

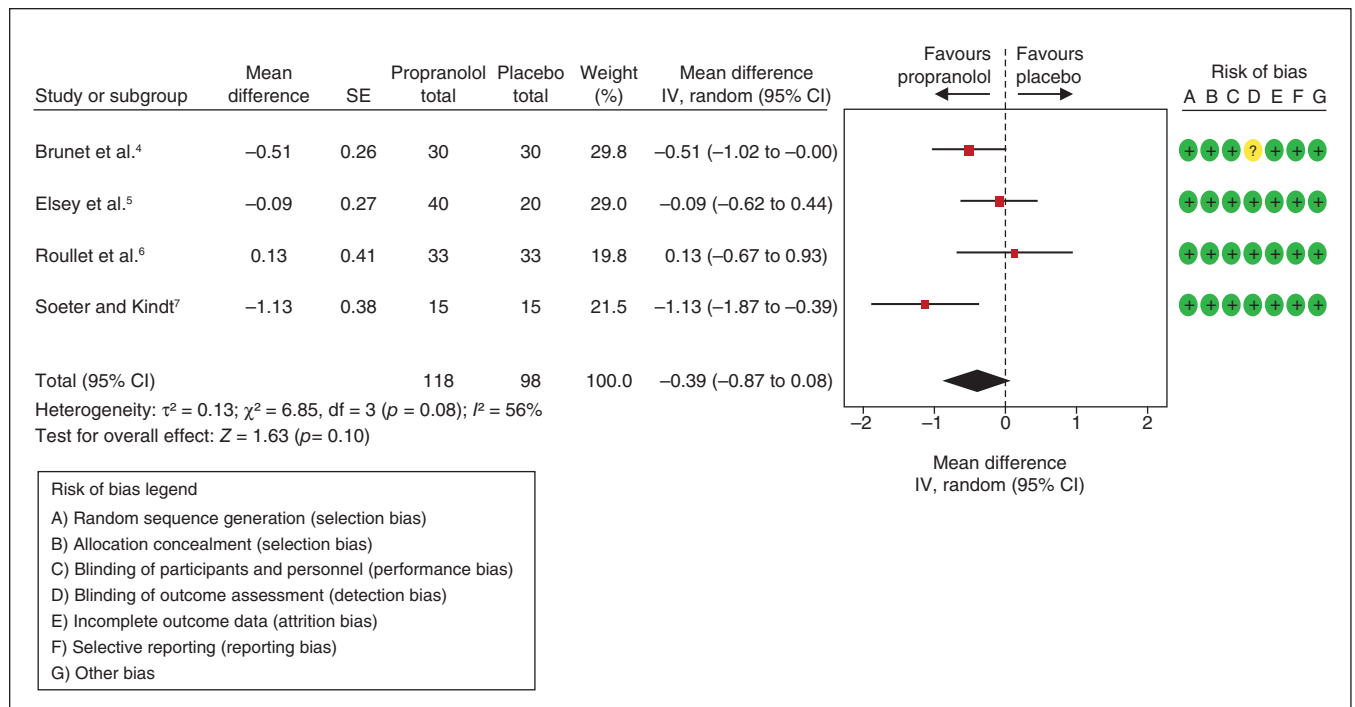
**Updated and rectified meta-analysis shows no effect of propranolol versus placebo on traumatic memory reconsolidation disruption**

A recent meta-analysis published in *JPN*, and new data on administration of propranolol to patients with psychotrauma-related conditions, raise a number of concerns that we would like to share with the readers. Pigeon and colleagues<sup>1</sup> performed a systematic review and meta-analysis of therapeutic approaches based on reconsolidation interference theory, in the hope for a paradigm shift in the treatment of mental disorders that have an emotional memory at their core. The authors included 14 experimental studies in healthy adults and 12 randomized placebo-controlled clinical trials (RCTs). A pooled analysis of the included clinical trials showed that, compared with placebo, reconsolidation impairment under propranolol alleviated psychiatric symptoms and reduced cue-elicited reactivity ( $g = -0.42, p = 0.01$ ). Accordingly, the authors concluded that propranolol's clinical use is promising and deserves further controlled investigation.<sup>1</sup>

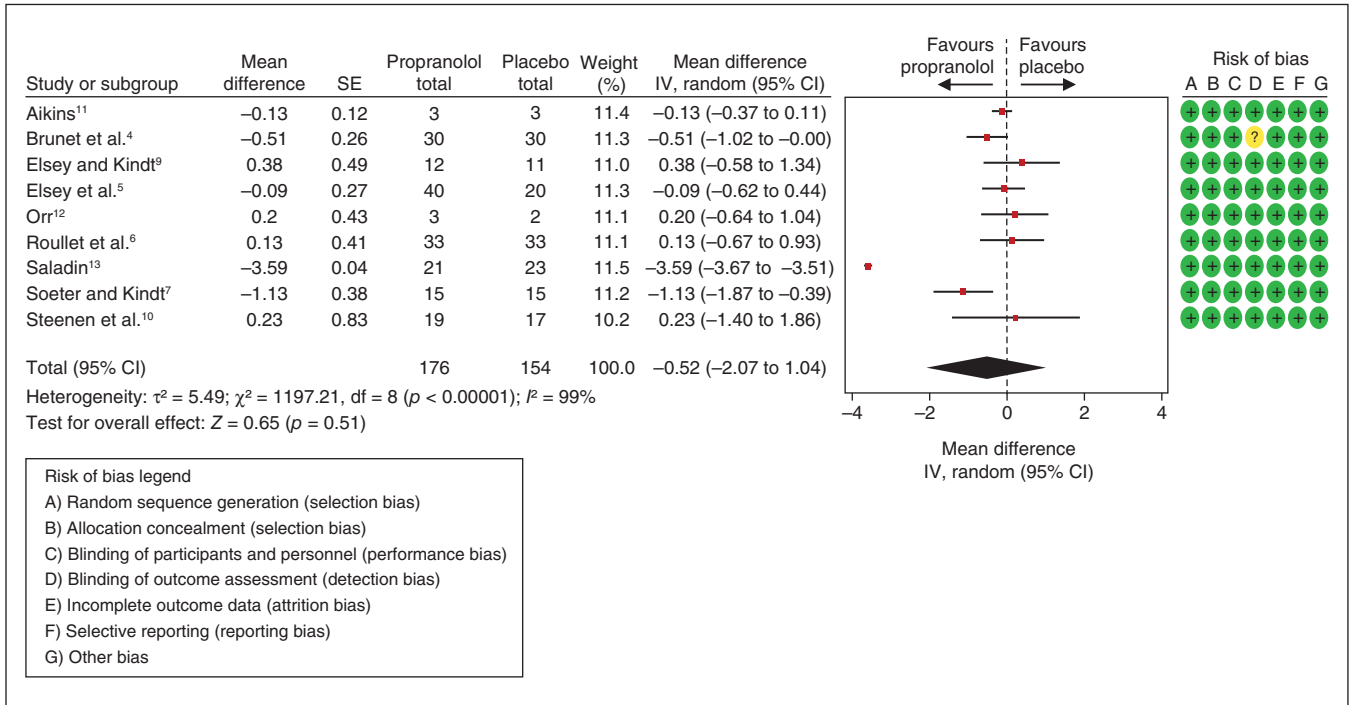
We argue that Pigeon and colleagues' results and conclusions are affected by limitations in methodology and that their conclusions are incorrect in the context of propranolol's effects on psychotrauma-related symptomatology. First, although the authors assessed publication bias and searched for unpublished work,<sup>1</sup> they seem to have missed 3 unpublished trials that may have increased the risk of publication

bias.<sup>2</sup> These 3 trials were identified on ClinicalTrials.gov (NCT00645450, NCT01055171) and Google Scholar (W81XWH-08-1-0491) in a very recent and highly similar meta-analysis involving posttraumatic stress disorder (PTSD) studies specifically.<sup>3</sup> Second, the authors failed to report risk of bias summary figures (Figure 1), and in their pooled analysis of clinical studies they included 2 trials in which physiologic response, instead of clinical symptom severity, was the primary outcome measure. Third, 5 studies involving substance dependence and abuse were included, disorders which, in the context of emotional memory, clearly have mechanistically different etiologies from disorders related to psychological trauma.<sup>48</sup> To ensure that the value of propranolol for the health care field has been estimated correctly, we re-analyzed the data on which Pigeon and colleagues based their conclusions. We found that, if their pooled analysis of clinical studies had been restricted to low-risk-of-bias RCTs into psychotrauma-related symptomatology,<sup>56</sup> the pooled analysis would have shown that propranolol was not statistically significantly superior to placebo (Figure 1). Moreover, if the pooled analysis is supplemented with missed and new trials,<sup>5,72,10</sup> the 95% confidence interval of the pooled mean difference is even wider (Figure 2).

The current state of affairs in the field of clinical application of propranolol for trauma-related conditions, such as posttraumatic stress disorder, does not fully support the notion that use of propranolol in the impairment of traumatic



**Figure 1:** Forest plot of rectified pooled analysis: propranolol versus placebo in psychotrauma-related conditions (outcome: Hedges g for symptom severity reduction). CI = confidence interval; IV = inverse variance; SE = standard error.



**Figure 2:** Forest plot of rectified pooled analysis, updated with new and missed studies: propranolol versus placebo in psychotrauma-related conditions (outcome: Hedges g for symptom severity reduction). CI = confidence interval; IV = inverse variance; SE = standard error.

memory reconsolidation is beneficial. In our view, it seems that modesty is called for in interpreting results of studies suggesting that debilitating problems might be solved with some tablets of propranolol. If we face the complexities of memory reconsolidation, we still have a long way to go.

**Serge A. Steenen, MD, DMD; Roos van Westrhenen, MD, PhD; Jan de Lange, MD, DMD, PhD; Ad de Jongh, DMD, PhD**

**Affiliations:** From the Department of Oral and Maxillofacial Surgery, Amsterdam University Medical Centers/Academic Center for Dentistry (ACTA), University of Amsterdam, Amsterdam, The Netherlands (Steenen, de Lange); the Department of Oral Public Health, Academic Centre for Dentistry Amsterdam, University of Amsterdam and VU University Amsterdam, Amsterdam, The Netherlands (Steenen, de Jongh); the Parnassia Psychiatric Institute, Amsterdam, The Netherlands (van Westrhenen); the Department of Psychiatry and Neuropsychology, Maastricht University Medical Center, Maastricht, The Netherlands (van Westrhenen); the Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London, London, UK (van Westrhenen); the Institute of Health and Society, University of Worcester, Worcester, UK (de Jongh); the School of Psychology, Queen’s University, Belfast, Northern Ireland (de Jongh).

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