Letters

Response to: "Updated and rectified meta-analysis shows no effect of propranolol versus placebo on traumatic memory reconsolidation disruption"

In their letter to the editor, Steenen and colleagues[1] argue that the conclusions of our meta-analysis[2] on the clinical efficacy of reconsolidation impairment using propranolol are "incorrect in the context of (...) psychotrauma-related symptomatology." They claim that we did not assess risk of bias and critique our omission of 3 unpublished studies (Aikins,[3] Saladin,[4] and Orr[5]). We are not convinced by their attempt to rectify our analysis.

Although this is a matter of debate,[6] we were asked during the *JPN* peer review of our manuscript to omit unpublished data from our meta-analysis because the methodological quality of such studies is difficult to verify. Indeed, we could not verify important methodological information with respect to

the unpublished results (*n* = 6) of Aikins,[3] such as the adequacy of blinding methods. Moreover, we verified methodological information in the study by Orr[5] with the author himself and concluded that the data from this pre-emptively terminated (rather than unpublished) study with *n* = 5 randomized participants were not suitable for meta-analytic purposes. The inclusion of studies with very small samples in a meta-analysis (*n* ≤ 3 per group) is bound to compromise the precision of the overall effect estimate.[6]

We also could not verify important information such as the outcomes used to compute the effect size for Saladin's unpublished study of reconsolidation interference in participants with posttraumatic stress disorder (PTSD) and comorbid alcohol dependence.[4] Considering that Steenen and colleagues[1] argue against including studies of addiction (but see Gisquet-Verrier and colleagues[7]), it is unclear why they included Saladin's study in their analysis. But even more problematic, we found
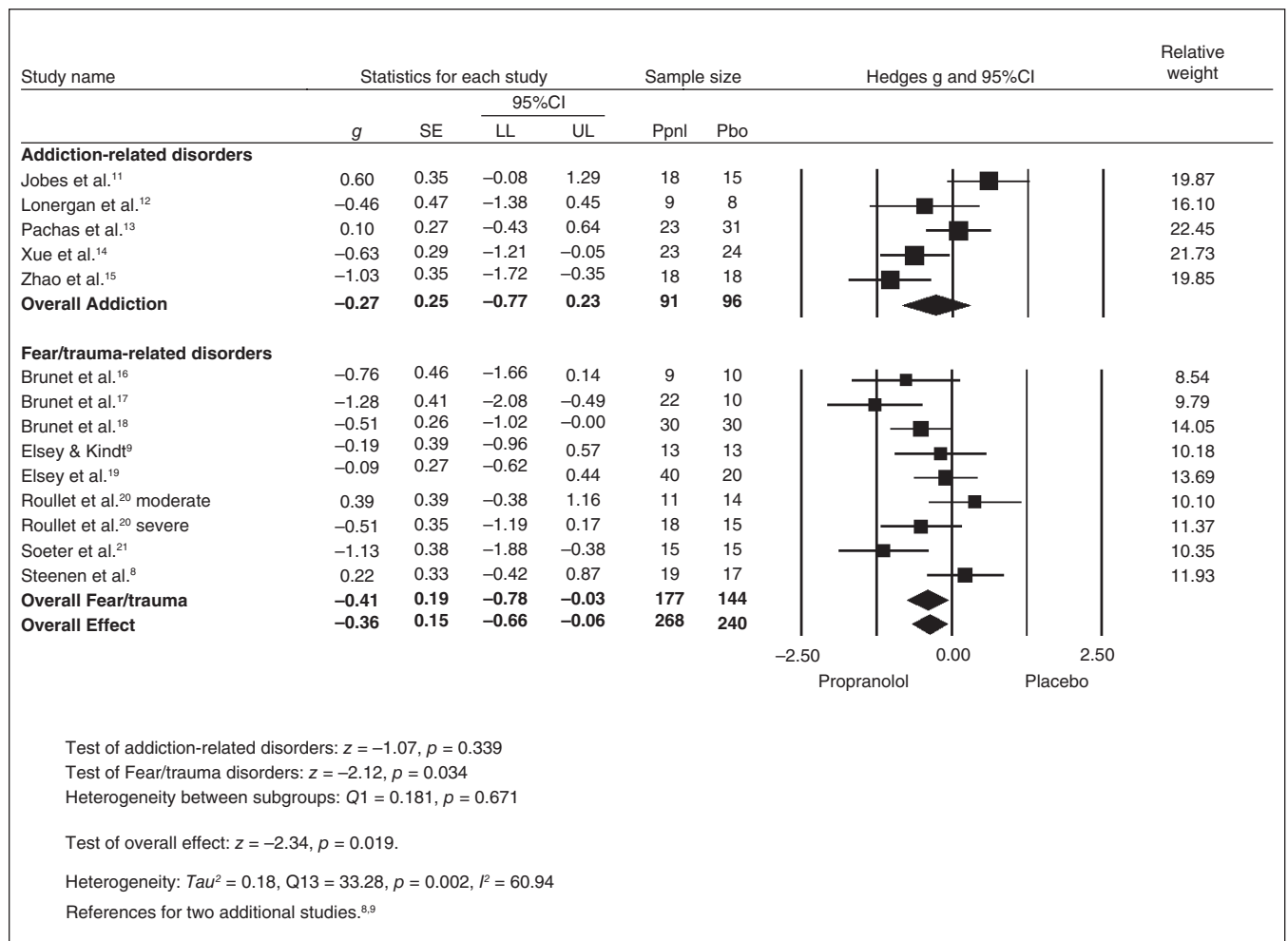

Figure 1: Forest plot results: reconsolidation interference by disorder. CI = confidence interval; LL = lower limit; Pbo = placebo; Ppnl = propranolol; SE = standard error; UL = upper limit.

discrepancies across public forums in how Saladin reported the results of this unpublished study,[4] casting reasonable doubts on the validity of the data used by Steenen and colleagues.[1] We also could not replicate the large effect size estimate of $d = -3.59$ that Steenen and colleagues[1] reported for the Saladin study,[4] as it seems to have been erroneously computed using standard errors rather than standard deviations on a measure of subjective distress to trauma and alcohol cues (based on data available at https://clinicaltrials.gov/ct2/show/results/NCT01055171?term = propranolol+and+alcohol&draw = 2&rank = 2&view = results). Scrutiny indicates that we were justified to not include such unpublished studies.

Steenen and colleagues[1] re-analyzed our data by excluding a number of studies that they deemed had high risk of bias (retaining only 4), adding to these the 3 unpublished studies mentioned above. They also included 2 studies published after our paper was completed and accepted for publication (see Steenen and colleagues[8] and Elsey and Kindt[9]). Exactly how they concluded that this set of studies had low risk of bias is not specified. Moreover, their computation of the effect size for Elsey and Kindt's phobia study suggests a possible outcome selection bias.[9] It appears that Steenen and colleagues[1] computed an effect size of $d = 0.45$ using the Behavioural Avoidance Test (reporting $n = 0$ per group when it appears to have been $n = 13$ per group). However, Elsey and Kindt also measured phobia severity with a posttreatment self-report questionnaire.[9] All available outcome data should be included in a meta-analysis to minimize bias;[10] this does not seem to have been considered by Steenen and colleagues.[1]

We agree that it would have been appropriate to include these 2 studies in our meta-analysis had they been available. However, a re-analysis of our data with these studies included indicates that our finding remains (Figure 1). Although not mentioned by Steenen and colleagues,[1] we noted in our original meta-analysis that study quality was assessed and did not significantly moderate the overall outcome effect.[2]

Considering these important issues, Steenen and colleagues'[1] results cannot and should not constitute evidence against our rigorous meta-analysis. Rather, we argue that our meta-analysis provides empirical support in favour of a reconsolidation-based treatment method involving narrative and pharmacological interventions that are more efficacious than simply giving "some tablets of propranolol."

Alain Brunet, PhD; Michelle Lonergan, PhD; Sereena Pigeon, MSc; Daniel Saumier, PhD; Scott Orr, PhD; Roger Pitman, MD

Affiliations: From the Department of Psychiatry, McGill University, Montreal, Que. (Brunet); the Douglas Mental Health University Institute, Montreal, Que. (Brunet, Saumier); the School of Psychology, University of Ottawa, Ottawa, Ont. (Lonergan); the Department of Educational & Counseling Psychology, McGill University, Montreal, Que. (Pigeon); the Department of Psychology, University of Sherbrooke, Longueuil, Que. (Saumier); the Department of Psychiatry, Harvard Medical School, Charlestown, Mass. (Orr, Pitman).

References

1. Steenen S, van Westrhenen R, de Lange J, et al. Updated and rectified meta-analysis shows no effect of propranolol versus placebo on traumatic memory reactivation disruption. *J Psychiatry Neurosci* 2022;47:E336-7.
2. Pigeon S, Lonergan M, Rotondo O, et al. Impairing memory reconsolidation with propranolol in healthy and clinical samples: a meta-analysis. *J Psychiatry Neurosci* 2022;47:E109-22.
3. Aikins D. Using propranolol to block memory reconsolidation in female veterans with PTSD. Fort Detrick (MD): Army Medical Research and Materiel Command; 2015. Available: https://apps.dtic.mil/sti/pdfs/AD1005283.pdf (accessed 2022 June 1).
4. Saladin ME. Treatment implications of trauma memory modulation for PTSD & alcohol dependence. ClinicalTrials.gov: NCT01055171; 2016. Available: https://clinicaltrials.gov/ct2/show/study/NCT01055171 (accessed 2022 June 1).
5. Orr SP. PTSD symptom reduction by propranolol given after memory activation. ClinicalTrials.gov: NCT00645450; 2019. Available: https://clinicaltrials.gov/ct2/show/NCT00645450 (accessed 2022 June 1).
6. Schmucker CM, Blümle A, Schell LK, et al.; OPEN consortium. Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. *PLoS One* 2017;12:e0176210.
7. Gisquet-Verrier P, Le Dorze C. Post-traumatic stress disorder and substance use disorder as two pathologies affecting memory reactivation: Implications for new therapeutic approaches. *Front Behav Neurosci* 2019;13:26.
8. Steenen SA, Su N, van Westrhenen R, et al. Perioperative propranolol against dental anxiety: a randomized controlled trial. *Front Psychiatry* 2022;13:842353.
9. Elsey JW, Kindt M. Placebo and non-specific effects in reconsolidation-based treatment for arachnophobia. *Front Psychiatry* 2021;12:775770.
10. Kirkham JJ, Altman DG, Chan AW, et al. Outcome reporting bias in trials: a methodological approach for assessment and adjustment in systematic reviews. *BMJ* 2018;362:k3802.
11. Jobes ML, Aharonovich E, Epstein DH, et al. Effects of pre-reactivation propranolol on cocaine craving elicited by imagery script/cue sets in opioid-dependent polydrug users: a randomized study. *J Addict Med* 2015;9:491-8.
12. Lonergan M, Saumier D, Tremblay J, et al. Reactivating addiction-related memories under propranolol to reduce craving: a pilot randomized controlled trial. *J Behav Ther Exp Psychiatry* 2016;50:245-9.
13. Pachas GN, Gilman J, Orr SP, et al. Single dose propranolol does not affect physiologic or emotional reactivity to smoking cues. *Psychopharmacology (Berl)* 2015;232:1619-28.
14. Xue Y-X, Deng J-H, Chen Y-Y, et al. Effect of selective inhibition of reactivated nicotine-associated memories with propranolol on nicotine craving. *JAMA Psychiatry* 2017;74:224-32.
15. Zhao LY, Sun LL, Shi J, et al. Effects of beta-adrenergic receptor blockade on drug-related memory reconsolidation in abstinent heroin addicts. *Drug Alcohol Depend* 2011;118:224-9.
16. Brunet A, Orr SP, Tremblay J, et al. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res* 2008;42:503-6.
17. Brunet A, Thomas É, Saumier D, et al. Trauma reactivation plus propranolol is associated with durably low physiological responding during subsequent script-driven traumatic imagery. *Can J Psychiatry* 2014;59:228-32.
18. Brunet A, Saumier D, Liu A, et al. Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. *Am J Psychiatry* 2018;175:427-33.
19. Elsey JWB, Filmer AI, Galvin HR, et al. Reconsolidation-based treatment for fear of public speaking: a systematic pilot study using propranolol. *Transl Psychiatry* 2020;10:179.
20. Roullet P, Vaiva G, Véry E, et al. Traumatic memory reactivation with or without propranolol for PTSD and comorbid MD symptoms: a randomised clinical trial. *Neuropsychopharmacology* 2021;46:1643-9.
21. Soeter M, Kindt M. An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. *Biol Psychiatry* 2015;78:880-6.