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Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

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Weighing up scientific evidence requires balance, not opinion

15 June 2020

We read the Analysis[1] regarding the evidence base for esketamine in treatment-resistant depression (TRD). We have concerns about selective reporting, misinterpretation and factual errors.

First, the authors state that 'stopping regular use causes a withdrawal syndrome'. The review states that withdrawal symptoms occurred in 12 of 30 people taking ketamine at high frequency,[2] some up to 9 g (considerably higher than that in treatment trials). No information on numbers, severity or time course is given in the primary paper. The other review cited as evidence of withdrawal syndrome gives 50% prevalence in regular ketamine users. With less than 50% of both samples of ketamine misusers developing withdrawal, and no criteria set, causal inference is unclear. Considering withdrawal to be a confounder for relapse in the maintenance trial, they cite the Food and Drug Administration (FDA), questioning the validity of the withdrawal checklist, which shares items with the Montgomery–Åsberg Depression Rating Scale (MADRS). They neglect that this report states: 'Acute esketamine withdrawal is likely not a factor, as dosing is infrequent during the maintenance phase'. The trial authors' statement 'No evidence of a distinct withdrawal syndrome was observed during the 2 weeks after cessation of esketamine nasal spray as assessed by the 20-item Physician Withdrawal Checklist' appears fairly self-explanatory.

Second, the authors state that ketamine probably exerts rapid effects by causing a 'high' and disregard evidence suggesting that this is maintained, stating that no randomised controlled trial evidence exists, citing a 2017 Royal College of Psychiatrists (RCPsych) report. This ignores the acute esketamine trial submitted to the FDA, covered in this Analysis piece, published subsequent to that RCPsych report, where a difference was seen at day 2 and maintained at day 28. Several studies of ketamine have shown an extended effect, albeit weeks rather than months – but certainly outwith the 'high'.

Third, in questioning the clinical significance of MADRS change (the primary endpoint in esketamine trials), they cite analysis of mirtazapine trials in depression, linking Clinical Global Impressions to MADRS. Extrapolating within-group findings from depression to group placebo data has been highlighted as a mistake,[3] and extrapolating this to TRD is difficult to understand.

Fourth, the authors mention the FDA raising concerns over one site in the maintenance trial, with re-analysis by one researcher excluding this site showing no effect of esketamine on relapse. They neglect that this author conducted his own analysis, using an incorrect statistical technique, with numerical errors – re-analysis using the prespecified test showed a difference.[4]

Fifth, regarding safety, the authors selectively report events (e.g. Table 1/1861) giving prevalence of bladder problems but do not mention that most side-effects were transient and minor (stated in the original papers and the FDA report the authors themselves cite).[5]

In summary, it is difficult, with the selective citing and factual error, to see how one can come to any balanced conclusions from this Analysis piece.

References

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Sameer Jauhar, Senior Research Fellow and Consultant Psychiatrist, King's College London, London, UK. Email: sameer.jauhar@kcl.ac.uk; **Steven Marwaha**, Professor of Psychiatry, Institute for Mental Health, University of Birmingham, Birmingham, UK; **Paul D Morrison**, Argyll and Bute Hospital, Lochgilphead, UK; **Rachel Upthegrove**, Professor of Psychiatry, Institute for Mental Health, University of Birmingham, Birmingham, UK

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Letter to BJPsych in response to Horowitz and Moncrieff

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We were dismayed to see that you recently published a piece calling patients taking esketamine 'unwitting guinea pigs participating in another pharmaceutical experiment'.[1] (Lack of) style aside, the arguments advanced by Horowitz and Moncrieff to support their inflammatory statement do not hold up.

First, the clinical trial programme to establish efficacy and safety of the esketamine nasal spray in treatment-resistant depression (TRD), a substantial group of those with depression,[2] was developed in agreement with health regulatory agencies, including the Food and Drug Administration and Committee for Medicinal Products for Human Use. After careful consideration, the health regulatory authorities approved the application of three short-term and two long-term studies. Do Horowitz and Moncrieff claim superior insight to the bodies that hold pharma to account?

Second, the authors observe that esketamine can be abused. This is true, as for many essential medications, just not material: the administration of esketamine nasal spray was and will be done under close supervision in a healthcare setting, and none of the patients in the development programme demonstrated a pattern of abuse. Furthermore, the dosage schedule becomes less frequent as treatment progresses, so the amount of drug administered falls, which is clearly not in keeping with addiction. They also imply that, for reasons of safety, ketamine is no longer used as an anaesthetic; this is completely false. Indeed, it is the converse of the truth. Ketamine is listed by the World Health Organization as an essential medicine because of its safety profile compared with other anaesthetics.[3]

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