Adjunctive music improves the tolerability of intravenous ketamine for bipolar depression

Kyle T Greenway*, Nicolas Garel, Nathalie Goyette, Gustavo Turecki, Stephane Richard-Devantoy*

Intravenous ketamine is an effective treatment of bipolar depression. One of its most important side-effects is a transient altered state of consciousness commonly referred to as dissociation. These states can be anxiety-provoking, distressing and even treatment-limiting, warranting research into mitigation strategies. In this article, we present two cases that demonstrate the potential of adjunctive music to diminish the distress associated with ketamine-induced dissociation – though not necessarily its degree – in bipolar 1 disorder. Both patients suffering from severe depression underwent their first ketamine infusion without music and opted for music with subsequent infusions. They reported that music significantly improved the tolerance of their dissociative symptoms, thereby reducing distress and facilitating subsequent treatments. Both patients achieved remission from their highly treatment-resistant depressive episodes following six ketamine infusions. This is the first report of music's benefits on ketamine for bipolar 1 depression, though there is precedence in the scientific literature on 'psychedelics' where the use of music in combination with medication-induced altered states has been studied. The principles regarding music selection that have resulted from this paradigm may be applicable to the use of ketamine in unipolar and bipolar depression. The optimal use of music with ketamine warrants further research. ***Int Clin Psychopharmacol*** **XXX: 000–000**

International Clinical Psychopharmacology 2021, **XXX**:000–000

Keywords: bipolar disorder, depression, dissociation, ketamine, music, psychedelics

Douglas Mental Health Research Institute, McGill University, McGill Group for Suicide Studies, Montréal, Québec, Canada

Correspondence to Kyle T Greenway, MD MSc, Department of Psychiatry, McGill University, McGill Group for Suicide Studies, Douglas Mental Health University Institute, FBC building, 3rd floor, 6875 boulevard Lasalle, Montréal (Qc) H3W 2N1, Canada
Tel: +1 514 761 6131 x 3310; fax: +1 514 888 4466;
e-mail: kyle.greenway@mail.mcgill.ca

*Kyle T Greenway and Stephane Richard-Devantoy both should be considered co-corresponding authors.

Received 16 January 2021 **Accepted** 30 March 2021

Background

The emergence of ketamine as a rapid antidepressant is among the most important pharmacological developments in psychiatry in decades (Duman, 2018). One of the major safety considerations with both ketamine and esketamine, its s-enantiomer, is the altered states of consciousness they temporarily induce (Correia-Melo *et al*., 2019). These states, typically referred to as dissociation, can be distressing and treatment-limiting. Pharmacological strategies against this distress, such as co-administering benzodiazepines, may reduce treatment efficacy (Andrashko *et al*., 2019). Alternative strategies are thus needed.

Recently, in this journal, music was described as a non-pharmacological intervention to reduce the distress (though not the degree) of esketamine-induced dissociation (Pereira *et al*., 2021). To our knowledge, this is the first such report with esketamine or racemic ketamine. However, a body of research on 'psychedelic' compounds has demonstrated that music can effectively reduce the distress associated with other medically induced altered states of consciousness. Indeed, the paradigm of Psychedelic-Assisted Psychotherapy emphasizes 'set and setting' as key components of both tolerability and efficacity (Johnson *et al*., 2008). 'Set' refers to the mindset of patients undergoing treatment, and 'setting' refers to the immediate treatment environment. The work by Pereira *et al* (2021), which also describes considerations for the treatment setting, suggests that these treatment aspects may also be relevant to (es-)ketamine, in line with previous studies on ketamine (Dore *et al*., 2019).

Here we describe two successful cases of intravenous (i.v.) ketamine in treatment-refractory bipolar depression where music and optimized treatment environments were highly beneficial. The same dosing regimen utilized in unipolar treatment-resistant depression has shown similar efficacy in treatment-resident bipolar depression (Wilkowska *et al*., 2020). Indeed, both patients remitted following six (off-label) 40-min i.v. infusions of ketamine at the standard dose of 0.5 mg per kg of bodyweight, which is two times more likely to engender dissociative symptoms than other routes like intranasal (Short *et al*., 2018). The first treatments for both patients were administered without music, which was then utilized during the second treatments. Each patient thereafter opted for music throughout their subsequent infusions, to which

0268-1315 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved. DOI: 10.1097/YIC.0000000000000363

they attributed significantly improved tolerability due to less dissociation-associated anxiety.

Cases

Case 1

A 41-year-old female known for the bipolar affective disorder I [by DSM-5 criteria (American Psychiatric Association, 2013)], refractory to adequate trials of more than a dozen psychotropic medications (including multiple antidepressants), was evaluated for treatment by i.v. ketamine infusions in August 2020. She was suffering from severe depression [53 of 63 on the Beck Depression Inventory-II (BDI-II) (Beck *et al.*, 1996)] with minimal response to a medication regimen, including therapeutic doses of bupropion, lithium, buspirone, as well as as-needed alprazolam and zopiclone. She described prominent psychiatric symptoms such as longstanding hopelessness, self-criticism, fatigue and anxiety. She also reported significant current suicidal ideation [26 of 38 on the Scale for Suicide Ideation (SSI) (Beck *et al.*, 1979)]. She was proposed and consented to, our institution's standard protocol of 6 i.v. ketamine infusions over 4 weeks.

During her first infusion, she experienced intense anxiety that she attributed to a feeling of losing control, as well as a dislike of unusual bodily sensations. She also reported auditory hypersensitivity, resulting in irritation associated with, for example, the faint sounds of her clinicians' writing. She required repeated reassurances of safety from the nurse and physician present throughout her infusion.

The next day, she reported significant hesitation about continuing with the planned infusions. With support and encouragement from the treatment team and her referring psychiatrist, she opted to continue the course, albeit with trepidation. On her second treatment, she listened to music throughout her infusion.

The music, largely classical, was described by the patient as significantly reducing her distress. Though the degree of dissociative symptoms was not reduced, she described being able to 'let go' of the associated anxieties, such as the loss of control and fears of medication effects.

She reported only slight benefits following this treatment but also a significant reduction in anxiety and fear about the altered state of consciousness induced by ketamine. She thereafter completed the course of six treatments, experiencing increasing symptomatic improvement throughout. She was encouraged to carefully select among various musical options throughout her treatments, including classical playlists or her own familiar music, and largely opting for the same playlist from her second treatment. Following the course, her depressive symptoms and suicidality improved significantly, evidenced by her BDI-II decreasing by 31 (from 53 to 22) and her SSI decreasing by 16 (from 26 to 10). Both responses were maintained for at least 1 month.

Case 2

A 43-year-old male known for the bipolar affective disorder I (DSM-V) was evaluated for i.v. ketamine in January 2020 while hospitalized for a treatment-resistant depressive episode (BDI-II of 34, SSI of 22). The patient had failed to achieve more than a partial response to more than 20 different psychotropic medications and 30 bitemporal electroconvulsive therapy treatments. He had been admitted to the hospital – his 10th admission in 5 years – with a specific, lethal suicide plan while receiving therapeutic doses of brexipiprazole, levomilnacipran, vortioxetine, quetiapine, benztropine, zopiclone and clonazepam.

As with the first case, he was accepted for treatment by a course of six i.v. ketamine infusions with the first infusion administered without music. During this treatment, he described audiovisual phenomena, a feeling that he 'might die', and anxiety about 'losing control' of his thoughts and feelings. He subsequently reported apprehension about pursuing treatment by ketamine.

Much like the first case, the patient also reported that the effects of ketamine were subjectively altered during the second treatment administered with music. Though their intensity did not differ from the first treatment, he described 'letting go' of negative appraisals about the dissociative effects, which he now described as dreamlike and nondistressing.

The remaining four treatments proceeded similarly and, following the course, he achieved remission from his depressive episode and was shortly thereafter discharged from hospital.

In the year since, the patient has been maintained in remission with additional infusions as per clinical judgment (approximately every 7 weeks). He has thus received a total of 12 ketamine infusions and, because the second, has opted to listen to music with each. His latest BDI-II and SSI were 10 and 0, respectively, and he has not required hospitalization since his discharge.

Discussion

These two cases demonstrate that music can significantly improve the tolerability of ketamine infusions for (severe) bipolar depression. While this is a novel finding, there is precedence in the scientific literature on Psychedelic-Assisted Psychotherapy. In this paradigm, careful attention to the treatment environment (including music) is considered integral to the treatment (Johnson *et al.*, 2008). This approach was largely pioneered with psilocybin and LSD, the former of which is undergoing clinical phase 2b trials for depression with the FDA's 'breakthrough therapy' designation (http://www.clinicaltrials.gov; NCT03866174). Although the states induced by ketamine are typically described differently from those induced by psilocybin – that is, dissociative versus 'psychedelic' – phenomenological studies show significant overlap between both (Studerus *et al.*, 2010), including 'experience of unity' and

'changed meaning of precepts'. These findings, alongside our cases and that reported with esketamine (Pereira *et al.*, 2021), suggest that the body of literature on 'psychedelic' substances may hold lessons for optimizing psychiatric uses of (es-)ketamine.

Indeed, our clinical experiences support other shared features between ketamine and the 'psychedelics'. Both appear to increase susceptibility to music's influence (Kaelen *et al.*, 2018), perhaps unsurprisingly as neuroimaging studies have found significantly altered auditory processing with both ketamine and 'psychedelic' compounds (Kaelen *et al.*, 2018; Schwertner *et al.*, 2018). Further, as with both cases above, numerous patients have experienced a reduction in treatment-associated distress attributable to their 'letting go' of negative thoughts and judgments, which is facilitated by music. 'Let go and be open' are common instructions to patients undergoing Psychedelic-Assisted Psychotherapy (Johnson *et al.*, 2008).

This phenomenological, neuroscientific and clinical evidence suggests that some of the principles of music selection from the psychedelic paradigm hold relevance for ketamine treatments. For instance, music featuring vocals in a language understandable to the patient can strongly influence thoughts during treatment. As this occurs in an unpredictable – and sometimes negative – manner, clinicians and patients may wish to avoid such music. Similarly, whereas calming music can reduce treatment-induced anxiety and agitation, energetic or intense music may have the opposite effect and should therefore be employed judiciously (Johnson *et al.*, 2008). Finally, as with the auditory hypersensitivity described above, a dislike of specific music can be particularly irritating to patients during ketamine treatments.

To our knowledge, no randomized controlled trials have studied music with ketamine for psychiatric indications. Nonetheless, our experiences with dozens of patients suggest that music is a feasible and valuable nonpharmacologic enhancement for ketamine infusions. In both cases described above, music appeared to greatly improve the tolerance of treatments, which were ultimately highly effective, by facilitating infusions and reducing anxiety associated with subsequent treatments.

Conclusion

As reported for esketamine and unipolar depression, music can significantly improve the tolerability of ketamine infusions for severe bipolar depression. The selection of music is important, and clinicians may find value in the principles of the Psychedelic-Assisted Psychotherapy paradigm.

Whether or not music can improve side-effects associated with ketamine beyond anxiety surrounding dissociation remains to be evaluated. A randomized clinical trial, actively enrolling, has been designed expressly to address these questions (http://www.clinicaltrials.gov; NCT03866174).

Acknowledgements

The authors thank the patients involved in this case report. They also thank Nick Murray for his support, including the valuable software of advancedcare.com.

Conflicts of interest

There are no conflicts of interest.

References

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: American Psychiatric Association.

Andrashko V, Novak T, Horacek J, Klirova M, Brunovsky M (2019). Concurrent benzodiazepines undermine the antidepressant effect of ketamine. *Eur Neuropsychopharmacol* **29**:S389–S390.

Beck AT, Kovacs M, Weissman A (1979). Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol* **47**:343–352.

Beck AT, Steer RA, Ball R, Ranieri W (1996). Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* **67**:588–597.

Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, *et al.* (2020). Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. *J Affect Disord* **264**:527–534.

Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, *et al.* (2019). Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs* **51**:189–198.

Duman RS (2018). The Dazzling Promise of Ketamine. *Cerebrum* **2018**:cer–c04.

Johnson M, Richards W, Griffiths R (2008). Human hallucinogen research: guidelines for safety. *J Psychopharmacol* **22**:603–620.

Kaelen M, Giribaldi B, Raine J, Evans L, Timmerman C, Rodriguez N, *et al.* (2018). The hidden therapist: evidence for a central role of music in psychedelic therapy. *Psychopharmacology (Berl)* **235**:505–519.

Pereira S, Brennan E, Patel A, Moran M, Wallier J, Liebowitz MR (2021). Managing dissociative symptoms following the use of esketamine nasal spray: a case report. *Int Clin Psychopharmacol* **36**:54–57.

Schwertner A, Zortea M, Torres FV, Caumo W (2018). Effects of subanesthetic ketamine administration on visual and auditory event-related potentials (ERP) in humans: a systematic review. *Front Behav Neurosci* **12**:70.

Short B, Fong J, Galvez V, Shelker W, Loo CK (2018). Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* **5**:65–78.

Studerus E, Gamma A, Vollenweider FX (2010). Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One* **5**:e12412.

Wilkowska A, Szałach Ł, Cubała WJ (2020). Ketamine in bipolar disorder: a review. *Neuropsychiatr Dis Treat* **16**:2707–2717.