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## The use of ketamine and esketamine in psychiatry: now and beyond

*O uso da cetamina e da escetamina na psiquiatria: o agora e o depois*

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Ketamine is a short-acting anesthetic that has been widely used by emergency physicians<sup>1</sup>. After the publication of a small randomized-controlled study describing the positive effects of injectable ketamine in major depression<sup>2</sup>, we have witnessed a growing interest in its potential use in mood disorders. Following this preliminary evidence, several studies investigated the effectiveness of ketamine and its *s*-enantiomer esketamine in other psychiatric conditions, such as treatment-resistant depression (TRD) and depression with suicidal behavior<sup>3</sup>. It is important to consider that, as this class of agents may exert its effects via N-methyl-D-aspartate (NMDA) glutamatergic receptors<sup>4</sup>, they could represent a new potential mechanism of action for the treatment of several mental disorders. In this way, there is a trend for expanding the investigation of the usefulness of ketamine and its derivatives for other psychiatric syndromes<sup>5</sup>.

Presently, several systematic reviews and meta-analyses have compiled the effectiveness of racemic ketamine in depression and other mental conditions<sup>3,5,6</sup>. Overall, these reviews consistently report that injectable ketamine was effective, significantly improving depression measures in participants with major depression and TRD with a robust, rapid, and short-lived antidepressant and anti-suicidal effect. Of note, ketamine administered by other routes of administration than the intravenous one appears to have a quite similar antidepressant effect when compared to injectable administration in patients with mood disorders<sup>5</sup>. However, the efficacy and safety of racemic ketamine in mood disorders in the long-term need to be better confirmed with more clinical and experimental data.<sup>7</sup> Remarkably, although it was not approved for the treatment of psychiatric disorders we are currently observing an escalating use of racemic ketamine for off-label indications.

Intranasal esketamine was approved by the U.S. Food and Drug Administration (FDA) in 2019 for TRD and major depression with suicidal ideation in adults. Data from phase III trials suggests that adjunctive intranasal esketamine is effective and safe in reducing depressive symptoms and achieving clinical response in patients with TRD<sup>8</sup>. Furthermore, the long-term trials showed that treatment with intranasal esketamine was associated with lower relapse rates and an improved safety profile. At last, intranasal esketamine was also effective in reducing depressive symptoms in individuals with major depression and suicidal ideation. Even though intranasal esketamine has a more convenient way of administration, has been approved by major regulatory agencies, and was studied in a robust development program, there are important information gaps that need to be addressed. For example, the ideal frequency and duration of the treatment are not yet known and there is a need for more information on its effectiveness in the long-term. Questions related to costs and reimbursement may also impact its usage in daily clinical practice.

The current data about the action of ketamine in other mental disorders than depression is also encouraging, but much more limited. There is some preliminary evidence, coming from a few clinical trials and case series that racemic ketamine may have potential usefulness for the management of bipolar depression, post-traumatic stress disorder, obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder, eating disorders, and substance use disorders<sup>5,9</sup>. However, although encouraging, the research on these indications was

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marred by a high risk of bias, since most studies were small and had several methodological flaws. Consequently, their conclusions must be interpreted with utmost caution. Therefore, more substantial evidence is needed with these new potential indications since there is often a trend to prescribe a new drug for several already existing diagnoses before its formal approval.

It is important to mention that despite the growing burden of mental disorders worldwide, in the past few decades we have observed a reduction in new drug discoveries of psychopharmacological agents<sup>10</sup>. Thus, ketamine and esketamine may be considered breakthrough agents, opening new avenues for future developments in the area and giving new hope to severely depressed patients. But, although these achievements must be celebrated, caution is necessary in terms of its specific indications, still unknown adverse events, and long-term effects in the usual daily practice. Despite promising, they are not a solution for all patients and new interventions should be continuously searched.

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