mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Intranasal ketamine as a treatment for psychiatric complications of long COVID: A case report

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How to cite: Baldwin K, Wanson A, Gilecki L-A, Dalton C, Peters E, Halpape K. Intranasal ketamine as a treatment for psychiatric complications of long COVID: A case report. Ment Health Clin [Internet]. 2023;13(5):239-43. DOI: 10.9740/mhc.2023.10.239.

Submitted for Publication: January 5, 2023; **Accepted for Publication:** June 20, 2023

Abstract

Background: Neuropsychiatric symptoms associated with long COVID are a growing concern. A proposed pathophysiology is increased inflammatory mediators. There is evidence that typical serotonergic antidepressants have limited efficacy in the presence of inflammation. Although ketamine has shown promise in MDD, there is limited evidence supporting the use of ketamine to treat depressive symptoms associated with long COVID.

Case Report: This case took place on an inpatient psychiatry unit in a Canadian hospital. The patient was admitted with a 10-month history of worsening depression and suicidality following infection with COVID-19. Depressive symptoms and suicidal ideation were assessed throughout treatment using the Montgomery-Asberg Depression Rating Scale (MADRS). Written informed consent was obtained prior to data collection. This patient received 4 doses of intranasal ketamine which resulted in rapid improvement of depressive symptoms and complete resolution of suicidality with no major adverse events.

Discussion: There is evidence to support long COVID symptoms result from dysregulated inflammatory processes. The presence of inflammation in patients with MDD has correlated to poor outcomes with first-line antidepressants. It has been demonstrated that IV ketamine is associated with decreased inflammatory mediators and proportional decrease in depressive symptoms.

Conclusions: Intranasal ketamine in this case was effective at treating depressive symptoms and suicidal ideation associated with long COVID. This is consistent with available data that demonstrates ketamine's efficacy in reducing inflammatory mediators associated with neuropsychiatric symptoms. Therefore, ketamine may be a potential therapeutic option to treat long COVID and persistent depressive symptoms.

Keywords: long COVID, ketamine, depression, suicidality, inflammatory mediators

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Disclosures: K. Halpape used funding from her University of Saskatchewan College of Pharmacy and Nutrition Faculty Recruitment and Retention Program to hire Kaitlyn Baldwin as a research assistant for this work. K. Halpape has also received honoraria for work as a chapter editor for the Clinical Handbook of Psychotropic Drugs and for presentations with the Canadian Society of Hospital Pharmacists (work unrelated to this manuscript). All other authors have no disclosures to declare. This work was supported by the University of Saskatchewan College of Pharmacy and Nutrition Faculty Recruitment and Retention Program.

Background

The prevalence of MDD in Canada has increased since the onset of the COVID-19 pandemic.[1] Approximately 30% of patients with MDD have treatment refractory depression (TRD), defined as a failure to respond to 2 oral antidepressants.[2,3] Evidence supports the antidepressant and anti-suicidal effects of ketamine in TRD. The 2021 Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline recommends IV racemic ketamine third-line for TRD, supported by systematic reviews or randomized control trials. Use of non-IV formulations of racemic ketamine are supported by small randomized control trials or observational studies and should be specialist guideded.[4] Ketamine is a racemic mixture of (R)-ketamine and (S)-ketamine; (S)-ketamine has higher affinity for NMDA receptors, potentially contributing more to the antidepressant effect.[3] A noninferiority study on TRD identified similar remission rates with IV racemic ketamine and (S)-ketamine; however, racemic ketamine had a more prolonged antidepressant effect, although not statistically significant.[5]

Bioavailability of intranasal (IN) vs IV ketamine is 8% to 45% and 100%, respectively; therefore, IN may produce less reliable benefit.[3,6] Evidence supports rapid reduction of depressive symptoms after administration of IN (S)-ketamine.[7,8] There is less research to support use of racemic IN ketamine (INK) which is a barrier as the cost of racemic INK is lower than (S)-ketamine, $42 vs $590 to $885 USD per treatment.[9] A single published randomized control trial of eighteen participants that completed two treatments of racemic INK supports the rapid antidepressant effect of INK.[10]

Long COVID-19 is a syndrome of prolonged symptoms that last more than 4 weeks after initial disease onset.[11] Recent evidence reports anxiety and depression as a component of long COVID-19 symptoms in 10% to 23% of patients 1 to 6 months after diagnosis.[11-16] Depression prevalence during hospitalization for COVID-19 has been reported as 50%.[13] Incidence of neuropsychiatric complications is more common in hospitalized patients with COVID-19 compared to matched groups of patients with other respiratory tract infections.[17] The proposed pathophysiological cause of neuropsychiatric sequalae in COVID-19 is related to inflammatory cytokines such as IL-6, which is supported by relation between inflammation and depression at 3 month follow-up of hospitalized patients with COVID-19.[17-19]

The relationship between inflammation and MDD is not isolated to COVID-19. A systematic review showed that serotonergic antidepressants had reduced response rates in patients with high inflammatory markers, IL-6 and C-reactive protein.[20] Symptom improvement in MDD is correlated with altered levels of IL-17A and IL-6.[21] These inflammatory factors are downregulated by ketamine.[20] However, there is limited efficacy and safety data of INK to treat psychiatric symptoms related to long COVID.

We present a patient experiencing neuropsychiatric symptoms related to long COVID who was treated with racemic INK, resulting in rapid improvement in symptoms including complete resolution of suicidal ideation (SI) with no adverse effects.

Case Report

This is a case study of a patient admitted to a Canadian inpatient psychiatric unit. Consent was obtained in writing before data collection. Electronic medical records were reviewed and summarized. The patient was a 41-year-old female who was admitted for depressive symptoms and SI. This was the patient's first psychiatric admission, and she had no prior suicide attempts.

The patient had episodes of depressed mood and panic attacks prior to COVID-19; however, she experienced deterioration in her mental health following her first COVID-19 infection, despite being vaccinated. Ten months prior to admission, when she had acute COVID-19, the patient reported low mood, "brain fog", low energy, difficulty concentrating, and was sleeping 11 or more hours per night. These symptoms persisted following infection resolution. At admission, the patient had a 3-week history of worsening mood, guilt, decreased appetite, and SI with no identifiable trigger.

A mental status exam at admission revealed emotional lability with the patient intermittently crying and irritable when discussing her frustration with her symptoms. The patient had psychomotor slowing and endorsed active SI. The patient did not exhibit any symptoms of mania nor psychosis.

Psychiatric history included self-reported MDD and generalized anxiety disorder, both diagnoses confirmed by the psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria. Family history included a first-degree relative with bipolar affective disorder. Active medical conditions included long COVID. The patient denied use of recreational substances.

The patient had a documented history of antidepressant use for years. At admission she had been taking fluoxetine for 7 years. For 10 months prior to being diagnosed with COVID-19 she was stabilized on fluoxetine 40 mg daily with no augmenting medications. Around the time she was diagnosed with COVID-19, she started quetiapine and buspirone, which she used along with fluoxetine until admission. Her medications prior to hospitalization, including over-the-counter medications, and a psychopharmacotherapy history are summarized in Table 1. Medication adherence was optimal as verified based on outpatient prescription refill history and patient report.

On admission, quetiapine extended release (ER) was increased to 150 mg orally at bedtime with the addition of quetiapine

TABLE 1: Medications at initial discharge, prior to hospitalization, and previous psychopharmaceutical trials

Medications At Discharge
Quetiapine ER 100 mg orally at bedtime
Fluoxetine 60 mg orally once daily
ASA 81 mg orally once daily
Ropinirole 0.5 mg orally twice daily
Vitamin B12 5000 mcg orally once daily
Ferrous gluconate 300 mg orally once daily
Desloratadine 5 mg orally once daily
Acetaminophen 500 mg orally 3 times daily
Medications Prior to Hospitalization
Quetiapine ER 50 mg orally at bedtime
Fluoxetine 40 mg orally once daily
ASA 81 mg orally once daily
Ropinirole 0.5 mg orally twice daily
Buspirone 10 mg orally three times daily
Vitamin B12 5000 mcg orally once daily
Ferrous gluconate 300 mg orally once daily
Desloratadine 5 mg orally once daily
Acetaminophen 500 mg orally 3 times daily
Previous Psychopharmaceutical Trials
Clonazepam 0.25 mg orally twice daily as needed; date of discontinuation unknown
Lamotrigine 25 mg orally in the morning and 50 mg at bedtime; discontinued 4 years ago
Gabapentin (dose unknown); discontinued 4 years ago
Propranolol (dose unknown); discontinued 4 years ago
Paroxetine (dose unknown); discontinued 16 years ago

ASA = acetylsalicylic acid; ER = extended release.

immediate release (IR) 12.5 mg to 50 mg as needed (PRN) for sleep and anxiety. Fluoxetine dose was increased to 60 mg daily for low mood. Lorazepam 1 mg to 2 mg 4 times daily PRN was added for anxiety and was used intermittently until ketamine was initiated and then no further doses were required. Two days after admission, buspirone was decreased to 5 mg 3 times daily for 5 days, then was stopped, as it was ineffective. Despite initial changes, the patient continued to experience severe low mood (Montgomery-Asberg Depression Rating Scale (MADRS) 38 at baseline), psychomotor retardation, cognitive dysfunction, and active SI. Given the diagnosis of TRD and severity of symptoms, INK or electroconvulsive therapy (ECT), in addition to optimized oral medications, were presented as treatment options. The patient selected ketamine treatment.

On the eighth day of hospitalization, the patient started a 4-dose INK treatment protocol that had been previously developed for use in this center with dosing based on a study by Lapidus et al (Table 2).[10] At the time of this case the protocol had nonformulary hospital approval and ketamine was compounded by a secondary pharmacy. Within this protocol the ketamine

TABLE 2: Intranasal ketamine protocol

Day 1: 50 mg dose given to assess tolerability. On Day 1 the psychiatrist will meet with patient and review with nurse after the treatment has been completed.
Day 2: 75 mg dose given. At the discretion of the psychiatrist, a 50 mg dose may be given instead (and must be indicated in the physician orders of the patient's chart). Psychiatrist will meet with patient and review with nurse after the treatment has been complete on Day 2.
Day 3: No ketamine given. Psychiatrist will meet with patient and complete MADRS scale to assess response. Treatment may be discontinued at this time if an inadequate response has been achieved.
Day 4: 75 mg dose given. At the discretion of the psychiatrist, a 50 mg dose may be given instead (and must be indicated in the physician orders of the patient's chart). Psychiatrist will meet with patient and review with nurse after the treatment has been complete on Day 4.
Day 5: No ketamine given. Psychiatrist will meet with patient and complete MADRS scale to assess response. Treatment may be discontinued at this time if an inadequate response has been achieved.
Day 6: 75 mg dose given. At the discretion of the psychiatrist, a 50 mg dose may be given instead (and must be indicated in the physician orders of the patient's chart). Psychiatrist will meet with patient and review with nurse after the treatment has been complete on Day 6.
Day 7: No ketamine given. Psychiatrist will complete final MADRS assessment and make community arrangements for follow-up, if needed.

MADRS = Montgomery-Asberg Depression Rating Scale.

doses are as follows: dose 1, 50 mg; doses 2 to 4, 75 mg; all administered as 25 mg per spray with 5 minutes between each spray. The doses administered and the patient's response are presented in Table 3. The patient's mental status and MADRS score improved substantially, from 38 to 3, over the treatment course, with notable improvements after the first 2 treatments. Her SI also remitted (MADRS suicide item score decreased from 4 to 0) after the first treatment and remained so throughout the remainder of her admission. There were no significant blood pressure changes, dissociative effects, or other adverse effects. The patient was discharged on day 15 with a prescription for fluoxetine 60 mg once daily and quetiapine ER 100 mg at bedtime; dose of quetiapine was decreased as insomnia had improved (Table 1). The patient reported lingering anxiety but significantly improved depressive symptoms and felt optimistic about discharge. She was scheduled to receive outpatient INK 6 weeks after discharge.

This patient represented to care 1 month after discharge with relapsing symptoms of low mood, SI, guilt, hypersomnia, low energy, and low concentration. The patient was discharged with prescriptions for fluoxetine 80 mg daily, quetiapine ER 100 mg at bedtime, bupropion ER 150 mg daily, and clonazepam 0.25 mg to 0.5 mg PRN. She maintained her scheduled outpatient appointment for INK and did not receive additional doses as an inpatient.

TABLE 3: Intranasal ketamine treatment and response

Admission Day	Ketamine Dose	MADRS	Mental Status Exam	Max Blood Pressure Postdose (mm Hg)
1 (Admission)	…	…	Active SI, low mood	…
8	50 mg	38 (prior to dose)	…	SBP: 116 DBP: 60
9	75 mg	…	Full affect, euthymic mood, no SI	…
10	…	16	Full affect, euthymic mood, no SI	SBP: 119 DBP: 64
11	75 mg	…	Bright affect, no SI	…
12	…	…	…	SBP: 111 DBP: 64
13	…	…	…	…
14	75 mg	14	Affect bright and reactive, mood good, no SI	…
15	…	3	Optimistic and improved mood, no SI	SBP: 112 DBP: 64

DBP = diastolic blood pressure; MADRS = Montgomery-Asberg Depression Rating Scale; SBP = systolic blood pressure; SI = suicidal ideation.

Discussion

There is growing evidence that supports the hypothesis that long COVID symptoms such as fatigue and depressed mood are a consequence of dysregulated inflammatory processes.[17-19] A systematic review of 174 studies evaluated the affects of low-grade inflammation on outcomes of patients treated with antidepressants. The presence of inflammation in patients with MDD was correlated with poor outcomes with first-line antidepressants. Furthermore, when anti-inflammatory agents (eg, infliximab, minocycline) were used in combination with serotonergic antidepressant, or if ketamine was used alone, patient response improved.[20]

A study reported that MADRS scores correlated with inflammatory markers decreased following IV ketamine infusions. Changes in IL-17A and IL-6 correlated with depressive symptom improvement by day 13.[21] Given the similar proposed pathophysiology, the results of this study could be extrapolated to long COVID.

There is a paucity of research regarding the treatment of depressive symptoms in the context of long COVID. This case describes the effectiveness and safety of INK, in combination with optimization of oral psychotropic medications, for treating TRD in general and suggests efficacy may extend to depressive symptoms associated with COVID. Similarly, Meha et al reported a case of successful use of IV ketamine for the treatment of severe depression with suicidality in the setting of recent COVID-19 infection.[22] Research is required to further evaluate ketamine in this population, including long-term efficacy. Furthermore, future research could compare the convenience and duration of effect of IN versus IV ketamine as a treatment for depressive symptoms associated with long COVID. Additionally, considering recent FDA warnings, research is needed to explore the potential risks of off-label use of INK.[23]

Conclusion

This case serves as preliminary evidence that INK is effective for treatment of depressive symptoms and suicidality associated with long COVID. It suggests that benefit from INK in this population may last 1 month. More research is required to understand the etiology of depressive symptoms in long COVID and the optimal regimen of ketamine for these patients.

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