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EDITORIAL

Intranasal esketamine and the dawn of precision psychiatry

Devon **Watts**,[1,2] Frederico D. **Garcia**,[3] Acioly L.T. **Lacerda**,[4,5,6,7] Jair de J. **Mari**,[8] Lucas C. **Quarantini**,[9,10] Flávio **Kapczinski**[1,2,7,11]

[1]*St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.* [2]*Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada.* [3]*Departamento de Saúde Mental, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.* [4]*Programa de Transtornos Afetivos (PRODAF), Departamento de Psiquiatria, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.* [5]*Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), UNIFESP, São Paulo, SP, Brazil.* [6]*Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Brazil.* [7]*CNS Unit, BR Trials, São Paulo, SP, Brazil.* [8]*Departamento de Psiquiatria, UNIFESP, São Paulo, SP, Brazil.* [9]*Laboratório de Neuropsicofarmacologia, Serviço de Psiquiatria, Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil.* [10]*Departamento de Neurociências e Saúde Mental, Faculdade de Medicina da Bahia, UFBA, Salvador, BA, Brazil.* [11]*Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, ON, Canada.*

One in twenty individuals worldwide suffer from depression,[1,2] and limited developments have been made in pharmacological treatments over the last four decades.[3] Current first-line treatment recommendations for major depressive disorder (MDD) involve medications that inhibit the reuptake of serotonin, norepinephrine, and dopamine through various mechanisms.[4] However, as indicated in the STAR*D study, roughly one in three patients fail to achieve clinical remission through these medications.[5] It is known that a sufficient clinical response to these medications can take an upwards of 8 to 12 weeks.[6] Moreover, up to 15% of patients with MDD have a treatment-resistant form of the disorder.[7] Altogether, this highlights the urgent need for rapid-acting antidepressants with a novel mechanism of action.

It has recently been shown that repeated infusions of ketamine have rapid, cumulative, and sustained antidepressant effects.[8] It has also been shown that ketamine infusions can reduce suicidal ideation in treatment-resistant depression.[9] This antidepressant effect persists in racemic formulations, such as esketamine,[10] which shows non-inferiority to ketamine.[11] However, the exact mechanism underlying its rapid antidepressant and anti-suicidal effects remains unknown.

There is growing evidence that dysregulations in the glutamatergic and GABAergic systems are implicated in the pathophysiology of depression,[12] which provides an opportunity for novel drug design and the repurposing of existing drugs. Ketamine has been shown to modulate extrasynaptic $GABA_A$ receptors in cortical neurons,[13] and the rapid increase in glutamate that ketamine produces appears to be an essential component of its antidepressant effect.[14]

While many candidate pathways have been proposed to mediate the antidepressant effects of ketamine,[15,16] few clinical trials have investigated biological predictors of treatment response. Among them, acute alterations in glutamate and glutamine levels, measured using in vivo magnetic resonance spectroscopy, appears to mediate the antidepressant effects of ketamine.[17] However, no studies have yet identified a set of candidate biological markers that can predict treatment response to ketamine on an individual level. Clearly defined clinical markers in treatment-resistant depression coupled with effective, innovative, and fast acting treatments such as intranasal esketamine marks the dawn of precision psychiatry.[18]

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Correspondence: Flavio Kapczinski, Department of Psychiatry and Behavioral Neurosciences, McMaster University, 100 West 5th Street, Hamilton, ON, L9C 0E3, Canada.
E-mail: flavio.kapczinski@gmail.com
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