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 studies[5] as well as practical experience[6] 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 Moncrief 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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## Esketamine: uncertain safety and efficacy data in depression

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### Esketamine efficacy

Six 4 week efficacy trials have now been published, of which only one reports a statistically significant difference between placebo nasal spray (and antidepressant) and esketamine (and antidepressant) on depression score at 4 weeks. There is debate about whether the 4.0 point difference found constitutes a clinically significant effect,[1] especially considering the large effect in the placebo plus antidepressant arm (15.8 points), possibly due to the hours of human contact involved. It is also less than the 6.5 point difference Janssen used in their sample size calculation (p. 91 and p. 157 in Ref. 2). More importantly, the time point of 4 weeks in all these studies means the data are rather uninformative, since treatment-resistant depression is usually treated for months or years.

### Food and Drug Administration (FDA)

Kasper et al consider that the regulatory agencies have employed 'careful consideration'. The FDA's convention to request two short-term studies to approve the efficacy of a drug ('each convincing on its own') has been criticised because it allows companies to conduct as many studies as are necessary to generate two positive studies. However, even that low bar was dropped: in 2014, in discussion with Janssen, the FDA 'agreed' that a withdrawal study could be used as one of two positive studies, 'along with a short-term fixed-dose study *with statistically very persuasive results*' (italics ours, p. 27 of Ref. 2). However, after further meetings with Janssen this was 'later switched to *any* short-term study in March 2018' (italics ours, p. 27 of Ref. 2). Many other commentators and national health service bodies, including the National Institute for Health and Care Excellence (NICE), have drawn different conclusions from those of the FDA and the Medicines and Healthcare Products Regulatory Agency and questioned the data on the safety and efficacy of esketamine.[3]

### Suicide

We acknowledge that comparing data from non-randomised groups (as in Table 1 in the Analysis) cannot establish causal attribution and that the larger numbers in the esketamine group and the longer duration of treatment might have inflated suicides in this group; also that participants might have a relatively high baseline rate of suicide. However, the meta-analysis identified by Kasper is not an appropriate comparison. The Janssen studies included people who had only 'failed' two antidepressants (which according to the STAR-D trial probably represents at least 44% of patients with depression) and excluded people with a recent history of suicidal intention, psychiatric co-morbidity, drug and alcohol problems, vagal nerve stimulation (VNS) and deep brain stimulation,[2] whereas the meta-analysis involved a more severe group of patients trialling ECT, deep brain stimulation and VNS among other 'end of the line' treatments. Furthermore, in the safety study, one in seven patients developed 'treatment-emergent' suicidal ideations, and six attempted suicide in a group selected for not being actively suicidal;[4] a disproportionate number of suicides have been attributed to esketamine in the first year of its use in the USA.[5]

**Table 1** Withdrawal symptoms recorded 4 weeks after stopping esketamine in the safety trial (adapted from Supplementary Table 5 ) to two significant figures

| New or worsened symptom at week 4 | Proportion (%) |
|---|---|
| Loss of appetite | 14% |
| Nausea/vomiting | 1.8% |
| Diarrhoea | 7.1% |
| Anxiety/nervousness | 18% |
| Irritability | 16% |
| Dysphoric mood/depression | 23% |
| Insomnia | 27% |
| Fatigue/lethargy/lack of energy | 16% |
| Poor coordination | 5.4% |
| Restlessness/agitation | 5.4% |
| Diaphoresis | 8.9% |
| Tremor/tremulousness | 7.1% |
| Dizziness/light headedness | 8.9% |
| Headaches | 11% |
| Muscle aches and stiffness | 8.9% |
| Weakness | 5.4% |
| increased acuity to sound, smell or touch | 3.6% |
| Paraesthesias | 5.4% |
| Difficulty concentrating, remembering | 18% |
| Depersonalisation/derealisation | 1.8% |

### Adverse effects

Even with weekly or fortnightly dosing, 17% of patients (136/802) in the long-term safety study demonstrated symptoms reminiscent of 'ketamine bladder', a known and potentially serious complication of ketamine use.[4] Jauhar et al and Kasper et al reiterate the FDA's claim that most of the bladder-related side-effects were transient and mild, but even in the shorter trials 33% of cases were not minor, and 24% of cases had not resolved at the subject's last assessment (p. 46 of Ref. 2). The FDA also commented that serious bladder conditions may have been missed or misidentified (p. 46 of Ref. 2).

### Withdrawal and relapse

As recognised by Kasper et al, ketamine causes tolerance, dependence and withdrawal, and the doses of esketamine employed in the studies were similar to recreational doses of ketamine. As Jauhar et al report, the FDA and Janssen claimed that withdrawal symptoms were probably not relevant in the relapse prevention study, but Janssen did not report the Physician Withdrawal Checklist data to justify this conclusion. However, Janssen did describe withdrawal effects ('new or worsened' effects) in the longer safety study shown in Table 1,[4] all recognised ketamine withdrawal effects. The presence of symptoms such as paraesthesia, diarrhoea and diaphoresis, occurring in concert with psychological symptoms, marks this as distinct from relapse.

Although it is difficult to be definitive about the nature of experiences that occur following drug discontinuation, the possibility that withdrawal effects were mistaken for relapse requires consideration, as withdrawal effects overlap with most items on the Montgomery–Åsberg Depression Rating Scale. NICE concluded



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