

Reasons for Maintaining the Classification of Esmethadone as an Investigational Uncompetitive NMDAR Antagonist Rapid Antidepressant:

Reply to Ferré and Michaelides

To the Editor: We appreciate the opportunity to respond to the letter by Drs. Ferré and Michaelides¹ regarding the mechanistic characterization of esmethadone (*S*-methadone).

In their letter, Ferré and Michaelides raise two main concerns in relation to the article by Fava and colleagues² titled “Long-Term Safety and Efficacy of Esmethadone in Patients with Major Depressive Disorder: Findings From a 12-Month Open-Label Study.” Their first concern relates to the classification by Fava and colleagues of esmethadone as a novel uncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist; their second concern is related to a statement regarding esmethadone’s lack of meaningful abuse liability.

Ferré and Michaelides exclude uncompetitive NMDAR antagonism as a plausible mechanism for the rapid antidepressant effects of esmethadone, based on the autoradiography and hot plate experiments presented by Levinstein and colleagues.³ We have already presented the reasons for maintaining the classification of esmethadone among the emerging class of uncompetitive NMDAR antagonists with therapeutic potential as rapid antidepressants in a letter to the editor of *Molecular Psychiatry*,⁴ which commented the Levinstein article.³ We have also seen Levinstein’s reply.⁵

As outlined by Dr. Pappagallo and colleagues,⁴ uncompetitive NMDAR antagonists may be uniquely effective as clinically tolerated rapid antidepressants because they only bind and block open channels (activity-dependent) at graded resting membrane potential in circuits relevant for major depressive disorder

(MDD).^{6–12} Importantly, esmethadone is a positively charged molecule at physiological pH¹³ and a low-affinity, high trapping uncompetitive NMDAR antagonist, which is expected to preferentially block pathologically hyperactive GluN2D subunit-containing NMDARs, the NMDAR subtype most sensitive to ambient glutamate and with the highest open-probability during graded resting membrane potential.⁸ Additionally, in order to be blocked by esmethadone, NMDARs must be in the open configuration (bound by glutamate and glycine) and free of Mg²⁺ at resting membrane potential. Under physiological conditions, most NMDAR are blocked by Mg²⁺ at resting membrane potential.¹⁴ Finally, these pathologically hyperactive GluN2D-containing NMDARs susceptible to esmethadone block are expected to be only expressed by relatively few neurons within the brain circuits relevant for MDD.^{9,10} This very selective NMDAR engagement by low-affinity uncompetitive NMDAR antagonists allows therapeutic effects without dissociative effects. The autoradiography experiment by Levinstein measures in vivo global receptor occupancy at NMDARs (via [³H]MK-801) in rat brain tissue. This experiment demonstrated that esmethadone does not measurably displace MK-801, indicating no detectable global NMDAR occupancy. However, this experiment lacks sensitivity for detecting esmethadone engagement at subtype-selective receptors (GluN2D-containing NMDARs), which are pathologically hyperactive at resting membrane potential and are localized within MDD relevant circuitry. The NMDAR interactions by esmethadone

postulated for its antidepressant and neuroplasticity effects are expected to occur below the detection threshold of the autoradiography experiment performed by Levinstein.

Uncompetitive NMDAR antagonists showing MK-801 displacement in the experiment by Levinstein would likely cause dissociative effects in humans because of global interference with physiological NMDAR activity during action potential in neurons relevant for cognitive processing. Notably, esmethadone doses up to 6–8 times higher than the daily dose used in MDD trials did not show signals of dissociative effects in healthy volunteers or in recreational users.^{15,16}

Selective block of hyperactive NMDARs at resting membrane potential was shown to reverse depressive-like behavior and to restore impaired neural plasticity over a decade ago.⁶ Those studies paved the way for the “homeostatic synaptic plasticity” hypothesis, one of the leading hypotheses for the mechanism of action of uncompetitive NMDAR antagonists as rapid antidepressants.^{7,9–12,17} In summary, Levinstein’s negative NMDAR occupancy result by esmethadone is consistent with the proposed mechanism of action of esmethadone as a nondissociative rapid antidepressant and is not adequate to convincingly argue against subtype-specific and brain region-specific NMDAR engagement, which is activity-dependent at graded resting potential in neurons localized within dysfunctional depression-related brain circuits.

Ferré and Michaelides go on to interpret Levinstein’s hot plate results showing analgesia with high-dose esmethadone as a demonstration of

opioid agonist effects and extend this interpretation to propose that esmethadone's antidepressant effects are mediated via opioid agonism. It should be noted that antidepressant-like effects were seen at 10 mg/kg esmethadone¹⁸; in contrast, at this dose, hot plate analgesic effects were minimal or absent.^{3,19}

The dose by Levinstein associated with consistent analgesia was 30 mg/kg. When such high doses are used, different receptor systems are likely to be recruited, including the glutamatergic system. Klein and colleagues demonstrated that ketamine's antidepressant-like effects are blocked by naltrexone but are not due to MOR agonism; they showed that endogenous opioid tone is permissive and necessary for ketamine's antidepressant-like effects.²⁰ Thus, esmethadone's antidepressant effects may also require both NMDA and opiate receptor signaling¹⁰ but are not due to direct opioid agonism, similar to what has been concluded in experiments with ketamine.²⁰

As an antidepressant candidate, 25 mg esmethadone was found to produce rapid and sustained antidepressant effects. Consistent effects, without additional benefit, were seen with 50 mg. Sustained antidepressant effects were noted after drug discontinuation, with no evidence of withdrawal. If the clinical antidepressant effects reported by Fava and colleagues^{2,21,22} were opioid related, we would expect heightened effects with doubling the dose. More importantly, opioid agonist effects would be expected to quickly disappear upon discontinuation and not be sustained, as was noted with esmethadone's antidepressant effects. Using body surface area (BSA) scaling, the human equivalent dose for 30 mg/kg in rats, which was consistently analgesic in Levinstein's hot plate experiments, corresponds to approximately 5 mg/kg, or approximately 300 mg/day for a 60 kg human adult, well above the maximum human-tolerated dose.^{15,23} Thus, the

potential antidepressant-effective dose in humans (25 mg/day) is less than 1/10 of the equivalent rat dose required to induce analgesia. The lower antidepressant-like rat dose (10 mg/kg)¹⁸ and the lower potentially effective dose in humans^{2,20,21} further support nonopioid antidepressant mechanisms.

Opioid agonist drugs are known to cause euphoria and improve mood and have been used in the past as antidepressants, before it became clear that their efficacy as antidepressants was offset by tolerance, withdrawal, and risk of addiction.²⁴

The second concern raised by Ferré and Michaelides is related to a sentence in the Fava article discussing the lack of abuse potential of esmethadone: "Within the racemic opioid compound, esmethadone may function as an opioid antagonist to reduce the opioid agonist effects of levomethadone."² In their letter,¹ Ferré and Michaelides summarize their own experimental findings by stating that "S-methadone binds but specifically loses its efficacy for the MOR that forms heteromers with Gal₁R, acting as a competitive antagonist." These 2 statements are, in fact, complementary, both referring to the same phenomenon of functional antagonism, both supporting the lack of meaningful abuse potential seen in clinical trials, and do not represent a contradiction.

The effects of esmethadone in humans have been characterized in healthy volunteers, recreational substance users, and patients with MDD.^{2,15,16,20,21} Across all clinical trials, there is no meaningful evidence for typical opioid effects, including no euphoria, respiratory depression, sedation, withdrawal, constipation, or signal for abuse potential.

In another recent article, Levinstein and colleagues²⁵ argue that the mechanism of action for the rapid antidepressant component of ketamine's effects is also related to opioid agonism. Ketamine, esketamine, dextromethorphan, and

memantine, molecules classified as uncompetitive NMDAR antagonists, are in clinical use and FDA-approved for various indications, including anesthesia, treatment-resistant depression, MDD, pseudobulbar affect, cough suppression, and moderate-to-severe Alzheimer disease. Esketamine and dextromethorphan/bupropion are approved for MDD indications. Esmethadone is under development as adjunctive treatment for MDD. As stated before, the comparative in vitro activity of these molecules at NMDARs was characterized in vitro by Bettini and colleagues.⁸ It is important to emphasize that when these molecules are administered to patients, the classic opioid effects of euphoria, addiction, tolerance, withdrawal, respiratory depression, or constipation are not seen. While ketamine and dextromethorphan exhibit abuse liability, they do not cause respiratory depression or show naloxone reversibility, hallmarks of opioid toxicity. Focusing on esmethadone, there are no documented cases of overdose or abuse involving esmethadone, and the maximum tolerated dose in clinical studies is related to vomiting, rather than sedation and respiratory depression.¹⁵ Furthermore, esmethadone and memantine, both devoid of clinically meaningful opioid-like effects, have not been found to induce typical dissociative NMDAR effects, and, as expected, both lack meaningful abuse potential. We think that this may be due to lower affinity (esmethadone) and lower trapping (memantine) at NMDARs, respectively, compared to ketamine.^{8,26} The clinical effects of these two uncompetitive NMDAR antagonists are clearly different from those of opioid agonists, including racemic methadone (*R,S*-methadone) and racemethorphan (*R,S*-methorphan), both potent racemic opioid agonists that include in their composition esmethadone and dextromethorphan, together with levomethadone and levomethorphan, respectively, confirming

stereoselective opioid agonist effects for the levoisomers and relative inactivity for opioid-like effects for the dextroisomers of both racemates. However, some of these molecules, currently characterized as uncompetitive NMDARs, also bind and likely activate other receptors, including opioid receptors, but the contribution of these pathways to their clinical effects is unclear. In summary, as supported by converging *in vitro*, *in vivo*, and clinical evidence, esmethadone and ketamine should continue to be classified as uncompetitive NMDAR antagonists, and not reclassified as opioid agonist antidepressant drugs as suggested by Ferré and Michaelides and Levinstein and colleagues.^{3,5,25} The discovery and characterization of the antagonist activity of esmethadone at the MOR-Gal₁R heteromer by Levinstein and colleagues is an example of the importance of moving beyond affinity when unraveling the mechanism of action of molecules.

For the reasons expressed above, the “homeostatic synaptic plasticity hypothesis,”^{7,12,27} first introduced for ketamine, and later repropose for esmethadone,^{9,10} is not contradicted by Levinstein’s experiments. The clinical pharmacology of esmethadone, showing no meaningful typical opioid effect across studies spanning decades and hundreds of subjects,^{2,15,18,21,22,28–30} is not reversed by Levinstein’s autoradiography and hot plate results, for the reasons detailed above. Instead, Levinstein’s experimental results complement prior experimental results for esmethadone, indicating lack of typical opioid effects at clinically meaningful doses.^{19,31–35} Additionally, Levinstein’s discovery that esmethadone loses efficacy at MORs forming heteromers with Gal₁R may provide a mechanistic explanation for the signals for improvements in opioid use disorder outcomes observed after the transition from racemic methadone to R-methadone.³⁶

The most compelling reason for not classifying ketamine and esmethadone

as opioid agonist drugs is that their clinical pharmacology profiles differ fundamentally from those of classical opioid agonist.

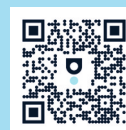
We agree that further studies are needed to definitively elucidate the mechanisms underlying the rapid antidepressant effects of uncompetitive NMDAR antagonists. In the meantime, the opioid agonist hypothesis proposed by Levinstein and colleagues for esmethadone and ketamine^{3,5,25} remains a third line hypothesis, as also reflected in recent reviews prioritizing glutamatergic modulation and neuroplasticity rather than opioid receptor agonism.^{10,17} Emerging clinical data on nondissociative uncompetitive NMDAR antagonists devoid of meaningful opioid agonist effects, including esmethadone, may help refine our understanding of these mechanisms and offer insights in MDD pathophysiology. Although we do not support their opioid agonist hypothesis as the primary explanation for the antidepressant effects of ketamine or esmethadone, we wish to commend Levinstein and colleagues²⁵ for their valuable contribution to advancing this important and rapidly evolving field of psychopharmacology.

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Mattarei, and Comai are inventors on patents related to esmethadone. Drs. Inturrisi and Manfredi are co-owners of technology related to esmethadone. The authors of this letter wish to further disclose that the determination of the antidepressant mechanism of action of esmethadone may have a direct impact on the schedule (ie, schedule II to V) classification of esmethadone, and ultimately on its availability to patients and commercial prospects.

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