

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of ketamine treatment on suicidal ideation: a qualitative study of patients' accounts following treatment for depression in a UK ketamine clinic
AUTHORS	Lascelles, Karen; Marzano, Lisa; Brand, Fiona; Trueman, Hayley; McShane, Rupert; Hawton, Keith

VERSION 1 – REVIEW

REVIEWER	Hélène Vulser Central Institute of Mental Health, Mannheim, Germany I report a research grant from Servier.
REVIEW RETURNED	14-Mar-2019

GENERAL COMMENTS	<p>This manuscript is interesting. Ketamine treatment for suicidal ideations is relatively recent and the mechanisms underlying this effect remain largely unknown. In this context, qualitative studies appear to be a good first start for a better understanding, by taking into account the patient's perspective.</p> <p>Minor changes should be considered.</p> <p>Title: The authors should add the term "qualitative" in the title.</p> <p>Abstract: The abstract could be improved, as it does not sufficiently reflect the important points of the article. In the objective section, the authors should explain that studying patient's perspective may be a good first step towards a better understanding of the underlying mechanisms of ketamine on SI. In the design and setting action, the part "all but one of whom who had received treatment with ketamine within the last year" of the first sentence is confusing, especially since the Participants section indicate that: "Fourteen patients (...) who received treatment with ketamine in the preceding year for treatment-resistant depression..."</p> <p>The authors may consider deleting the part "with treatment-resistant depression, including SI, all but one of whom who had received treatment with ketamine within the last year" and to keep only "who had received treatment with ketamine" since the Participants are described in the following part of the abstract. The conclusion part of the abstract does not correspond enough to the manuscript. The authors should write another conclusion for the abstract, inspired by their excellent conclusion of the article.</p> <p>The introduction well introduces the manuscript.</p> <p>Method section. Recruitment part: In the sentence "Standard treatment at this clinic is an initial three intravenous ketamine</p>
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	<p>treatments (infusions) [0.5mg/kg] followed by oral ketamine or a combination or oral and intravenous treatments”, “combination or oral” should be replaced by “combination OF oral”.</p> <p>Results/Discussion: Hopelessness does not appear in the thematics reported. The authors should address this issue in the results and/or in the discussion if patients did not report improvement in hopelessness. Indeed, several studies and case reports have reported a significant improvement in hopelessness after ketamine treatment, which is a well-recognized risk factor for suicide attempt. The authors may cite for this: Burger et al . Mil Med. 2016;181:1195–1199; DiazGranados et al. J Clin Psychiatry. 2010;71:1605–1611; Price et al. Depress Anxiety. 2014;31:335–343; Vulser et al. J Psychiatr Pract. 2018;24(1):56-59.</p> <p>Discussion: The first paragraph of the discussion should sum up the study and not the introduction section.</p>
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REVIEWER	Domenico De Berardis National Health Service, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, "G. Mazzini" Hospital, p.zza Italia 1, 64100 Teramo, Italy
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	<p>The aim of this qualitative study was to explore patient perspectives on the impact of ketamine treatment on suicidal ideation (SI) in the context of treatment-resistant depression, including perceived benefits and how these might occur. The Authors interviewed fourteen patients (8 females, 6 males, aged 24-64 years) who received treatment with ketamine in the preceding year for treatment-resistant depression, who also had SI at the initiation of treatment. Eight subjects had a history of self-harm. Overall, I found the paper very interesting, timely and scientifically sound. I have only some minor comments on it:</p> <ol style="list-style-type: none"> 1) I suggest Authors to add a brief note in the Discussion on the potential neurobiological mechanisms underlying the action of ketamine on PSD, glutamate and SI with appropriate references (see Tomasetti et al. Curr Pharm Des 2019 and Int J Mol Sci 2017;18(1); De Berardis et al. Int J Mol Sci 2018;19(10). 2) Which kind of adverse effects patients reported and which treatment was prescribed after or in concomitance of ketamine?
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REVIEWER	Mirko Manchia University of Cagliari, Cagliari, Italy
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	<p>This is a qualitative analysis of patients' reports of the impact of ketamine treatment on suicidal ideation including duration of effects and possible mechanisms.</p> <p>The investigators studied 14 treatment-resistant depression and suicidal ideation patients taking ketamine in the preceding year for, of whom eight had a history of self-harm. Thematic analysis was carried out applying the six stages of analysis method.</p> <p>In general, treatment with ketamine was reported as reducing suicidal ideation in 12 out of 14 participants but the intensity and duration of effects on suicidal ideation varied greatly. The study is well written and performed impeccably. I found very relevant that</p>
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	<p>patients' perspective on ketamine efficacy are analyzed qualitatively with proper methodology.</p> <p>Minor points:</p> <ul style="list-style-type: none"> - Stating that ketamine is only a NMDAR antagonist is too simplistic, please mention briefly some of the mechanisms of action proposed (see Zanos and Gould 2018) - Heterogeneity: among the 14 participants meeting criteria for treatment-resistant depression there were diverse diagnoses: bipolar disorder type 1, unstable personality disorder, and depression. I wonder whether this heterogeneity has impacted the results: for instance how was the perception of ketamine in the patient with personality disorder? Further, the presence of diverse diagnoses should be reported in the abstract - There is a discrepancy between the inclusion criteria (diagnosis of unipolar or bipolar treatment resistant depression) and the presence of a patient with personality disorder.
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1.

1. Title: The authors should add the term “qualitative” in the title.

Our response: Thank you, we have amended our title accordingly as noted under Editors comments above.

2. Abstract: The abstract could be improved, as it does not sufficiently reflect the important points of the article.

Our response: Thank you for your points which have helped us improve the quality of our abstract. We have responded to each point below.

- In the objective section, the authors should explain that studying patient's perspective may be a good first step towards a better understanding of the underlying mechanisms of ketamine on SI.

Our response: we have added a sentence in the abstract clarifying that studying patients' perspectives can contribute to greater understanding of the mechanisms underlying impact of ketamine treatment on suicidal ideation (page 2).

- In the design and setting action, the part “all but one of whom who had received treatment with ketamine within the last year” of the first sentence is confusing, especially since the Participants section indicate that: “Fourteen patients (...) who received treatment with ketamine in the preceding year for treatment-resistant depression...” The authors may consider deleting the part “with treatment-resistant depression, including SI, all but one of whom who had received treatment with ketamine within the last year” and to keep only “who had received treatment with ketamine” since the Participants are described in the following part of the abstract.

Our response: Thank you, we have amended as you suggest and referred to the one participant who had received ketamine over one year ago in the Methods section (page 5) and Results section (page 8).

- The conclusion part of the abstract does not correspond enough to the manuscript. The authors should write another conclusion for the abstract, inspired by their excellent conclusion of the article.

Our response: We have changed our conclusion as below and agree it is now improved, thank you.

Generally, ketamine treatment was experienced as effective in reducing suicidal ideation, although duration of effects varied considerably. Patients' perspectives indicated similarities in the mechanisms of reduction in suicidal ideation, but some differences in their manifestation, particularly in relation to chronology. Experiences of this cohort suggest that reduced anxiety and improvement in ability to think and function were important mechanisms alongside, or in some cases independently of, improvement in mood. Further studies of patients' experiences are required to gain enhanced understanding of the variability of effects of ketamine on suicidal ideation and functionality.

3. Method section. Recruitment part: In the sentence “Standard treatment at this clinic is an initial three intravenous ketamine treatments (infusions) [0.5mg/kg] followed by oral ketamine or a combination or oral and intravenous treatments”, “combination or oral” should be replaced by “combination OF oral”.

Our response: thank you for picking up this typo; we have amended accordingly.

4. Results/Discussion: Hopelessness does not appear in the thematics reported. The authors should address this issue in the results and/or in the discussion if patients did not report improvement in hopelessness. Indeed, several studies and case reports have reported a significant improvement in hopelessness after ketamine treatment, which is a well-recognized risk factor for suicide attempt. The authors may cite for this: Burger et al. *Mil Med.* 2016;181:1195–1199; DiazGranados et al. *J Clin Psychiatry.* 2010;71:1605–1611; Price et al. *Depress Anxiety.* 2014;31:335–343; Vulser et al. *J Psychiatr Pract.* 2018;24(1):56-59.

Our response: Thanks for raising this important point. Hopelessness did not emerge as a key theme in our analysis, possibly because we did not specifically ask participants about this. However, some accounts did suggest that hopelessness reduced as mood improved and because participants experienced a sense of hope because the treatment was providing symptomatic relief. We have now added a paragraph in the Results and Discussion sections to convey this (pages 18 and 19) and suggested that hopelessness is studied in future research in the Conclusion (page 21).

5. Discussion: The first paragraph of the discussion should sum up the study and not the introduction section.

Our response: Thank you; we have amended the first sentence of the Discussion section to: *In this study we explored patients' accounts of the impact of ketamine treatment on their suicidal thinking and perspectives of the associated mechanisms.*

Reviewer: 2

1. I suggest Authors to add a brief note in the Discussion on the potential neurobiological mechanisms underlying the action of ketamine on PSD, glutamate and SI with appropriate references (see Tomasetti et al. *Curr Pharm Des* 2019 and Int J Mol Sci 2017;18(1); De Berardis et al. *Int J Mol Sci* 2018;19(10)).

Our response: Thank you. We agree that this would be helpful and have added to the introduction (page 4).

2. Which kind of adverse effects patients reported, and which treatment was prescribed after or in concomitance of ketamine?

Our response: Thank you, we have elaborated on the adverse experiences experienced by one participant as below and added a sentence in the 'other side effects' section to state that no participant required medication to address side effects. In addition, we have revised the side effects section to improve flow and clarity.

"For one participant, who went on to stop treatment due to side effects, this was experienced as malevolent hallucinations and an acute increase in pre-existing intrusive and disturbing thoughts and mental images. These effects continued for two days post treatment, and the participant reported a sustained worsening of the pre-existing thoughts and images even at the point of interview."

We have also added a sentence regarding adjunctive treatments that participants were taking in addition to ketamine, *"Participants were in receipt of a range of other antidepressant, anxiolytic, mood stabiliser and psychological treatments, which were not prescribed by the ketamine clinic"*.

(page 5).

Reviewer: 3

1. Stating that ketamine is only a NMDAR antagonist is too simplistic, please mention briefly some of the mechanisms of action proposed (see Zanos and Gould 2018)

Our response: Thank you. Please see our response to Reviewer 2 above and the Introduction section (page 4).

2. Heterogeneity: among the 14 participants meeting criteria for treatment-resistant depression there were diverse diagnoses: bipolar disorder type 1, unstable personality disorder, and depression. I wonder whether this heterogeneity has impacted the results: for instance, how was the perception of ketamine in the patient with personality disorder? Further, the presence of diverse diagnoses should be reported in the abstract.

Our response: Thank you, this is a good point. We have reported the presence of diverse diagnoses in the abstract in addition to the reporting in the results section. In the perceived mechanisms

contributing to reduced suicidal ideation section (pages 14 and 15) we have included the following sentence:

“These perceptions were consistent across the sample, and accounts of individuals with primary diagnoses of bipolar disorder or emotionally unstable personality disorder did not appear to differ significantly from those of participants with a primary diagnosis of depression.”

3. There is a discrepancy between the inclusion criteria (diagnosis of unipolar or bipolar treatment resistant depression) and the presence of a patient with personality disorder.

Our response: All participants met criteria for treatment resistant depression, including those with diagnosed personality disorders as specified in the Methods section (page 5) and Results section (page 8).

VERSION 2 – REVIEW

REVIEWER	Mirko Manchia University of Cagliari, Cagliari, Italy Dalhousie University, Halifax, Nova Scotia, Canada
REVIEW RETURNED	12-Jun-2019
GENERAL COMMENTS	I have no further comments