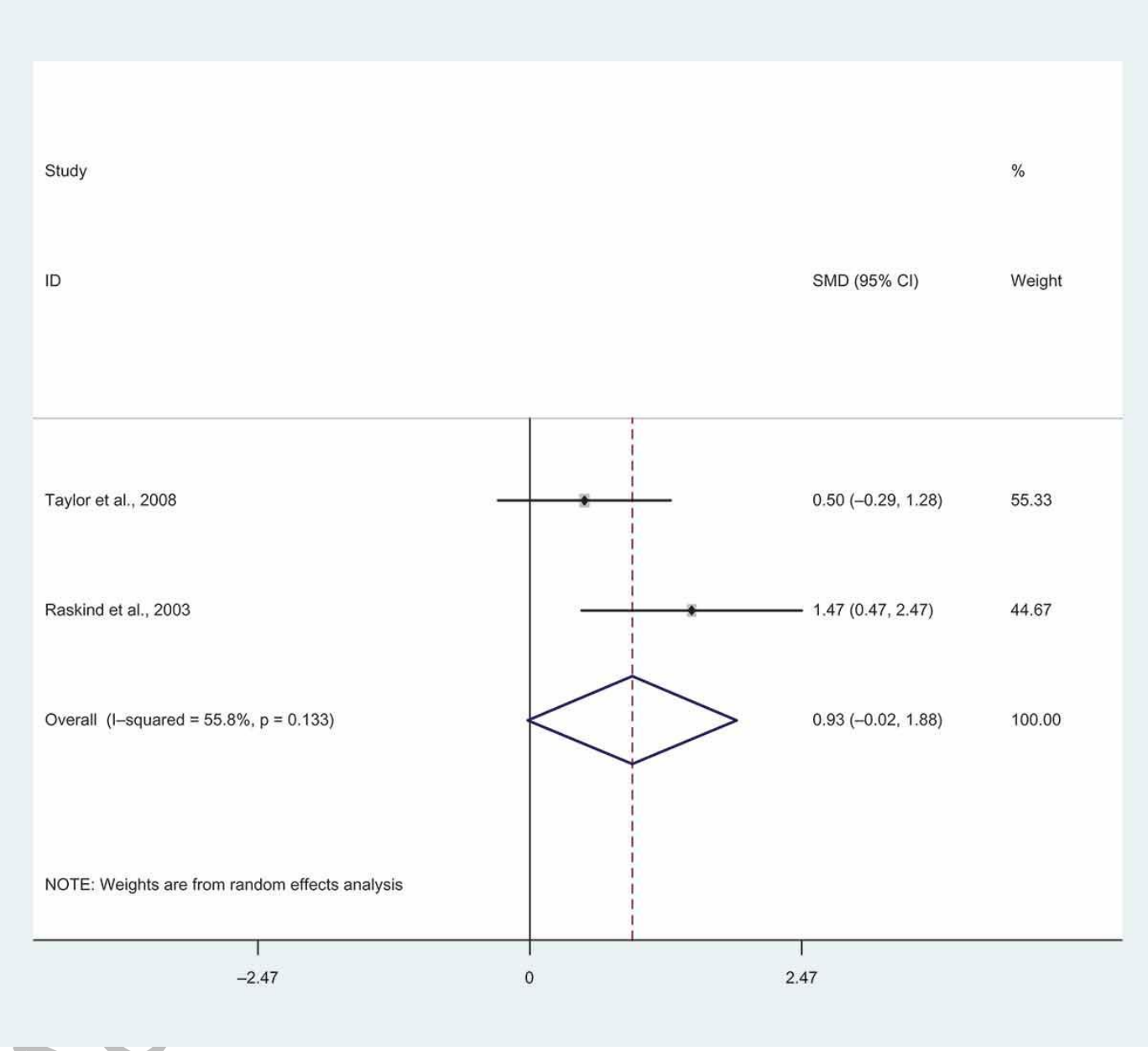

Figure 4: Forest plot of sleep quality outcome (PSQI).

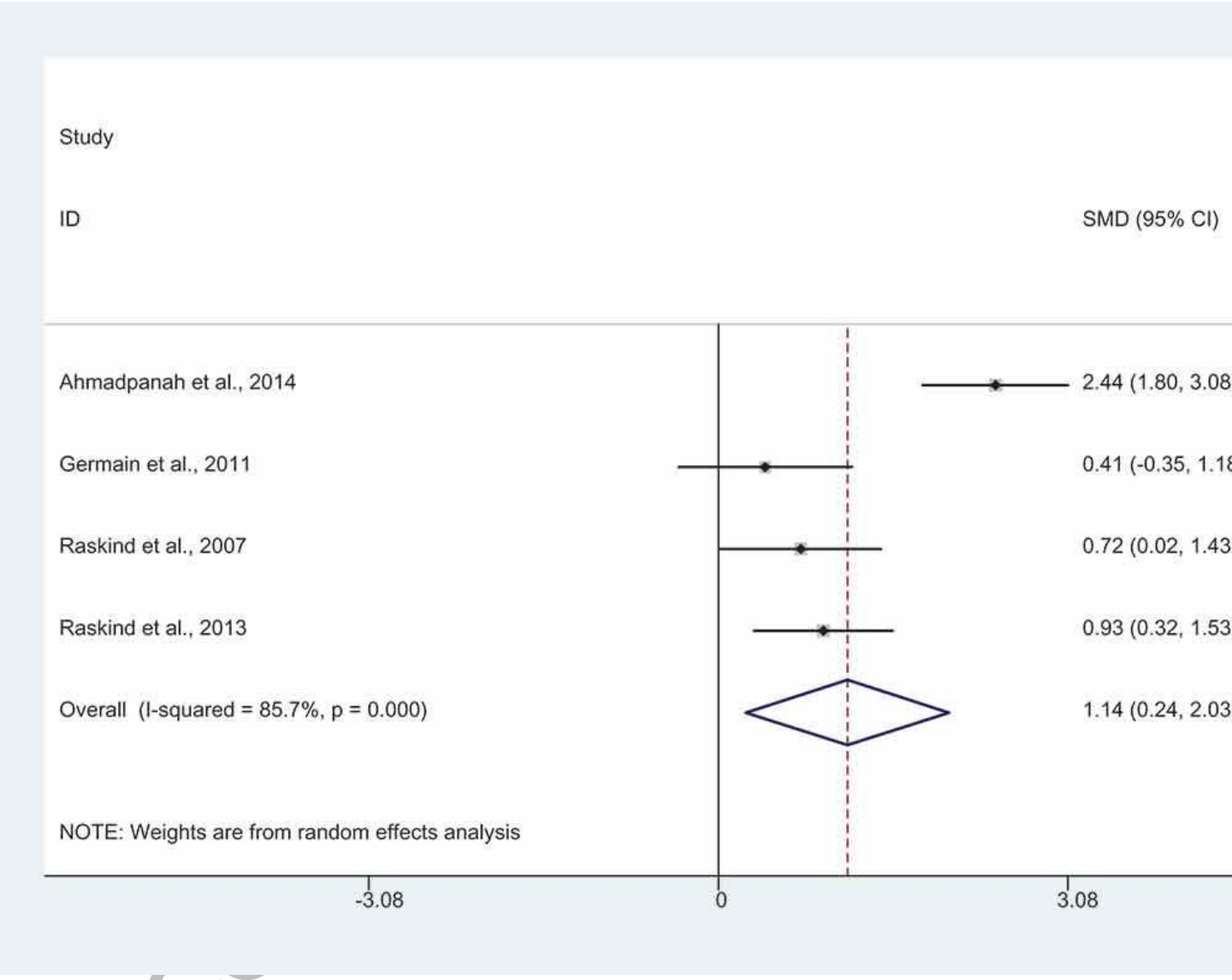

Figure 5: Forest plot of illness severity outcome (CGI).

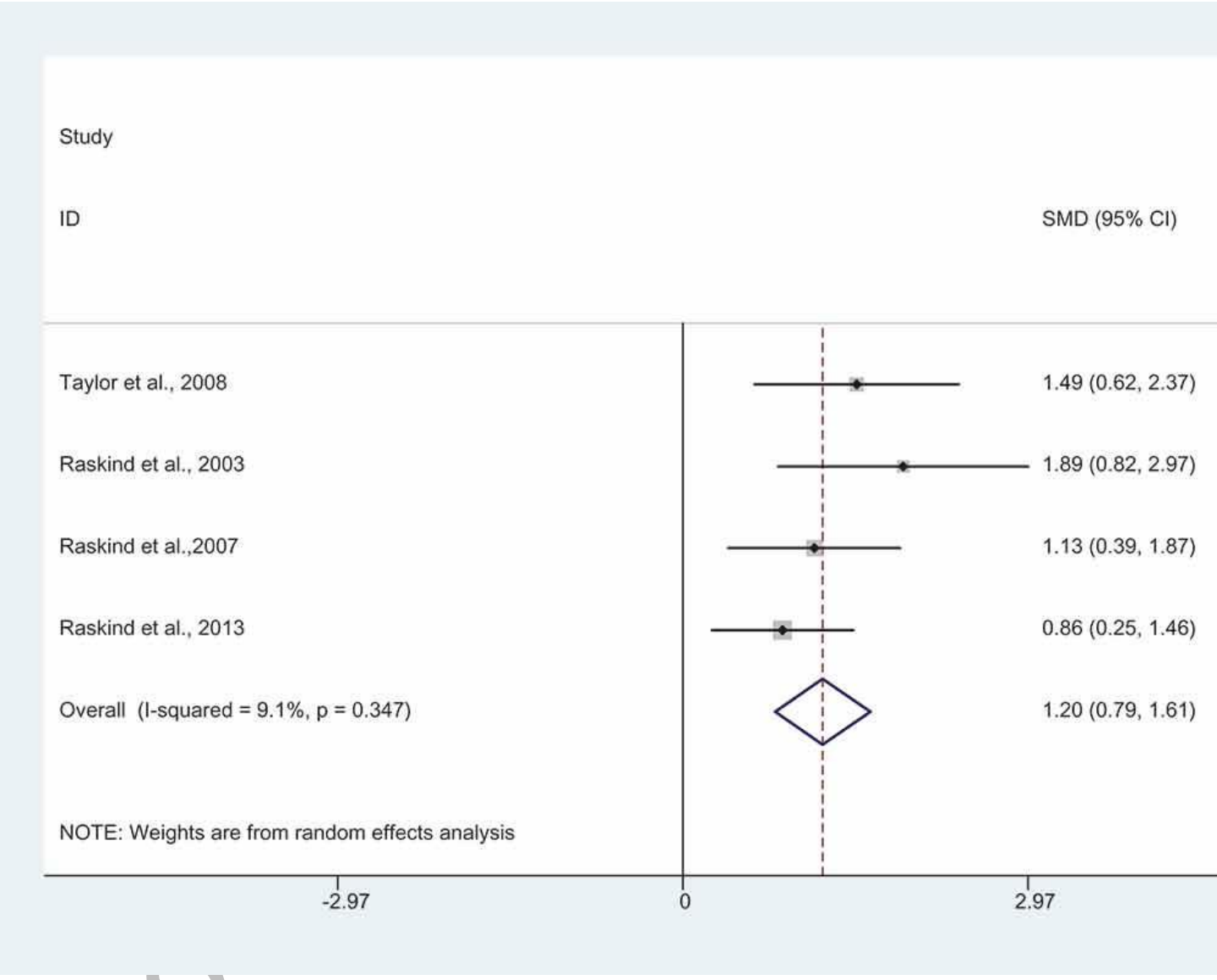

Figure 6: Forest plot of systolic blood pressure (SBP) outcome.

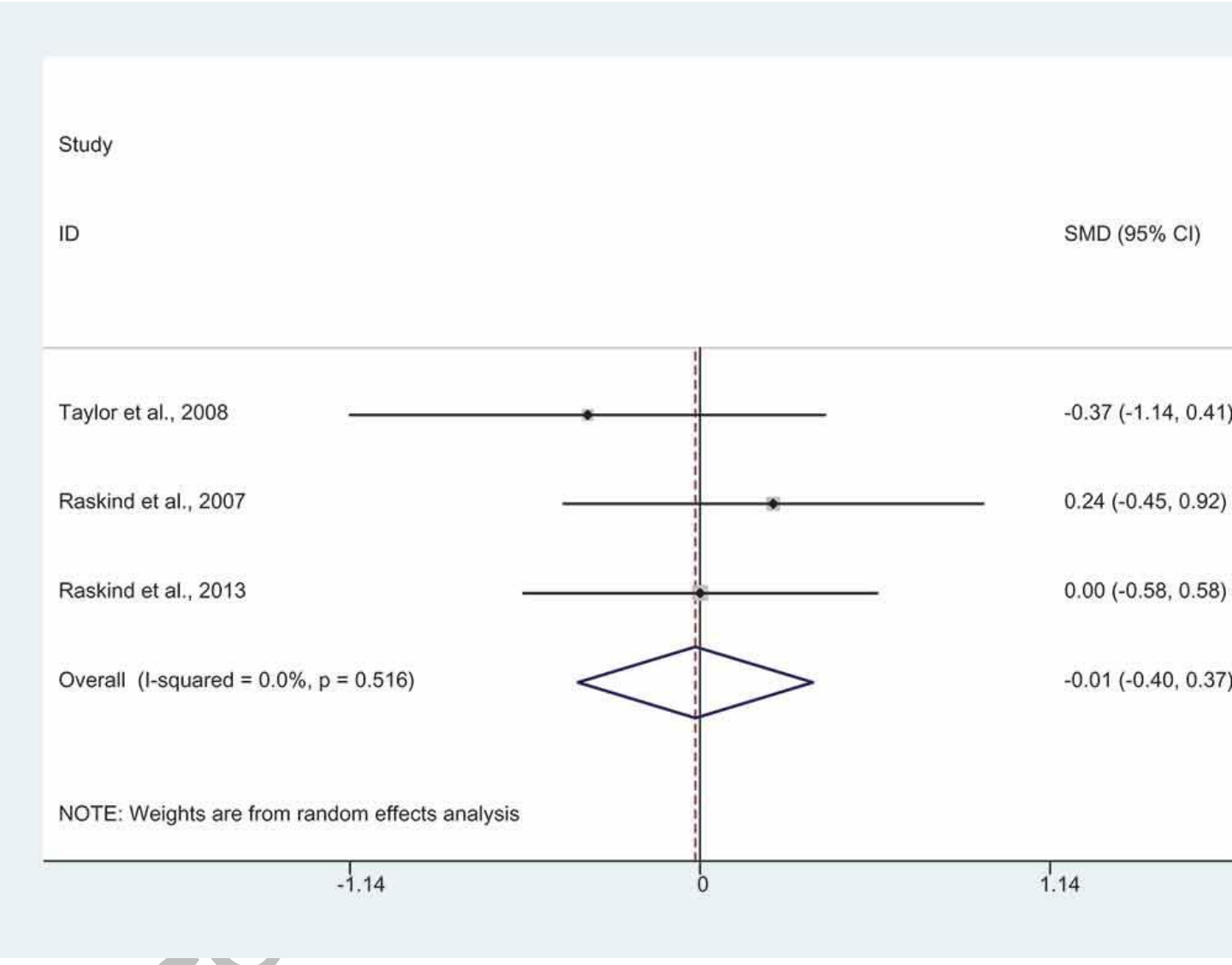

Figure 7: Forest plot of diastolic blood pressure (DBP) outcome.