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Commentary

Efficacy and safety of a 4-week course of repeated subcutaneous ketamine injections for treatment-resistant depression (KADS study): commentary, Joks et al

Gero Joks, Steve Su and Jarrad King

Regarding the article, 'Efficacy and safety of a 4-week course of repeated subcutaneous ketamine injections for treatment-resistant depression (KADS study): randomised double-blind active-controlled trial', we commend Loo et al[1] for undertaking the Ketamine for Adult Depression Study (KADS). In the interest of ensuring that accurate and balanced information is presented to healthcare professionals on treatment-resistant depression, we raise several points herein to help clarify and provide additional perspective to the researchers' interpretation of their findings in the Discussion.

Keywords

Esketamine; ketamine; major depressive disorder; depression.

Loo et al[1] stated ' … adequately dosed racemic ketamine [i.e. cohort 2, not cohort 1] was shown to have superior antidepressant efficacy to an [psycho] active [placebo] control drug, with the proportional increase in remission comparing favourably to that of studies of intranasal esketamine tested against a non-active placebo'. An indirect comparison such as this requires that the data being compared are obtained from studies using fundamentally similar methods and similar populations.[2] In this regard, the study design of the Ketamine for Adult Depression Study (KADS)[1] and that of the esketamine TRANSFORM-2 study,[3] which the authors cited for comparison, differed substantially on variables known to affect treatment response (e.g. baseline illness severity, comparator). For example, patients in KADS cohort 2 had less severe baseline depressive symptoms per the Montgomery–Åsberg Depression Rating Scale (MADRS) (baseline mean total score: 30.3, midazolam/antidepressant; 28.9, ketamine/antidepressant) compared to those in TRANSFORM-2 (37.3, inactive placebo/antidepressant; 37.0, esketamine/antidepressant). Despite these differences in baseline MADRS scores, the authors stated that 'participants in this study [had] a higher level of treatment resistance … than the [TRANSFORM-2] pivotal study of Popova et al',[3] which they based on a 24% failure rate to electroconvulsive therapy, an exclusion criterion of TRANSFORM-2.

In the KADS,[1] subcutaneous ketamine was compared to psychoactive placebo (subcutaneous midazolam), each combined with *ongoing* oral antidepressant initiated ≥4 weeks before study enrolment), whereas esketamine nasal spray was compared to placebo nasal spray, each combined with *newly initiated* oral antidepressant, with fixed-dose titration to the maximum labelled dose, in TRANSFORM-2.[3] Thus, patients enrolled into the KADS knew they would continue an antidepressant to which they had not responded and had a 50% likelihood of receiving an anxiolytic drug that lacked antidepressant efficacy, whereas all esketamine-treated patients knew they would receive a new oral antidepressant that they had *not* previously failed, with resulting differences in expectation bias likely. Furthermore, titration to maximum labelled dose of oral antidepressant in TRANSFORM-2 increased the likelihood of improvement in MADRS score from baseline in the control arm and decreased the likelihood of achieving larger differences between the placebo and esketamine arms. These differences in dosing of oral antidepressant may account for, at least in part, differences in outcomes (e.g. remission rate [defined by MADRS ≤12]: 4.1% and 21.6% in the psychotropic placebo control and ketamine arms, respectively, of the KADS, and 31.0% and 52.5% in the placebo control and esketamine arms, respectively, of TRANSFORM-2).

In the Discussion, Loo et al state 'these results appear compatible with a prior meta-analysis,[4] indicating that racemic ketamine showed a larger treatment effect than esketamine'. However, several research groups[5] have noted limitations of the meta-analysis[4] cited as supportive, most notably that the meta-analysis included data from trials that used markedly differing study designs and patient populations.

Taken together, disparities in study design, including patient population and control arms, make indirect comparisons of efficacy between esketamine and ketamine unfounded. With regard to such comparisons, we agree with Loo et al[1] in their statements that ' … clearly uncertainty remains on comparative efficacy and large, direct, randomized comparisons are required' and that 'future research questions include head-to-head comparisons of racemic, R- and S-ketamine … '.

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Author contribution

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Psychiatry in movies

Inside Out 2: the adolescent mind and the role of anxiety

Harry Barker

Inside Out 2, Pixar's 2024 coming-of-age sequel, continues the exploration of 13-year-old Riley's mind as she navigates the challenges of adolescence and begins high school. On the eve of ice hockey camp, Riley's 'puberty alarm' triggers a comedic overhaul of her brain's control centre. The original emotions from *Inside Out* (2015) – Joy, Anger, Sadness, Fear and Disgust – are joined by new additions: Anxiety, Envy, Embarrassment and Ennui. These emotions bring fresh conflict to Riley's emotional landscape, as the control console becomes more sensitive, intensifying her reactions and leaving the original emotions struggling to maintain balance.

One of the most compelling aspects of *Inside Out 2* is Pixar's nuanced portrayal of anxiety during adolescence. Anxiety, depicted as hyperactive with messy hair and an eager smile, is not a villain but a well-meaning force. The film cleverly distinguishes between fear and anxiety – Anxiety explains, 'Fear keeps Riley safe from the things she can see, I keep Riley safe from the things she can't see. I plan for the future'. Initially, her obsessive planning for every potential outcome seems helpful, as it pushes Riley to impress the older girls on the ice hockey team, reflecting the natural fear of social rejection – a common concern as peer relationships gain importance in adolescence.

However, Anxiety quickly becomes overwhelming, operating Riley's imagination like a frantic office, with workers endlessly sketching out worst-case scenarios. This culminates in a powerful depiction of a panic attack, with Anxiety swirling chaotically around the control console, desperate to maintain order. At the centre of this storm is Anxiety herself, immobilised and powerless, a tear rolling down her cheek. Through this portrayal, the film demonstrates how anxiety, left unchecked, can spiral into a paralysing force. Anxiety's eventual realisation that she cannot control everything – mirrored by Joy's own admission – offers an insightful reflection on the challenges of emotional regulation during adolescence.

By presenting Anxiety as both a protector and a source of distress, the film educates viewers on the dual nature of this emotion. It normalises anxiety as part of life while highlighting the importance of managing it effectively. In the film's resolution, Anxiety is assigned a specific task and given a calming cup of tea, symbolising that while anxiety will always be present, it can be controlled and channelled positively when managed with care. This message is important for young people given that anxiety disorders often emerge in early adolescence, although there is a clear distinction to be made between anxiety as a normal emotion and clinical anxiety.

Inside Out 2 again makes emotional education both accessible and engaging, encouraging children to understand their emotions and talk openly about them. By portraying the turbulence of adolescence, the film normalises psychological distress as a natural part of development. Through its creative storytelling and use of metaphor, it opens essential conversations about mental health, helping young audiences recognise that emotional challenges are common – and that learning to navigate them is a key part of growing up.

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