

Correspondence

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Weighing up scientific evidence requires balance, not opinion

15 June 2020

We read the Analysis¹ 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.

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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

Third, with regard to suicide, the results presented in their Table 1 are misleading, since all three suicides were within the open-label study phase, e.g. a phase where there was no placebo control. To tabulate these suicides against placebo is invalid. Suicidality is a main component of TRD.² The completed suicide rate in the esketamine development programme is 0.17 per 100 patient years, less than the completed suicide rate of 0.47 per 100 patient years in a recent meta-analysis of 15 000 patients with TRD.⁴

Fourth, the long-term efficacy and safety of TRD are better than the authors insinuate. Safety studies⁵ as well as practical experience⁶ indicate that most treatment-emergent side-effects occurred on dosing days, were mild or moderate in severity, and resolved on the same day. Cognitive performance generally either improved or remained stable post baseline. Treatment-emergent dissociative symptoms were transient and generally resolved within 1.5 h post dose. There was no case of interstitial cystitis or respiratory depression.⁶

Esketamine nasal spray is a treatment for TRD which has a novel mechanism of action and offers an additional therapeutic option for patients who have already failed several lines of treatment. Your instructions require authors of 'analysis' papers to provide 'an unbiased approach in evaluating the relevant evidence'. Patients, their therapists and the research teams who have worked on esketamine across the world deserve them to be observed better than this.

Declaration of interest

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Interpretation of the Montgomery–Åsberg Depression Rating Scale (MADRS)

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Horowitz and Moncrieff evaluated the use of esketamine in the management of treatment-resistant depression, following its approval by the USA, UK, and EU.¹ The authors addressed the five trials evaluated by the Food and Drug Administration (FDA) and concluded that the evidence was scant and that safety concerns have not been addressed sufficiently.

The TRANSFORM-2 efficacy trial was among these studies and was described as 'pivotal' by the FDA.² The trial demonstrated that the use of esketamine nasal spray alongside a newly initiated antidepressant resulted in a decrease of 19.8 points on the MADRS after 28 days. By comparison, there was a reduction of 15.8 points in the control group.^{2,3} Leucht et al interpreted the clinical relevance of MADRS responses and defined a clinical change of 'very much improved' as a MADRS reduction of 27–28 points, 'much improved' as a reduction of 16–17 points and 'minimally improved' as a reduction of 7–9 points.⁴ Horowitz and Moncrieff therefore concluded that the 4.0 point difference observed between the treatment and control groups in the TRANSFORM-2 trial corresponded to a 'less than minimal' clinical improvement.

Leucht et al, however, did not analyse the clinical relevance of the difference in MADRS scores between treatment and placebo groups but rather looked at the absolute change of MADRS scores in 'both placebo and drug treated patients' from a variety of open-label, comparator-controlled or placebo-controlled studies. Therefore, the absolute reduction of 19.8 points in the TRANSFORM-2 treatment group would confer a clinical benefit between 'much improved' and 'very much improved'.

I urge Horowitz and Moncrieff to reconsider the results from the TRANSFORM-2 trial and reflect on their views on esketamine's efficacy.

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