

## Antidepressant Response and Dissociative Effects After Ketamine Treatment: Two Sides of the Same Coin?

**To the Editor:** In recent years, there has been growing interest in research on *N*-methyl-D-aspartate (NMDA) antagonists as rapid-acting agents for treating depression<sup>1</sup> and related suicidal ideation.<sup>2</sup> Ketamine has shown preliminary efficacy for the rapid treatment of both unipolar and bipolar depression, although it has been also associated with high rates of dissociative and psychotomimetic symptoms, especially within 60 minutes after the infusion.<sup>3</sup> For this reason, we read with great interest the update recently published in JCP<sup>4</sup> that synthesized issues related to efficacy, adverse effects, and mechanism of action of ketamine for treating depression. In particular, in analyzing ketamine-related adverse effects, this overview highlighted that subanesthetic doses of ketamine may induce dissociative and psychotomimetic symptoms, although these effects are often mild and short-lasting.<sup>4</sup> In addition, the authors of a recent review<sup>5</sup> suggest that intranasal route of administration and lower doses of ketamine, as well as alternative NMDA-modulating agents, all might mitigate dissociative and psychotomimetic effects.

However, ketamine-induced dissociative symptoms, whether therapeutic or side effects, may deserve additional insight. Findings from a randomized controlled trial<sup>6</sup> showed that significant, though transient, dissociative effects can occur after ketamine infusion in about 1 out of 5 subjects with treatment-resistant depression. However, a significant correlation between dissociative symptoms 40 minutes after ketamine infusion and improvement in depressive symptoms (230 minutes and 7 days after infusion) has been reported in subjects with treatment-resistant major depressive or bipolar disorder.<sup>7</sup> Among the potential mediators tested, only dissociative effects predicted a robust and sustained antidepressant response attributable to ketamine. This issue may well be supported by a biological rationale, since dissociative symptoms may be the consequence of the enhancement of glutamate release induced by ketamine.<sup>7</sup> In addition, a recent study based on a retrospective chart review<sup>8</sup> evaluating efficacy and safety of intravenous subanesthetic doses of esketamine in 27 subjects with treatment-resistant or bipolar depression found that mild to severe dissociative symptoms occurred in about one tenth of subjects. Nevertheless, 2 out of 3 subjects with dissociative symptoms remitted from depression within 3 weeks after esketamine infusion. Thus, also in this case, it seems that ketamine-related dissociation and therapeutic efficacy might be linked, possibly as “two sides of the same coin.” Nonetheless, available evidence is limited and not conclusive, since other studies, although based on small sample sizes, showed that dissociative symptoms were not correlated with changes in depression scores<sup>9</sup> or could be even associated with suicidal ideation.<sup>10</sup> Although a number of different factors involved in the efficacy of ketamine can be hypothesized,<sup>11</sup> including induced psychotomimetic effects,<sup>12</sup> the mechanisms of its antidepressant activity are far from being fully understood. In particular, it should be elucidated if transient

dissociative effects induced by ketamine should be considered physiological conditions linked to antidepressant response, rather than intrinsic side effects that could decrease clinical confidence in terms of tolerability. Research should clarify strategies that can decrease ketamine-induced dissociative effects<sup>5</sup> while not challenging its promising antidepressant properties.

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Dr Andrade Replies

**To the Editor:** Dr Bartoli and colleagues<sup>1</sup> suggest that the dissociative and antidepressant effects of ketamine are two sides of the same coin or, to use a different metaphor, that they go hand in hand. This is hardly surprising. The efficacy and adverse effects of most treatments are dose-dependent, to a point, so higher doses of a drug may be associated with greater chances of improvement but also with a higher risk of adverse effects. In other words, if the dose of ketamine in an individual patient is sufficient for efficacy, it may also suffice to produce dissociative adverse effects, and vice versa.

This does not mean that efficacy and adverse effects are mediated by the same mechanisms, nor even that one predicts the other. It is common experience that patients may experience treatment benefits without adverse effects, or may suffer adverse effects without improvements in indices of illness. I agree, though, that the relationship between the dissociative and antidepressant actions of ketamine merits study and that if the adverse effect is not necessary for the benefit, it would be nice to identify strategies that block dissociation without blocking the antidepressant action.

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