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Content

Potential differences in antidepressant effects of oral ketamine liquid suspension versus compounded capsules

It was with great interest that I read the recent article by Domany *et al* regarding the antidepressant effects of oral ketamine in treatment-resistant depression.[1] In brief, the authors found a rapid and robust antidepressant effect of oral ketamine (liquid suspension 1 mg/kg thrice weekly) compared with placebo, with clinically and statistically significant antidepressant effects observed within 40 min of the first dose. These robust effects persisted over the course of the 21-day trial with a between-group difference in Hamilton Rating Scale for Depression (HRSD) scores of 10.2 in favour of ketamine versus placebo on day 21 compared with baseline. These results strongly differ compared with previous randomised controlled trials, which demonstrated minimal benefits of oral ketamine compared with controls.[2,3]

Jafarinia *et al*, in 2016, found no significant improvements after 3 weeks of treatment ($P = 0.12$). At week 6, a small between-group difference of only 2.8 on the HRSD was observed ($P = 0.017$) (the minimal clinically important difference (MCID) for the HDRS is >3).[2] Similarly, in 2018, Arabzadeh *et al* found minimal benefit of oral ketamine compared with placebo over the course of their 6-week trial, with a between-group difference in HRSD scores of only 3.4 (week 2), 2.6 (week 4) and 1.9 (week 6) in favour of ketamine, below the MCID for the HRSD.[3] The between-group difference on the HRSD of only 2–3 observed by Jafarinia *et al* and Arabzadeh *et al* is in stark contrast with the >10-point difference found by Domany *et al*.[1–3]

Numerous factors may explain the differences in outcomes, namely, differences in samples (such as level of treatment resistance, baseline depressive symptom severity, psychiatric and medical comorbidity and demographic factors), the intervention (such as different ketamine doses and dosing schedules) and study design (for example adequate masking, the characteristics of the control group and other sources of study bias). These factors are fairly generalisable to comparing study results for any intervention, however, oral ketamine may have an additional important factor to consider, namely, the use of oral capsules versus a liquid oral suspension. Notably, Domany *et al* used a liquid oral suspension and had rapid and robust antidepressant effects.[1] Conversely, Jafarinia *et al* and Arabzadeh *et al* used capsules with limited antidepressant effects.[2,3] Moreover, the effects reported in open-label trials, retrospective chart reviews, case series and case reports similarly show a fairly consistent pattern of limited effects with ketamine capsules with potent effects with the oral liquid suspension.[4,5]

Numerous factors may explain the differences in outcomes of capsules versus liquid suspension, including pharmacokinetic differences, which may be particularly important for ketamine, as the rate of infusion plays an important role in both efficacy and adverse effects for intravenous ketamine, suggesting there may be an optimal 'effective infusion rate', which might differ with liquid (increased immediate bioavailability with some sublingual absorption as well) versus capsules. Alternatively, the observation of differential antidepressant effects with liquid suspension versus capsule might be entirely spurious and better explained by the other differences in samples, dosing and study design. Functional unmasking of the participants may also be a factor as the liquid suspension is bitter (in the absence of added flavour), whereas the capsules are tasteless. Nevertheless, investigators and clinicians should not assume the effects of liquid versus capsules of ketamine are equivalent.

Declaration of interest

Dr. Rosenblat has no conflicts of interest to declare.

1 Domany Y, Bleich-Cohen M, Tarrasch R, Meidan R, Litvak-Lazar O, Stoppleman N, et al. Repeated oral ketamine for out-patient treatment of resistant depression: randomised, double-blind, placebo-controlled, proof-of-concept study. *Br J Psychiatry* 2019; **214**: 20–6.

2 Jafarinia M, Afarideh M, Tafakhori A, Arbabi M, Ghajar A, Noorbala AA, et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: a double-blind, randomized, controlled trial. *J Affect Disord* 2016; **204**: 1–8.

3 Arabzadeh S, Hakkikazazi E, Shahmansouri N, Tafakhori A, Ghajar A, Jafarinia M, et al. Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial. *J Affect Disord* 2018; **235**: 236–41.

4 Al Shirawi MI, Kennedy SH, Ho KT, Byrne R, Downar J. Oral ketamine in treatment-resistant depression: a clinical effectiveness case series. *J Clin Psychopharmacol* 2017; **37**: 464–7.

5 Schoevers RA, Chaves TV, Balukova SM, aan het Rot M, Kortekaas R. Oral ketamine for the treatment of pain and treatment-resistant depression. *Br J Psychiatry* 2016; **208**: 108–13.

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