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).[2] More importantly, the time point of 4 weeks in all these studies means the data is rather uninformative, since treatment resistant depression is usually treated for months or years.

FDA

Kasper et al consider 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).[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).[2]

Many other commentators and national health service bodies, including NICE, have drawn different conclusions from the FDA and MHRA 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 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 amongst other "end of the line" treatments. Furthermore, in the safety study, one in seven patients developed "treatment-emergent" suicidal ideations, and 6 attempted suicide in a group selected for not being actively suicidal;[4] there have been a disproportionate number of suicides attributed to esketamine in the first year of its use in the US.[5]

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 re-iterate 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).[2] The FDA also commented that serious bladder conditions may have been missed or misidentified (p.46 of ref 2).[2]

Withdrawal and relapse

As recognised by Kasper et al, ketamine causes tolerance, dependence, and withdrawal; and 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 likely 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 like 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 MADRS. NICE concluded that "any withdrawal effect would be difficult to distinguish from a change in depressive symptoms"(p.14-15 of ref 3).[3] Lastly, relapse rates were higher in the patients who stopped esketamine than those randomised to placebo in prospective trials, suggesting that relapse represented more than unmasking of the condition, and may reflect withdrawal effects.[3]

High

Ketamine, like some other anaesthetics, causes a pleasurable 'high' in some users and reduces depression scores within hours, and it is not clear how drug-induced euphoria and antidepressant effects can be distinguished. Jauhar argues it is the persistence of the effect that marks it as 'antidepressant', but, as described above, the esketamine trials do not confirm that a clinically relevant effect occurs.

Outlier Site

Along with others, including the FDA, we highlighted that the relapse prevention study is influenced by an outlier site.[2,6] Janssen conducted a sensitivity analysis excluding this site using a 'time to event' analysis and results remained statistically significant (p=0.048),[7] whereas Turner compared proportions of relapses which showed a non-significant effect (p= 0.13).[6] The correct way to analyse such data is contested.[7]

We apologise if the term "guinea pigs," referring to potential trial participants, caused offence, and perhaps could have chosen our words differently. We used this strong language to communicate our concern that the public might be exposed to a pharmacological agent for which robust efficacy and safety have not yet been demonstrated.

Conclusion:

Overall, the central points of our Analysis remain: esketamine has a clinically uncertain effect at 4 weeks, and there are no studies with longer follow-up periods more relevant for the care of people with depression. The discontinuation trial potentially conflates relapse and withdrawal and there are concerning safety signals.

New or worsened symptom at week 4	n (%)
Loss of appetite	8 (14.3)
Nausea-vomiting	1 (1.8)
Diarrhea	4 (7.1)
Anxiety-nervousness	10 (17.9)
Irritability	9 (16.1)
Dysphoric mood - depression	13 (23.2)
Insomnia	15 (26.8)
Fatigue-lethargy-lack of energy	9 (16.1)
Poor coordination	3 (5.4)
Restlessness-agitation	3 (5.4)
Diaphoresis	5 (8.9)
Tremor-tremulousness	4 (7.1)
Dizziness/light-headedness	5 (8.9)
Headaches	6 (10.7)
Muscle aches and stiffness	5 (8.9)
Weakness	3 (5.4)
Increased acuity sound smell touch	2 (3.6)
Parasthesias	3 (5.4)
Difficulty concentrating, remember	10 (17.9)
Depersonalization-derealization	1 (1.8)

Table 1 Withdrawal symptoms recorded 4 weeks after stopping esketamine in the safety trial (adapted from Supplementary Table 5[4])

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