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Authors' Reply to Pappagallo et al.: Comment on “Novel Glutamatergic Modulators for the Treatment of Mood Disorders: Current Status”

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We read with interest the comment by Dr. Pappagallo and colleagues [1], written in response to our recently published review article [2].

The authors highlight the putative risk and safety profile of dextromethadone (REL-1017). In particular, they note that a recent statement from the US Drug Enforcement Administration states that dextromethadone “lacks significant respiratory depressant action and abuse liability” [3]. This important point certainly adds to our growing base of knowledge about dextromethadone. However, few real-world data exist for its use in depression, and this is the basis for our caution. In particular, the currently available data indicate that few patients with depression have received dextromethadone [4–6].

Nevertheless, we believe that this agent holds promise, which is why we included it in our review [2]. We thank Dr Pappagallo and colleagues for their comments [1] and look forward to seeing the results of the Phase 3 trial of dextromethadone that is now underway ([NCT04688164](https://clinicaltrials.gov/ct2/show/study/NCT04688164)).

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Conflict of interest

Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2R,6R)-hydroxynorketamine, (S)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose, financial or otherwise.

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Authors' contributions All authors contributed equally to the writing of this letter and approved the final version of the letter.

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