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LETTER TO THE EDITOR

Comment on "Novel Glutamatergic Modulators for the Treatment of Mood Disorders: Current Status"

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We truly appreciated the thorough article by Henter and colleagues published in the May 2021 issue of *CNS Drugs* titled "Novel Glutamatergic Modulators for the Treatment of Mood Disorders: Current Status" [1].

In regard to dextromethadone, the authors state: "as an enantiomer of the opioid methadone, concerns persist about its abuse and dependence potential" [1]. Chiral configuration is known to impart opioid activity to molecules: as a rule, for chiral molecules, only one of the two enantiomers is opioid active. In regard to methadone, dextromethadone is the opioid-inactive enantiomer and levomethadone is the opioid-active enantiomer [2–7]. According to a recent US Drug Enforcement Administration statement on racemic methadone, dextromethadone "lacks significant respiratory depressant action and abuse liability" [8]. Dextromethorphan, another molecule discussed by the authors as a potentially rapid-acting antidepressant [1], is the dextroisomer of a full opioid agonist drug, racemethorphan, and, like dextromethadone, it does not have clinically meaningful opioid agonist activity, in contrast with the levoisomer, levomethorphan.

We agree with the authors about the need to fully characterize the abuse potential of novel antidepressants, including dextromethadone. However, we hope that overconcern about abuse will not unjustifiably bias the development of potentially safe and highly effective medications that may impact on disease mechanisms of mood disorders and bring meaningful and lasting changes in the quality of life of suffering patients.

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Declarations

Conflicts of interest Marco Pappagallo, Charles Inturrisi and Paolo Manfredi are paid consultants for Relmada Therapeutics. Charles Inturrisi and Paolo Manfredi are inventors on patents and patent applications related to dextromethadone.

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