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Time will tell. Reply to “Comments to pharmacological and behavioral divergence of ketamine enantiomers by Jordi Bonaventura et al.” by Chen et al

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We thank Chen et al. for their commentary[1] on our study[2] which focused on the pharmacological pleiotropy of (R,S)-ketamine's enantiomers, and in particular, their interactions with opioid receptors and their performance in preclinical assays predictive of human abuse liability. Based on our experimental findings, and prior work, we made three main conclusions: (i) the clinical effects of racemic ketamine ((R,S)-ketamine) should not be attributed exclusively to NMDA receptor (NMDAR) antagonism but may also involve mu (MOR) and kappa (KOR) opioid receptors, (ii) the abuse liability profile of (R,S)-ketamine is likely due to (S)-ketamine's pharmacological effects, and (iii) if (R)-ketamine is effective at treating depression, it should be preferred over (S)-ketamine, because of its

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Contributions

J.B., Y.S. C.J.Z. and M.M. wrote the manuscript with input from all coauthors. All authors critically reviewed the content and approved the final version before submission.

lower preclinical abuse liability profile. In their commentary, Chen et al.[1] state that these conclusions are not justified. We address their criticisms below.

Clinical effects of (R,S)-ketamine should not be attributed exclusively to NMDAR antagonism but may also involve opioid receptors

(R,S)-ketamine binds to and activates MORs and KORs [2, 3] and its efficacy has been associated with endogenous opioid activity[4]. Yet, in their commentary[1], Chen et al. claim that (R,S)-ketamine's and (S)-ketamine's antidepressant effects are exclusively due to NMDAR antagonism. This interpretation, however, is not supported by recent findings[3]. For example, Williams et al.[5] showed that the preferential MOR antagonist naltrexone decreased (R,S)-ketamine's antidepressant but not its dissociative effects. This finding suggests that (R,S)-ketamine's antidepressant effects are mediated by MORs, do not require NMDAR antagonism, and that NMDAR-dependent dissociative effects are not required for (R,S)-ketamine's antidepressant effects.

Additional evidence to the notion that (R,S)-ketamine's effects are mediated by MORs is a recent study[6] reporting rapid antidepressant effects of REL-1017, the (S)- enantiomer of the MOR agonist (R,S)-methadone. REL-1017 is also a MOR agonist ($K_i \sim 20$ nM, $EC_{50} \sim 600$ nM)[7, 8] that shows weak NMDAR antagonism ($K_i \sim 7.4$ μ M)[9]. As expected, REL-1017 did not induce dissociation at antidepressant doses[6]. Other evidence against the notion that (R,S)-ketamine's antidepressant effects are mediated exclusively by NMDARs is that NMDAR antagonists like MK-801 and memantine do not show reliable antidepressant-like effects in rodent models, and clinical studies with selective NMDA antagonists were not successful[3].

Finally, Chen et al.[1] estimate the free concentration of (S)-ketamine in the human brain at antidepressant doses to be ~ 0.4 μ M, which, based on its binding affinity, would represent only a 5% occupancy at MORs. However, even low occupancy levels at GPCRs could cause significant signaling and receptor internalization, depending on the receptor reserve, the state of the receptor, and the machinery it is coupled to. Hence, binding affinity is rarely correlated with *in vivo* efficacy[10].

The abuse liability profile of (R,S)-ketamine is likely due to the pharmacological actions of (S)-ketamine

Chen et al.[1] state that this conclusion overlooks the likelihood that if (R)-ketamine is used to treat depression, achieving antidepressant effects would require doses equipotent at NMDARs to (S)-ketamine's dose and that this would result in comparable abuse liability. This argument is centered on the assumptions that NMDAR antagonism is the sole mechanism responsible for (R,S)-ketamine's clinical effects and that (S)-ketamine and (R)-ketamine would exhibit similar effects at equipotent concentrations. However, in studies that looked at antidepressant-like effects in rodents, equipotent doses of (R)-ketamine have typically been similar, if not lower, than (R,S)-ketamine[11, 12]. Additionally, our intravenous self-administration (IVSA) data do not support this argument. The rats failed to

acquire reliable self-administration of (R)-ketamine at a training dose of 0.5 mg/kg/infusion even though they pressed the lever, averaging ~15 infusions/h leading to an (R)-ketamine dose of ~7.5 mg/kg/h. A prior study suggested that ~1.5 mg/kg, IV, (R,S)-ketamine over 40 min in rats produces equivalent NMDAR occupancy as a human antidepressant dose (i.e., 0.5 mg/kg, IV, over 40 min)[13]. In our study, rats were exposed to a ~5-fold greater (R)-ketamine dose (i.e., ~7.5 mg/kg/h) than the rat (R,S)-ketamine dose estimated to lead to equivalent NMDAR occupancy as a human antidepressant dose. Notably, doses of drugs self-administered by rats are higher than doses used by humans or self-administered by monkeys. Therefore, the (R)-ketamine dose range in our study would be sufficient to engage NMDARs at a similar or greater occupancy level necessary for (R,S)-ketamine's human antidepressant effects.

In contrast, rats reliably pressed more for the same (S)-ketamine unit dose, receiving a dose of ~20 mg/kg during the same conditions (~2.5-fold difference over (R)-ketamine) and acquired IVSA. Notably, the rats did not increase their pressing for (R)-ketamine even when the unit dose was increased to 1 mg/kg/infusion (a cumulative dose of ~15 mg/kg/h). In contrast, the lowest (S)-ketamine dose that was self-administered was 0.125 mg/kg/infusion and at this dose rats received more than double the infusions of (S)-ketamine than (R)-ketamine. This (S)-ketamine dose is 4-fold lower than the (R)-ketamine training dose, suggesting that the (R)-ketamine dose used for IVSA acquisition was equipotent to the minimum dose at which rats lever-pressed for (S)-ketamine. An optimal experiment would be to show that rats exposed to a unit dose of 0.125 mg/kg (S)-ketamine during training would acquire IVSA. Given that rats acquire IVSA at 0.125 mg/kg of (R,S)-ketamine[14], it is likely that a similar or perhaps even lower (S)-ketamine dose would also induce reliable IVSA.

In their argument regarding equipotency of the two enantiomers, Chen et al. do not account for their known pharmacokinetic differences. Prior studies have shown that (S)-ketamine has faster elimination[15] and is more rapidly metabolized[16] than (R)-ketamine. This may lead to greater brain exposure of (R)-ketamine at equimolar doses, a result that is supported by our biodistribution experiments[2].

Chen et al. claimed that (R,S)-ketamine's abuse liability is mediated by its dissociative effects. This interpretation is consistent with the greater abuse liability we observed for (S)-ketamine in our preclinical assays, and recent human findings suggesting that (R)-ketamine has less side-effects than (S)-ketamine[15]. Furthermore, this notion is consistent with results of Øye et al.[17] who reported that NMDAR-mediated sensory effects required a 4-fold greater dose of (R)-ketamine than (S)-ketamine[17]. Interestingly, another study[18] found that at equimolar doses of (S)- and (R)-ketamine, only (S)-ketamine produced dissociation and brain activity, indicating that the two enantiomers engage different brain mechanisms, a finding also supported by our study[2, 19].

Taken together, the above indicate that Chen et al.'s[1] argument for increasing the dose of (R)-ketamine to match equivalent occupancy of NMDARs by (S)-ketamine does not necessarily mean that the two enantiomers will have similar abuse liability.

If (R)-ketamine is effective for treating depression, it would be preferred over (S)-ketamine, because of its lower preclinical abuse liability profile

Chen et al. correctly stated[1] that clinical evidence regarding the antidepressant effects of either enantiomer is limited. Although (R)-ketamine seems promising, results from the only study performed to date are inconclusive[20] and consequently, it is unknown whether (R)-ketamine doses that produce antidepressant effects will also produce dissociation. Importantly, even though FDA-approved, the efficacy of intranasal (S)-ketamine itself requires more long-term systematic studies[21, 22].

Chen et al. also correctly stated[1] that the only approved clinical indication for (R,S)-ketamine or its enantiomers in the subanesthetic dose range is the approved use of (S)-ketamine for reducing depressive symptoms in patients with treatment-resistant depression or major depressive disorder with acute suicidal ideation. As of 2017, the off-label use of (R,S)-ketamine had been increasing over the previous decade[23] and it is likely that this trend has continued since then. It is currently unknown whether (R,S)-ketamine is more effective than (S)-ketamine and comparative clinical trials are underway. Nevertheless, a recent study that compared (R,S)-ketamine with (S)-ketamine on standardized neuropsychological and psychopathological measures concluded that (R)-ketamine was not responsible for the psychotomimetic effects of (S)-ketamine and the authors suggested that antidepressant doses of (R,S)-ketamine should include (R)-ketamine with an ideal enantiomer ratio ranging from 2:1 to 4:1 (R)-ketamine:(S)-ketamine[24].

Overall, the preclinical literature supports the notion that (R)-ketamine produces greater antidepressant-like effects than (S)-ketamine at equipotent doses and that (R)-ketamine shows potential for less side effects[24, 25]. Our data indicate that antidepressant-like doses of (S)-ketamine are self-administered in a rat model predictive of human abuse liability[26], while antidepressant doses of (R)-ketamine are not. However, whether these findings will translate to the human condition is of course an empirical question and a subject for future research, and time will tell.

Finally, we acknowledged that our preclinical data suggest that recreational non-medical use of (S)-ketamine is less likely to result in a substance use disorder (as defined by DSM-5) than opioid or psychostimulant drugs[2]. Chen et al.[1] argued that because the drug is being administered in a restricted clinical setting, it is unlikely to be harmful. However, abuse potential is defined as the tendency of a drug to be used in non-medical situations, and it is important to keep in mind that (S)-ketamine's approval was accompanied by a boxed warning for abuse liability. In fact, addictive opioid drugs are very safe in a clinical "controlled" environment. However, some individuals who are exposed to opioids in a clinical setting may eventually develop opioid addiction or use disorder. Since (R,S)-ketamine has known abuse potential, we do not think that it is misleading to state that (S)-ketamine, which is more potent than (R,S)-ketamine, may lead a subset of vulnerable patients to seek non-prescribed ketamine in a non-clinical setting[19, 27, 28].

Acknowledgments

Conflict of interest

CAZ is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation. CAZ is listed as co-inventor on a patent for the use of (2R,6R)- hydroxynorketamine, (S)-dehydronorketamine, and other stereo- isomeric dehydro 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 posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. PJM and CJT are coinventors on patents regarding the use and methods of production for (2R,6R)-hydroxynorketamine. They have assigned their patent rights to the US government but will share a percentage of any royalties that may be received by the government. M.M. has received research funding from AstraZeneca, Redpin Therapeutics, and Attune Neurosciences. All other authors declare no conflict of interest.

References

- Chen G, Mannens G, De Boeck M, Daly EJ, Canuso CM, Teuns G, et al. Comments to pharmacological and behavioral divergence of ketamine enantiomers by Jordi Bonaventura et al. *Mol Psychiatry*. 2022;in press.
- Bonaventura J, Lam S, Carlton M, Boehm MA, Gomez JL, Solís O, et al. Pharmacological and behavioral divergence of ketamine enantiomers: implications for abuse liability. *Mol Psychiatry*. 2021. 2021. 10.1038/s41380-021-01093-2.
- Hess EM, Riggs LM, Michaelides M, Gould TD. Mechanisms of ketamine and its metabolites as antidepressants. *Biochem Pharmacol*. 2022;197:114892. [PubMed: 34968492]
- Pacheco DDF, Romero TRL, Duarte IDG. Central antinociception induced by ketamine is mediated by endogenous opioids and μ - and δ -opioid receptors. *Brain Res*. 2014;1562:69–75. [PubMed: 24675031]
- Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *Am J Psychiatry*. 2018;175:1205–1215. [PubMed: 30153752]
- Fava M, Stahl S, Pani L, De Martin S, Pappagallo M, Guidetti C, et al. REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial. 10.1176/appi.ajp.2021.21020197.
- Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther*. 1995;274. [PubMed: 7562560]
- Matsui A, Williams JT. Activation of μ -opioid receptors and block of KIR3 potassium channels and NMDA receptor conductance by l- and d-methadone in rat locus coeruleus. *Br J Pharmacol*. 2010;161:1403–1413. [PubMed: 20659105]
- Gorman AL, Elliott KJ, Inturrisi CE. The d- and l- isomers of methadone bind to the non-competitive site on the N-methyl-d-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett*. 1997;223:5–8. [PubMed: 9058409]
- Kenakin T, Christopoulos A. Analytical pharmacology: The impact of numbers on pharmacology. *Trends Pharmacol Sci*. 2011;32:189–196. [PubMed: 21397341]
- Zhang JC, Li SX, Hashimoto K. R (-)-ketamine shows greater potency and longer lasting antidepressant effects than S (+)-ketamine. *Pharmacol Biochem Behav*. 2014;116:137–141. [PubMed: 24316345]
- Zanos P, Highland JN, Liu X, Troppoli TA, Georgiou P, Lovett J, et al. (R)-Ketamine exerts antidepressant actions partly via conversion to (2R,6R)-hydroxynorketamine, while causing adverse effects at sub-anaesthetic doses. *Br J Pharmacol*. 2019;176:2573–2592. [PubMed: 30941749]
- Shaffer CL, Osgood SM, Smith DL, Liu J, Trapa PE. Enhancing ketamine translational pharmacology via receptor occupancy normalization. *Neuropharmacology*. 2014;86:174–180. [PubMed: 25063581]

14. De Luca MT, Badiani A. Ketamine self-administration in the rat: Evidence for a critical role of setting. *Psychopharmacology (Berl)*. 2011;214:549–556. [PubMed: 21069515]
15. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth*. 1993;70:666–671. [PubMed: 8329260]
16. Portmann S, Kwan HY, Theurillat R, Schmitz A, Mevissen M, Thormann W. Enantioselective capillary electrophoresis for identification and characterization of human cytochrome P450 enzymes which metabolize ketamine and norketamine in vitro. *J Chromatogr A*. 2010;1217:7942–7948. [PubMed: 20609441]
17. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *J Pharmacol Exp Ther*. 1992;260.
18. Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol*. 1997;7:25–38. [PubMed: 9088882]
19. Heifets BD, Bentzley BS, Williams N, Schatzberg AF. Unraveling the opioid actions of S-ketamine and R-ketamine: comment on Bonaventura et al. *Mol Psychiatry* 2021 2611. 2021;26:6104–6106. [PubMed: 34006965]
20. Leal GC, Bandeira ID, Correia-Melo FS, Telles M, Mello RP, Vieira F, et al. Intravenous arketamine for treatment-resistant depression: open-label pilot study. *Eur Arch Psychiatry Clin Neurosci*. 2021;271:577–582. [PubMed: 32078034]
21. Takahashi N, Yamada A, Shiraishi A, Shimizu H, Goto R, Tominaga Y. Efficacy and safety of fixed doses of intranasal Esketamine as an add-on therapy to Oral antidepressants in Japanese patients with treatment-resistant depression: a phase 2b randomized clinical study. *BMC Psychiatry*. 2021;21:1–13. [PubMed: 33388029]
22. Sapkota A, Khurshid H, Qureshi IA, Jahan N, Went TR, Sultan W, et al. Efficacy and Safety of Intranasal Esketamine in Treatment-Resistant Depression in Adults: A Systematic Review. *Cureus*. 2021;13.
23. Wilkinson ST, Toprak M, Turner MS, Levine SP, Katz RB, Sanacora G. Letters to the editor. *Am J Psychiatry*. 2017;174:695–696. [PubMed: 28669202]
24. Passie T, Adams HA, Logemann F, Brandt SD, Wiese B, Karst M. Comparative effects of (S)-ketamine and racemic (R/S)-ketamine on psychopathology, state of consciousness and neurocognitive performance in healthy volunteers. *Eur Neuropsychopharmacol*. 2021;44:92–104. [PubMed: 33487513]
25. Hashimoto K. Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. *Biochem Pharmacol*. 2020;177.
26. Brady JV. Animal models for assessing drugs of abuse. *Neurosci Biobehav Rev*. 1991;15:35–43. [PubMed: 2052196]
27. Schatzberg AF. A word to the wise about ketamine. *Am J Psychiatry*. 2014;171:262–264. [PubMed: 24585328]
28. Schatzberg AF. A word to the wise about intranasal esketamine. *Am J Psychiatry*. 2019;176:422–424. [PubMed: 31109197]