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Short communication

Real-world effectiveness of repeated ketamine infusions for treatment resistant depression during the COVID-19 pandemic

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ABSTRACT

Herein we evaluate the impact of COVID-19 restrictions on antidepressant effectiveness of intravenous (IV) ketamine in adults with treatment-resistant depression (TRD). We conducted a case series analysis of adults with TRD ($n = 267$) who received four ketamine infusions at an outpatient clinic in Ontario, Canada, during COVID-19 restrictions (from March 2020 - February 2021; $n = 107$), compared to patients who received treatment in the previous year (March 2019 - February 2020; $n = 160$). Both groups experienced significant and comparable improvements in depressive symptoms, suicidal ideation, and anxiety with repeated ketamine infusions. Effectiveness of IV ketamine was not attenuated during the COVID-19 period.

1. Introduction

Since March of 2020, when the Coronavirus disease 2019 (COVID-19) outbreak was declared a global pandemic by the World Health Organization (WHO), many countries across the world adopted public health measures to prevent the spread and/or lessen the burden of the disease. These public health measures, which have largely remained in place since the WHO declaration, have included the closure of non-essential services/businesses, such as fitness facilities and many workplaces, as well as prolonged periods of social isolation and quarantines. Evidence shows quarantine/social isolation measures (although effective at lessening the burden of COVID-19) increase the risk of negative mental health outcomes, especially among vulnerable groups such as individuals with pre-existing mood disorders (Hao et al., 2020; Wang et al., 2021).

Indeed, social support is a key factor in maintaining good physical and psychological health, resilience to stress, and achieving positive outcomes in individuals with mood disorders (Ozbay et al., 2007; Wang et al., 2018). Furthermore, individuals with mood disorders are at greater risk of COVID-19-related morbidity and mortality, and needing post-acute care after hospital discharge (Castro et al., 2021). Despite the well-demonstrated negative effects of social isolation measures on overall health outcomes, especially in individuals with prior mood disorders, no study has yet investigated the impact of these measures on the outcomes of individuals receiving antidepressant therapies. For example, social isolation, loneliness, circadian rhythm disturbance and pandemic-related stressors may be hypothesized to attenuate the antidepressant effects of both pharmacological and non-pharmacological interventions (Lee et al., 2018; Maj et al., 2020; McIntyre et al., 2020a; Park et al., 2020).

Intravenous (IV) ketamine is a rapid-acting treatment option that has demonstrated effectiveness in adults with treatment-resistant depression (TRD) who have not responded to multiple other treatment trials (McIntyre et al., 2020b). Rapid-onset reduction in suicidal ideation has also been observed, making ketamine a potentially lifesaving treatment for some individuals (Bartoli et al., 2017). After acquiring an adequate

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supply of personal protective equipment, our IV ketamine outpatient program remained operational throughout the pandemic as providing rapid-acting antidepressant, and potentially anti-suicidal treatment for patients with TRD was deemed an essential service (McIntyre et al., 2021).

Given the rapid, widespread adoption of prolonged social isolation measures and their impacts on mental health, an investigation into their impact on the outcomes of patients receiving antidepressant therapy, such as ketamine, is a priority question for both treatment providers and patients. Herein, we compared the antidepressant effects of ketamine in patients receiving treatment during the COVID-19 pandemic versus patients receiving treatment prior to the emergence of COVID-19 in Ontario, Canada.

2. Methods

We performed a retrospective case series analysis of adults receiving four IV ketamine infusions (0.5–0.75 mg/kg) over ~2 weeks for TRD in an outpatient clinic in Ontario, Canada to evaluate treatment response during COVID-19. Treatment outcomes were compared between adults who received treatment during COVID-19 (i.e., March 2020-February 2021, inclusive) and before COVID-19 (i.e., "controls" - March 2019-February 2020, inclusive). The full treatment protocol has been described elsewhere (McIntyre et al., 2020c).

During COVID-19, our clinic followed provincial and regional public health guidelines to protect patients and staff members, with updates every 3–7 days. Initial consult appointments and follow-up appointments with a staff psychiatrist were completed virtually, either over the phone or using provincial telemedicine. These appointments were not delayed at any point by COVID-19. During ketamine infusion treatments, only one patient was allowed in the waiting room at a time, and caregivers were not permitted to enter the clinic or be in the room with the patient during the treatment. Upon arrival, all patients were actively screened for COVID-19 symptoms and were required to wash their hands. Immediately after handwashing, patients were directed into individual patient rooms to complete all forms and clinical measures, instead of in the waiting room. All staff and patients were required to wear personal protective equipment (PPE) while at the clinic. From March 10th 2020 to April 9th 2020, all out-of-province patients and new initial infusions were suspended, treatment capacity was reduced, and treatment booking times were increased from 40 minutes to 60 minutes. The clinic began accepting new patients for initial treatments in April 2020, and infusions were resumed for out-of-province patients in May 2020. Securing PPE was a limiting factor in treatment capacity. In May 2020, the clinic returned to pre-COVID-19 capacity and infusion booking times were decreased from 60 minutes to 45 minutes.

Analysis of this data was approved by a community research ethics board. All statistical analyses were conducted in SPSS V. 26.0 (Armonk, NY: IBM Corp). Mixed models were performed to compare changes in depressive symptoms, measured using the Quick Inventory for Depressive Symptomatology - Self Report 16 (QIDS-SR16) and suicidal ideation (SI; QIDS-SR16 SI item) from pre-treatment to post-infusion 4, with symptoms measured after each infusion . Mixed models comparing changes in anxiety symptoms (i.e., measured using the Generalized Anxiety Disorder-7 [GAD-7] scale) and functional disability (i.e., Sheehan Disability Scale [SDS] total score) from pre-treatment to post-infusion 3 and post-infusion 4 were also conducted. In all models, we used an autoregressive covariance structure and adjusted for age, sex, number of past antidepressant trials, and baseline symptom severity. Bonferroni corrections were used to account for multiple post-hoc between-group comparisons.

3. Results

A total of 267 subjects were included in our analyses, including 107 cases who received ketamine treatment during the COVID-19 pandemic (mean age = 44.5, SD = 13.3; 52.0% female) and 160 comparators who received ketamine treatment before the COVID-19 pandemic (mean age = 46.2, SD = 15.2; 56.3% female). Level of treatment resistance was comparable between cases and controls, with a mean of 8 past antidepressant trials in both groups (SD = 5). Overall, mixed model analyses did not show statistically significant differences in response to IV ketamine treatment in adults who received IV ketamine during the COVID-19 pandemic compared to the 'control' group (**Fig. 1**). Overall, significant reductions in depressive symptoms ($F(4, 630) = 48.73$, $p < .001$), SI ($F(4, 627) = 17.34$, $p < .001$), anxiety ($F(2, 344) = 52.84$, $p < .001$, and function were observed with repeated infusions ($F(2, 318) = 36.17$, $p < .001$. There was a significant *group by infusion* interaction on GAD-7 scores, with follow-up pairwise comparisons showing significantly greater reductions in anxiety from baseline to post-infusion 3 ($p = .044$) in the control group compared to those receiving treatment during the COVID-19 pandemic, but no significant difference from baseline to post-infusion 4 ($p = .078$).

4. Discussion

In this study, we report that adults with TRD who received four IV ketamine infusions during the COVID-19 pandemic experienced commensurate symptomatic improvements compared to patients who received the same treatment prior to the pandemic. To our knowledge, no other studies have evaluated the possibility of attenuated antidepressant efficacy during periods of restrictions on in-person social interactions, despite the importance of social support in the treatment of mental illness. As IV ketamine must be administered in-person, both patients and healthcare providers must weigh the risks and benefits of increased chance of exposure to COVID-19 with an important, and potentially life-saving, medical treatment. The effectiveness of IV ketamine, despite restrictions and lockdowns that limit social interactions, should be considered during the decision-making process.

Furthermore, emerging evidence suggests that individuals with serious mental illness, including treatment-resistant depression (TRD), are at increased risk for contracting COVID-19 and are more likely to experience adverse health outcomes if hospitalized (Wang et al., 2021). Although underlying pathophysiological mechanisms that contribute to this increased risk have not yet been sufficiently evaluated, it can be conjectured that treating serious mental illness may reduce adverse outcomes related to COVID-19 in this population (Rosenblat et al., 2014).

Taken together, patients and treatment providers should not expect that individuals receiving IV ketamine treatment during the COVID-19 pandemic would experience an attenuated treatment response. The extent to which these findings can be generalized to other mental illnesses or psychiatric treatment modalities remains to be determined.

Disclosures

JDR is the medical director of the Braxia Health (formally known as the Canadian Rapid Treatment Center of Excellence and is a fully owned subsidiary of Braxia Scientific Corp) which provides ketamine and esketamine treatment for depression; he has received research grant support from the American Psychiatric Association, the American Society of Psychopharmacology, the Canadian Cancer Society, the Canadian Psychiatric Association, the Joseph M. West Family Memorial Fund, the Timeposters Fellowship, the University Health Network centre for Mental Health, and the University of Toronto and speaking, consultation, or research fees from Allergan, COMPASS, Janssen, Lundbeck, and Sunovion.

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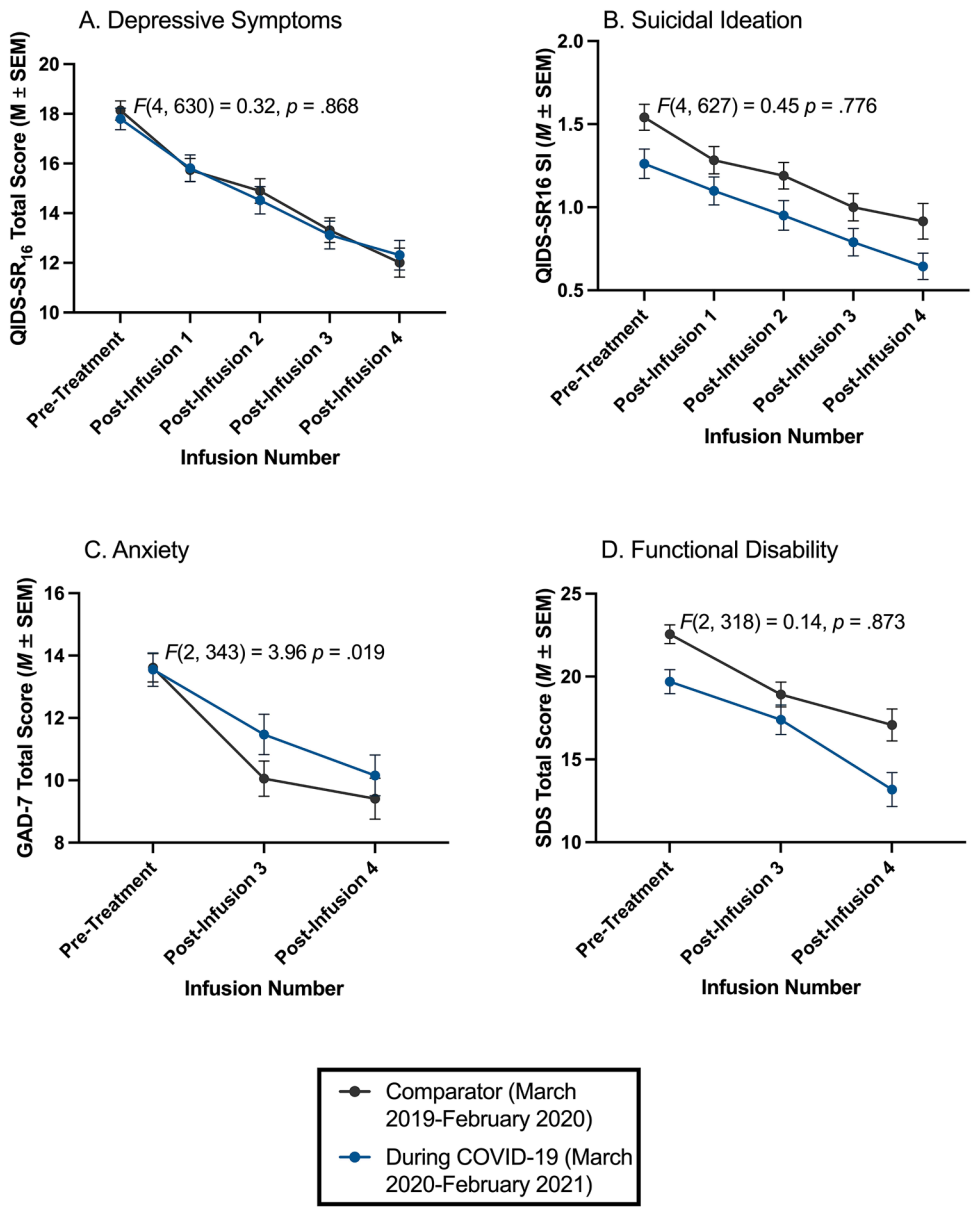

Fig. 1. Changes in depressive symptoms (QIDS-SR16), suicidal ideation (QIDS-SR16 suicidal ideation item), anxiety symptoms (GAD-7), and functional disability (SDS) with four ketamine infusions in adults with treatment-resistant depression receiving treatment before ($n = 160$) and during ($n = 107$) the COVID-19 pandemic.

Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. RSM is a CEO of Braxia Scientific Corp.

YL received salary support from the Global Alliance for Chronic Diseases/Canadian Institutes of Health Research (CIHR)/National Natural Science Foundation of China's Mental Health Team Grant and the CIHR Frederick Banting and Charles Best Canada Graduate Scholarship; personal fees from Braxia Scientific Corp.

KK is the Vice President of Operations at Braxia Health and is a shareholder of Braxia Scientific Corp.

AKA, AA, EHC, WS, and LW are staff physicians at the Canadian Rapid Treatment Center of Excellence.

CRediT authorship contribution statement

Joshua D. Rosenblat: Writing – original draft, Data curation, Writing – review & editing. **Orly Lipsitz:** Writing – original draft, Data curation, Writing – review & editing. **Joshua D. Di Vincenzo:** Writing – original draft, Data curation, Writing – review & editing. **Nelson B. Rodrigues:** Data curation, Writing – review & editing. **Kevin Kratiuk:** Data curation, Writing – review & editing. **Mehala Subramaniapillai:** Data curation, Writing – review & editing. **Yena Lee:** Data curation, Writing – review & editing. **Anil K. Arekapudi:** Data curation, Writing – review & editing. **Amir Abrishami:** Data curation, Writing – review & editing. **Edmond H. Chau:** Data curation, Writing – review & editing. **Witold Szpejda:** Data curation, Writing – review & editing. **Leslie Wong:** Data curation, Writing – review & editing. **Rodrigo B. Mansur:** Data curation, Writing – review & editing. **Roger S. McIntyre:** Data curation, Writing – review & editing.

References

Bartoli, F., Riboldi, I., Crocamo, C., Di Brita, C., Clerici, M., Carrà, G., 2017. Ketamine as a rapid-acting agent for suicidal ideation: a meta-analysis. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.03.010.

Castro, V.M., Gunning, F.M., McCoy, T.H., Perlis, R.H., 2021. Mood disorders and outcomes of COVID-19 hospitalizations. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2020.20060842 appi.ajp.2020.2.

Hao, F., Tan, W., Jiang, L., Zhang, L., Zhao, X., Zou, Y., Hu, Y., Luo, X., Jiang, X., McIntyre, R.S., Tran, B., Sun, J., Zhang, Z., Ho, R., Ho, C., Tam, W., 2020. Do psychiatric patients experience more psychiatric symptoms during COVID-19

pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain Behav. Immun. 87, 100–106. https://doi.org/10.1016/j.bbi.2020.04.069.

Lee, Y., Ragguett, R.M., Mansur, R.B., Boutilier, J.J., Rosenblat, J.D., Trevizol, A., Brietzke, E., Lin, K., Pan, Z., Subramaniapillai, M., Chan, T.C.Y., Fus, D., Park, C., Musial, N., Zuckerman, H., Chen, V.C.H., Ho, R., Rong, C., McIntyre, R.S., 2018. Applications of machine learning algorithms to predict therapeutic outcomes in depression: a meta-analysis and systematic review. J. Affect. Disord. https://doi.org/10.1016/j.jad.2018.08.073.

Maj, M., Stein, D.J., Parker, G., Zimmerman, M., Fava, G.A., De Hert, M., Demyttenaere, K., McIntyre, R.S., Widiger, T., Wittchen, H., 2020. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry 19, 269–293. https://doi.org/10.1002/wps.20771.

McIntyre, R.S., Carvalho, I.P., Lui, L.M.W., Majeed, A., Masand, P.S., Gill, H., Rodrigues, N.B., Lipsitz, O., Coles, A.C., Lee, Y., Tamura, J.K., Iacobucci, M., Phan, L., Nasri, F., Singhal, N., Wong, E.R., Subramaniapillai, M., Mansur, R., Ho, R., Lam, R.W., Rosenblat, J.D., 2020a. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. J. Affect. Disord. https://doi.org/10.1016/j.jad.2020.06.050.

McIntyre, R.S., Rodrigues, N.B., Lee, Y., Lipsitz, O., Subramaniapillai, M., Gill, H., Nasri, F., Majeed, A., Lui, L.M.W., Senyk, O., Phan, L., Carvalho, I.P., Siegel, A., Mansur, R.B., Brietzke, E., Kratiuk, K., Arekapudi, A.K., Abrishami, A., Chau, E.H., Szpejda, W., Rosenblat, J.D., 2020b. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian rapid treatment center of excellence. J. Affect. Disord. 274, 903–910. https://doi.org/10.1016/j.jad.2020.05.088.

McIntyre, R.S., Rodrigues, N.B., Lee, Y., Lipsitz, O., Subramaniapillai, M., Gill, H., Nasri, F., Majeed, A., Lui, L.M.W., Senyk, O., Phan, L., Carvalho, I.P., Siegel, A., Mansur, R.B., Brietzke, E., Kratiuk, K., Arekapudi, A.K., Abrishami, A., Chau, E.H., Szpejda, W., Rosenblat, J.D., 2020c. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian rapid treatment center of excellence. J. Affect. Disord. 274, 903–910. https://doi.org/10.1016/j.jad.2020.05.088.

McIntyre, R.S., Rosenblat, J.D., Nemeroff, C.B., Sanacora, G., Murrough, J.W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D.V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J.G., Lee, Y., Lui, L.M.W., Mansur, R.B., Papakostas, G.I., Subramaniapillai, M., Thase, M., Vieta, E., Young, A.H., Zarate, C.A., Stahl, S., 2021. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2020.20081251 appi.ajp.2020.2.

Ozbay, F., Johnson, D.C., Dimoulas, E., Morgan, C.A., Charney, D., Southwick, S., 2007. Social support and resilience to stress: from neurobiology to clinical practice. Psychiatry (Edgmont) 4, 35–40.

Park, C., Majeed, A., Gill, H., Tamura, J., Ho, R.C., Mansur, R.B., Nasri, F., Lee, Y., Rosenblat, J.D., Wong, E., McIntyre, R.S., 2020. The effect of loneliness on distinct health outcomes: a comprehensive review and meta-analysis. Psychiatry Res. https://doi.org/10.1016/j.psychres.2020.113514.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., Johnson, S., 2018. Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. BMC Psychiatry 18, 156. https://doi.org/10.1186/s12888-018-1736-5.

Wang, Y., Shi, L., Que, J., Lu, Q., Liu, L., Lu, Z., Xu, Y., Liu, J., Sun, Y., Meng, S., Yuan, K., Ran, M., Lu, L., Bao, Y., Shi, J., 2021a. The impact of quarantine on mental health status among general population in China during the COVID-19 pandemic. Mol. Psychiatry 1–10. https://doi.org/10.1038/s41380-021-01019-y.

Rosenblat, J.D., Cha, D.S., Mansur, R.B., McIntyre, R.S., 2014. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 53, 23–34. https://doi.org/10.1016/j.pnpbp.2014.01.013.

Wang, Q., Xu, R., Volkow, N.D., 2021. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiatry 20, 124–130. https://doi.org/10.1002/wps.20806.