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Research paper

The effects of ketamine on symptoms of depression and anxiety in real-world care settings: A retrospective controlled analysis

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ABSTRACT

Introduction: Ketamine intravenous therapy (KIT) appears effective for treating depression in controlled trials testing a short series of infusions. A rapidly proliferating number of clinics offer KIT for depression and anxiety, using protocols without a strong evidence basis. Controlled comparison of mood and anxiety from real-world KIT clinics, and the stability of outcomes, is lacking.

Methods: We performed a retrospective controlled analysis on patients treated with KIT in ten community clinics across the US, between 08/2017-03/2020. Depression and anxiety symptoms were evaluated using the Quick Inventory of Depressive Symptomatology-Self Report 16-item (QIDS) and the Generalized Anxiety Disorder 7-item (GAD-7) scales, respectively. Comparison data sets from patients who did not undergo KIT were obtained from previously published real-world studies.

Results: Of 2758 patients treated, 714 and 836 met criteria for analysis of KIT induction and maintenance outcomes, respectively. Patients exhibited significant and concordant reduction in both anxiety and depression symptoms after induction (Cohen's d = -1.17 and d = -1.56, respectively). Compared to two external datasets of KIT-naive depressed patients or patients starting standard antidepressant therapy, KIT patients experienced a significantly greater reduction in depression symptoms at eight weeks (Cohen's d = -1.03 and d = -0.62 respectively). Furthermore, we identified a subpopulation of late-responders. During maintenance, up to a year post-induction, increases in symptoms were minimal.

Limitations: Due to the retrospective nature of the analyses, interpreting this dataset is limited by incomplete patient information and sample attrition.

Conclusions: KIT treatment elicited robust symptomatic relief that remained stable up to one year of follow-up.

1. Introduction

Ketamine intravenous therapy (KIT) is a rapid, safe, and effective treatment for depression when delivered as a limited series of infusions (Alnefeesi et al., 2022; McIntyre et al., 2021; Nikayin et al., 2022; Yavi et al., 2022). However, a rapidly growing number of community clinics employ KIT treatment models with unknown real-world effectiveness for symptoms of depression, suicidality, and anxiety. A common community KIT practice model involves an induction phase of 4 to 8 infusions over 28 days, with 6 infusions being the most common (McInnes et al., 2022;

Abbreviations: EHR, Electronic Health Record; KIT, ketamine infusion therapy; TRD, treatment resistant depression.

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Phillips et al., 2019; Singh et al., 2016). In community clinics, induction treatment is generally followed by a maintenance phase of additional infusions spaced at longer intervals (Kryst et al., 2020; McInnes et al., 2022; Phillips et al., 2019).

In addition to depression, KIT also has independent efficacy for anxiety symptoms in adults with treatment-resistant depression (TRD) or anxious bipolar depression (Murrough et al., 2015; Nikayin et al., 2022; Salloum et al., 2019), as well as for suicidal ideation (Ballard et al., 2014; Ionescu et al., 2015; McInnes et al., 2022; Wilkinson et al., 2018). Furthermore, comorbid anxiety symptoms are often associated with a poorer prognosis and treatment resistance (Fava et al., 2008; McIntyre et al., 2020a, 2020b). In contrast to most controlled prospective studies, real-world clinic patients often present with comorbid anxiety and depression, highlighting the need to understand KIT outcomes in this heterogeneous patient population.

Our aim was to measure the impact of KIT on both depression and anxiety symptoms, spanning both induction and maintenance phases in a large real-world dataset. While real-world data has greater pragmatic value to clinicians than prospective randomized trials, effect size estimates derived from real-world datasets do not have the benefit of a non-treated comparison group to control for placebo response and regression to the mean (Bland and Altman, 1994). Thus, we aimed to compare the effects of KIT on symptom severity with two external data sets: control TRD patients who did not receive KIT (McInnes et al., 2022) and patients assessed for treatment with standard antidepressant monotherapy in the international study to predict optimized treatment for depression (iSPOT-D) (Williams et al., 2011). We hypothesize that KIT provides a superior treatment effect to these control groups and that treatment effects remain stable across the induction and maintenance phases.

2. Methods

2.1. Dataset

This HIPAA compliant, de-identified, pooled dataset had 2758 patients who received KIT through Actify Neurotherapies at one of ten locations across nine states (USA). Patients were treated between 08/2017–03/2020 inclusive. Payment for treatment was out-of-pocket and patients were largely self-referred. The clinics utilized an electronic health record (EHR) platform to monitor the progress of their patients. Available demographic information included age, sex, and clinical diagnoses (Suppl. Table 1). Medical history information including concomitant medications, vital signs and side-effects were not available. Outcome measures included the Generalized Anxiety Disorder 7-item (GAD-7) and Quick Inventory of Depressive Symptomatology-Self Report 16-item (QIDS).

Additionally, KIT patients were compared to two different samples of depressed patients: (1) A control sample of TRD patients who were evaluated in ketamine clinics from our previous study but did not receive KIT (McInnes et al., 2022), and (2) patients with depression from the iSPOT-D study randomized to one of three traditional antidepressants (Williams et al., 2011), measuring depression symptoms via Patient Health Questionnaire-9 (PHQ9) and QIDS, respectively. This research was exempt under 45 CFR § 46.104(d) (4) as determined by Western IRB.

2.2. Clinical procedures

Patients self-administered the QIDS (scores range from 0 to 27) and the GAD-7 (scores range from 0 to 21) on their initial visit via a tablet prior to their appointment, again at their first maintenance treatment (most typically the seventh infusion), and at subsequent visits thereafter. For the statistical analysis induction was defined a priori as four or more infusions within 28 days, although all included subjects actually received at least seven infusions due to the measurement schedule described above. Any infusions following the induction period were classified as maintenance infusions. Criteria for our analyses included having an initial QIDS and GAD-7 pre-treatment, followed by a complete induction phase and a follow-up QIDS and GAD-7 at the start of maintenance.

2.3. Patient retention during induction and progression to maintenance

Of 2758 subjects in the original dataset, $n = 533$ (19 %) had zero induction visits logged, mainly due to their induction phase predating the creation of the database. These subjects were removed for analyses of retention during the induction phase, leaving a sample of 2225 who attended at least one induction visit. Retention was $n = 2032$ (91.3 %) at visit 2, $n = 1920$ (86.3 %) at visit 3, $n = 1775$ (79.8 %) at visit 4, $n = 1638$ (73.6 %) at visit 5, and $n = 1365$ (61.3 %) at visit 6. A total of 836 subjects attended at least one maintenance visit. These 836 subjects represented 38 % of the sample who attended at least one induction visit, and 63 % of the sample that completed visit 6.

2.4. Statistical analysis

Within-sample *t*-tests analyzed within-group differences in repeated measures of continuous variables. Between-group *t*-tests and univariate linear regressions estimated group differences in continuous variables. Group differences in categorical variables were estimated using chi-square tests. Pearson's correlations estimated associations between continuous variables. Effect sizes for differences in within-group and between-group means were estimated with Cohen's *d*. For comparison of the current sample to external control samples, we conducted between-group t-tests and computed effect sizes on normalized change scores, defined as $(y_{\text{FOLLOW-UP}} - y_{\text{BASELINE}}) / SD_{\text{BASELINE}}$. This approach allowed us to compare samples that used different outcome measures (i.e QIDS vs. PHQ9). To estimate time trends during maintenance, we utilized multilevel models with random intercepts for subjects and a fixed linear time effect. The alpha level used for all null-hypothesis tests and individual model coefficients was 0.05. All analyses were conducted in Python 3.8.

3. Results

3.1. Sample description and ketamine infusion utilization

From an original sample of 2758 subjects, 836 met inclusion criteria for analysis of clinical outcomes (Fig. 1) and were included in maintenance phase analyses. Analyses of post-induction outcomes included 714 subjects (a subset of the $n = 836$ sample) whose first post-induction visit occurred within 28 days after their final induction infusion. This criterion controlled for potential bias induced by patients who did not provide outcomes measures shortly after finishing their induction. Analyses of baseline QIDS showed that subjects included in the post-induction outcomes analysis (*median* = 18.0) had significantly more severe depression at baseline than other subjects (*median* = 15.7), $t = 9.76$, $p < 0.001$, $d = 0.42$.

All subjects included in clinical outcomes analysis (n = 836) completed at least seven total infusions, with a mean of 13.3 total infusion visits ($SD = 7.9$, median = 11) across induction and maintenance. During induction the mean days between consecutive infusions was 3.2 days ($SD = 2.3$, median = 2). The first maintenance visit occurred at a mean of 41 days after baseline ($SD = 36.0$, median = 34) and a mean of 16 days after induction ($SD = 12.5$, median = 14). During maintenance the distribution of visit intervals was positively skewed (mean = 26.6 days, $SD = 35.5$, median = 20, 25th percentile = 10, 75th percentile = 29).

3.2. Clinical outcomes from induction phase

Among subjects included in post-induction outcomes analyses ($n =$

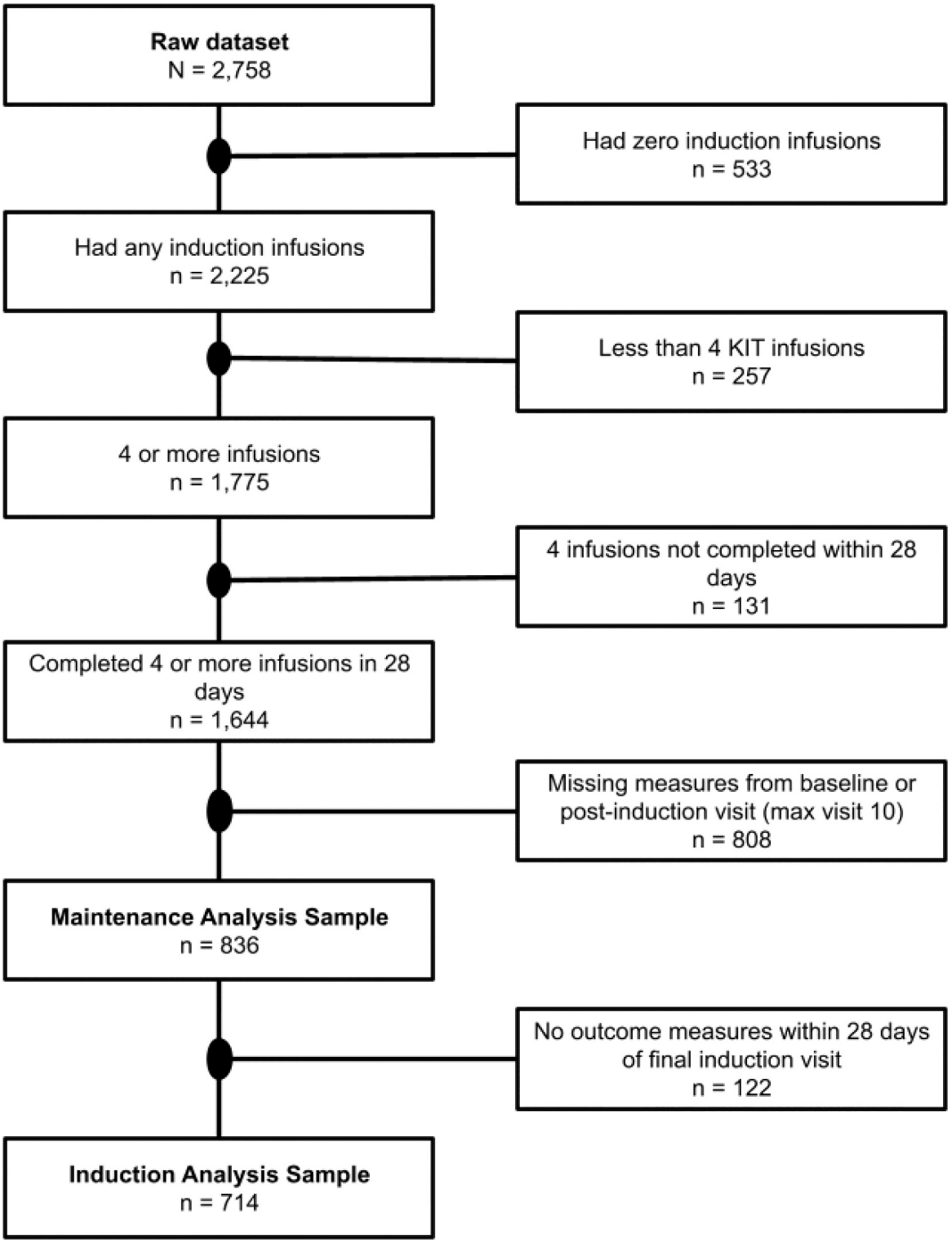

Fig. 1. Consort diagram. From a dataset of $n = 2758$ patients, $n = 2225$ had more than one infusion. Of these, $n = 1775$ had >4 infusions within the induction period. For maintenance analysis, $n = 836$ completed induction and had at least one follow-up measure. For induction analysis, $n = 714$ had completed induction and had a follow-up outcome within 28 days after completing induction.

714), $n = 648$ (91 %) had post-induction measures obtained at visit 7 and at a mean of 12 days after the end of induction ($SD = 6.8$, median = 10), consistent with previous work (McInnes et al., 2022). The sixth infusion occurred at a mean of 23.6 days after baseline (median = 18, 25th percentile = 15, 75th percentile = 23).

The mean QIDS score was 18.0 at baseline ($SD = 4.6$) and 9.6 at post-induction ($SD = 5.3$; Fig. 2A). The mean change in QIDS from baseline to post-induction was −8.36 ($SD = 5.4$; Suppl. Fig. 1A). This reduction was statistically and clinically significant, $t = 41.6$, $p < 0.001$, 95 % CI [−8.76, −7.97], $d = -1.56$, representing a change from severe to mild depression. As shown in Fig. 2B, for depression $n = 351$ (49.2 %) of the sample responded and $n = 187$ (26.2 %) remitted. The mean GAD-7 score was 15.2 at baseline ($SD = 5.7$) and 8.6 at post-induction ($SD = 5.6$; Fig. 2A). The mean change in GAD-7 from baseline to post-induction was −6.68 ($SD = 5.7$; Suppl. Fig. 1B). This was a statistically and clinically significant reduction, $t = 31.0$, $p < 0.001$, 95 % CI [−7.09, −6.26], $d = -1.17$. As shown in Fig. 2B, for anxiety $n = 337$ (47.5 %) of the sample responded and $n = 183$ (25.6 %) remitted. Baseline scores were strongly and negatively correlated with change scores for both QIDS ($r = -0.45$, $p < 0.001$) and GAD-7 ($r = -0.51$, $p < 0.001$), such that subjects with greater baseline severity had greater decreases post-induction.

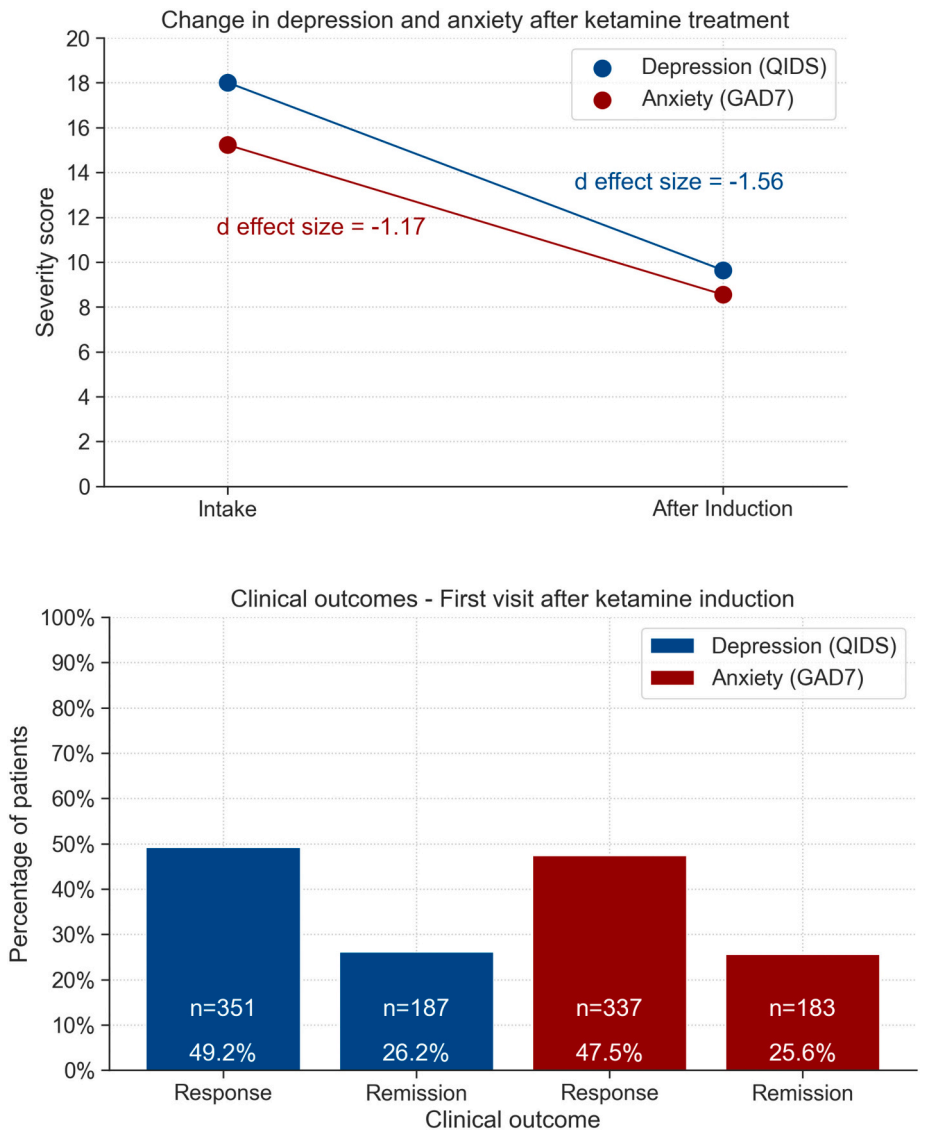

Fig. 2. Effect size at the end of KIT induction and proportion reaching clinical response and remission. (A) Comparison of severity score between intake and after induction phase of treatment (n = 714), between self-reported symptoms of depression (QIDS) and anxiety (GAD-7). (B) Rates of response and remission as a percentage of patients within the dataset (n = 714) for both depression and anxiety symptoms.

Suicidal ideation (SI) was evaluated with QIDS item 12 raw scores and binary classes (0 vs. 1–3). At baseline $n = 597$ (81.6 %) of the sample exhibited any SI. Among these subjects with any SI at baseline, at post-induction $n = 409$ (70 %) reported improvement in SI and $n = 290$ (49 %) reported no SI. Of the 126 patients with no baseline SI, nine (7 %) patients had an increase in SI after induction, with eight out of nine patients reporting a one point increase in SI. Across all patients, $n = 41$ (5.7 %) had a worsening of SI scores at follow-up compared to baseline. Of these patients, n = 40 worsened by one point and one patient worsened by two points.

We examined the overlap between changes in depression and anxiety from baseline to post-induction. There was a strong, positive correlation between change scores for QIDS and GAD-7, $r = 0.60$, $p < 0.001$ (Suppl. Fig. 2). On both the QIDS and GAD-7, subjects were classified as the same or improved vs. worse. Univariate rates of same/improved were ($n = 682$) 95.5 % for QIDS and ($n = 663$) 92.9 % for GAD-7. There was a high rate of agreement across measures, with ($n = 657$) 92.0 % in the same class for QIDS and GAD-7, and ($n = 644$) 90.2 % were same or improved on both.

3.3. Comparison to non-treated and treated controls

We analyzed post-treatment data for subjects who completed KIT induction. In order to estimate the ketamine-specific effect on outcome, we compared our results to other observational and experimental samples. First we derived an observational "no ketamine treatment" sample from a comparable dataset, utilized in our prior study on KIT (McInnes et al., 2022). We identified 276 subjects who attended a KIT intake, completed a PHQ9 at baseline and at 21–42 days of follow-up (median of 28 days), and had 0 visits for KIT. This sample had a statistically and clinically significant reduction in PHQ9, $b = -5.34$, $t = 14.00$, $p < 0.001$, 95 % CI [−6.10, −4.59], $d = -1.00$. In a comparison between normalized depression change scores, the current KIT induction sample had a significantly greater reduction in depression, $t = -10.01$, $p < 0.001$ (Fig. 3a), with a large effect-size difference ($d = -1.03$). Subjects in the KIT sample were also significantly less likely to have worsened depression scores at follow-up ($n = 32$, 4.5 %) than the non-treatment sample ($n = 46$, 16.7 %), $x^2 = 39.1$, $p < 0.001$.

We also derived outcomes data from 1008 subjects randomized to treatment with antidepressants in the iSPOT-D study (Williams et al.,

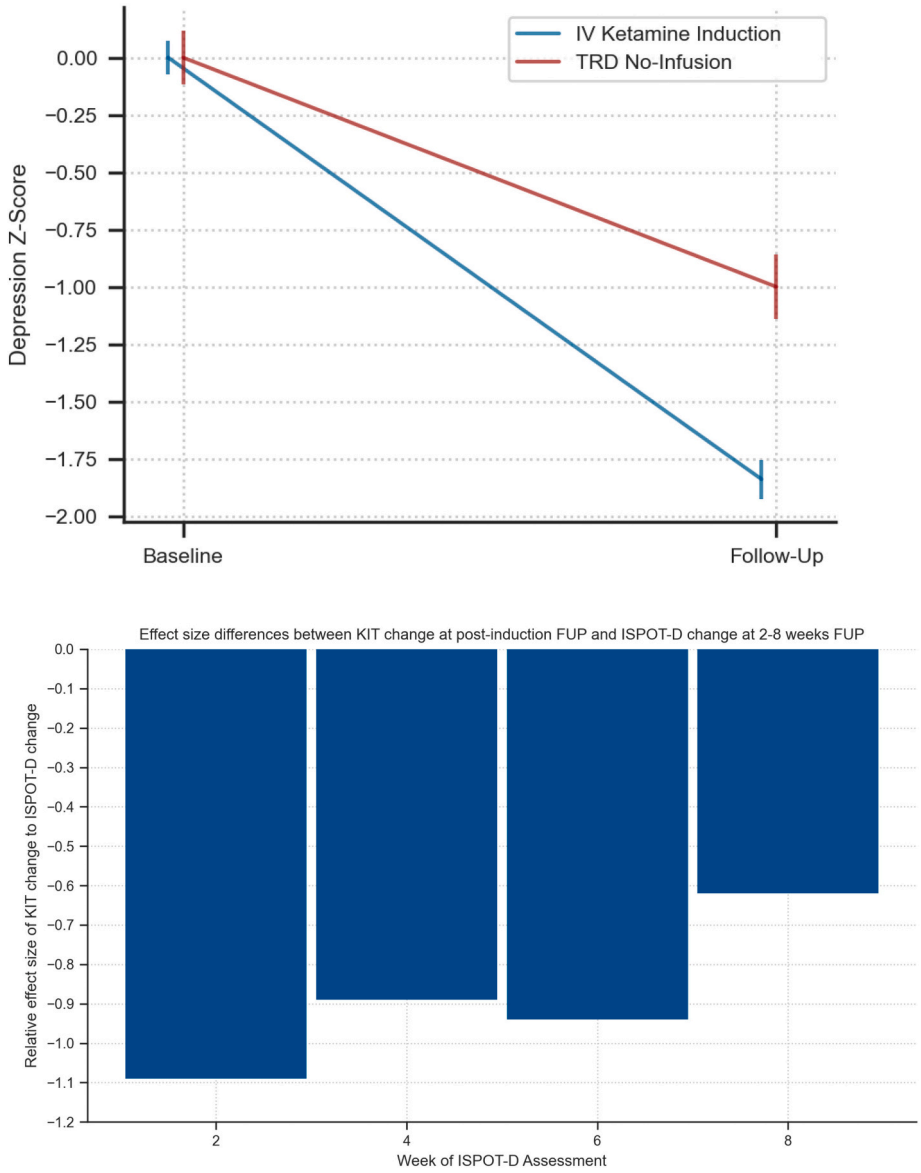

Fig. 3. Change in depression from baseline to follow-up: KIT vs. two independent comparator samples. (a) Change in depression score (normalized to baseline) between two datasets; IV ketamine (n = 714) compared to no treatment (n = 276). (b). Effect size differences in change scores between the current IV ketamine induction sample at post-induction follow-up compared to iSPOT-D change scores at 2–8 weeks of follow-up. TRD = treatment resistant depression.

2011). These subjects received either active escitalopram (n = 336), sertraline (n = 336), or venlafaxine-XR (n = 336), and were assessed with the QIDS at baseline and biweekly follow-up, with eight weeks as the primary outcome timepoint. The reduction in QIDS from baseline to eight weeks was statistically and clinically significant, $b = -3.48$, $t = 26.05$, $p < 0.001$, 95 % CI [−3.75, −3.22], $d = -0.92$ (Fig. 3b). When comparing the normalized change scores for depression, the KIT induction group exhibited a significantly greater decrease in depression symptoms, $t = -16.26$, $p < 0.001$. Subjects in the KIT sample were also significantly less likely to have worsened depression at 8-week follow-up (n = 32; 4.5 %) than the iSPOT-D sample ($n = 96$; 9.5 %), $x^2 = 14.7$, $p < 0.001$. Furthermore, patients undergoing KIT had a greater reduction in depression symptoms at every follow-up time point, from 2 to 8 weeks in iSPOT-D, ranging from a large effect size difference ($d = -1.09$) at 2 weeks to a medium effect size difference ($d = -0.62$) at 8 weeks (Fig. 3b).

3.4. Clinical outcomes from maintenance phase

During the maintenance phase, depression and anxiety severity increased gradually from visit 7 until visit 26 (Fig. 4). In a multilevel model of QIDS scores, the linear effect of time indicated a statistically-significant increase, $b = 0.063$, $SE = 0.013$, $z = 4.86$, $p < 0.001$, 95 % CI [0.038, 0.089]. An identical model of GAD-7 also showed a statistically-significant increase, $b = 0.066$, $SE = 0.013$, $z = 5.14$, $p < 0.001$, 95 % CI [0.041, 0.092]. Despite the statistically-significant time effects, we observed change per-visit coefficients that were quite small relative to standard deviations in the outcome measures during maintenance (QIDS: $b = 0.052$, $SD = 5.75$; GAD-7: $b = 0.074$, $SD = 6.13$). We supplemented these models by computing effect size measures of within-group change. For QIDS, per-visit estimates of d ranged from −0.36 to 0.16, never surpassing $d = 0.20$, the traditional cutoff for "small" effects (Cohen, 2013). For GAD-7, estimates of d ranged from 0 to 0.25, only rising above $d = 0.20$ once at visit 16. Of note, outcomes at later maintenance visits were impacted by heavy attrition such that inferences regarding symptom severity trajectory were less reliable

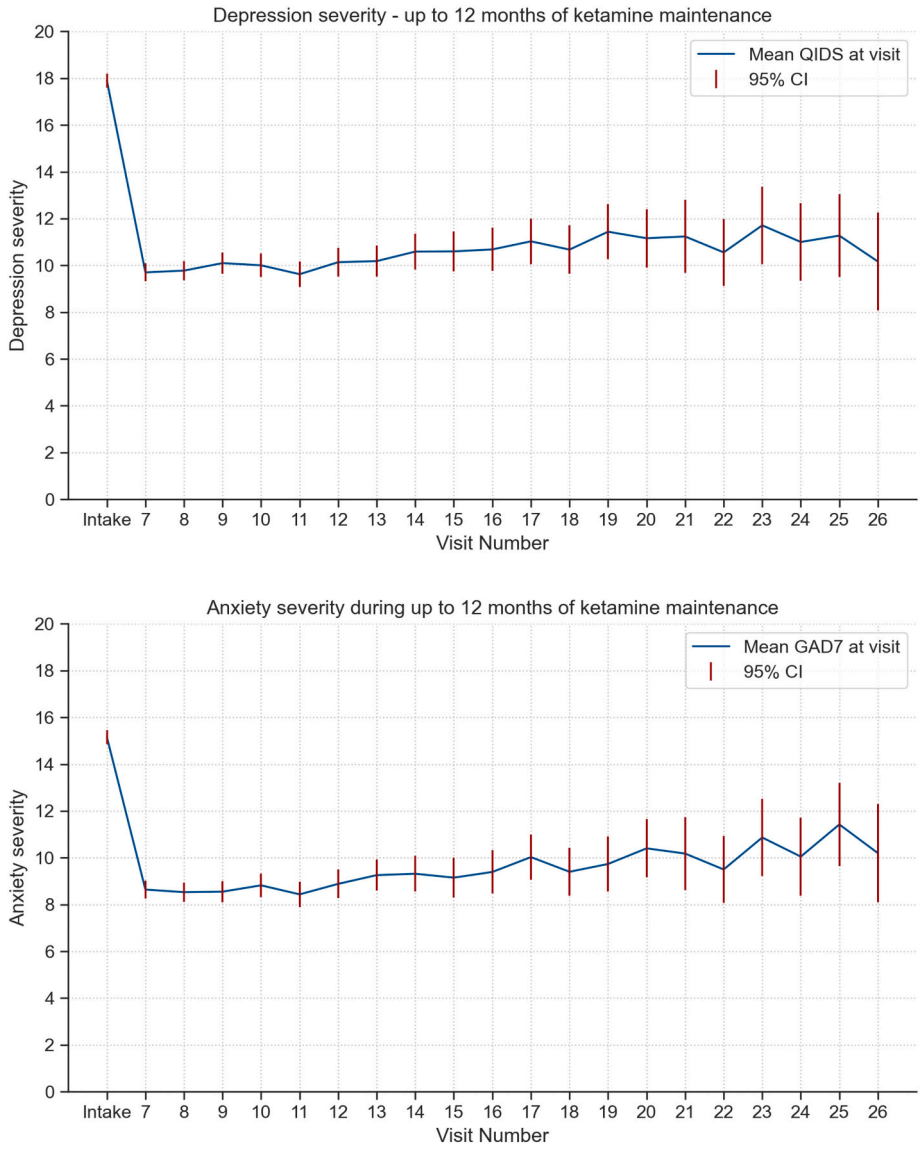

Fig. 4. Stability of mood response to KIT over time. Self-reported (A) depression score (QIDS) and (B) anxiety (GAD-7), across intake and maintenance phase of treatment (n = 836). Results shown as mean ∓ 95 % CI.

(Suppl. Fig. 3). For example, only 357 (42.7 %) of maintenance phase subjects provided outcomes at visit 12, and only 174 (20.8 %) provided outcomes at or beyond visit 16. We do not have data to impute the reasons for this attrition.

During the first half of maintenance phase data, both response and remission rates remained stable relative to the first post-induction visit (Suppl. Fig. 4). From visits 7 to 16, response rates ranged from 44.9 % (160/356) to 48 % (361/747) for depression symptoms (QIDS) and from 45.8 % (163/356) to 50.1 % (217/433) for anxiety symptoms (GAD-7). Beyond visit 16 (where <20 % of the sample was retained), response was less stable, ranging from 33.3 % (11/33) to 48.1 % (26/54) for QIDS and 33.3 % (11/33) to 50.0 % (27/54) for GAD-7. Remission rates followed a similar pattern. From visits 7 to 16 remission rates ranged from 20 % (34/170) to 27.7 % (120/433) for QIDS and 24.0 % (59/246) to 28.9 % (103/356) for GAD-7, with less stability thereafter.

Given that a majority of subjects were not classified as responders after the initial KIT induction, we conducted a secondary analysis to describe the propensity of induction non-responders to achieve clinical response during maintenance. This analysis included maintenance phase subjects who were not classified as responders at their first post-induction visit and had data from subsequent visits (n = 386 for QIDS, n = 400 for GAD-7). Cumulative rates of delayed response during maintenance reached (n = 148) 38.3 % for QIDS and (n = 162) 40.5 % for GAD-7 (Suppl. Fig. 5). For the induction non-responders who achieved delayed response during maintenance, cumulative response by visit 12 was 93.2 % (n = 138/148) for QIDS and 93.8 % (n = 152/162) for GAD-7. Across all post-induction visits (including the initial responders), clinical response was achieved for approximately two-thirds of subjects (QIDS: n = 571 (68.3 %), GAD-7: n = 574 (68.7 %); Fig. 5).

4. Discussion

In this real-world population, KIT is associated with a significant reduction in self-reported symptoms of anxiety, depression and suicidality in individuals that complete 6 induction infusions with these effects remaining relatively stable across the maintenance period. However, as ~40 % of the patients who initiated KIT dropped out prior to completing a minimum of 4 infusions, these effects are an overestimate of the effectiveness of KIT. To address these confounds, we drew from two independent datasets, assessing mood survey data from firstly, patients evaluated for, but not receiving ketamine therapy, and secondly, from patients treated with conventional antidepressant (i.e.

Fig. 5. Cumulative response rate to KIT during maintenance. Self-reported reduction of symptoms >50 % from baseline across infusions within maintenance (n = 836).

SSRIs or SNRIs); in both cases, we found a consistently greater effect of KIT. We also noted lower rates of symptomatic worsening in individuals receiving KIT compared to those who did not receive KIT over a similar time period. Finally, we identified a subpopulation of delayed responders, who achieved a clinical response after induction, during the early maintenance phase of treatment.

4.1. Symptom relief in KIT trials

The current study adds to the previous work by our group and others who have reported response rates to KIT ranging from 45 % to 54 % at the end of induction (Alnefeesi et al., 2022; McInnes et al., 2022; McIntyre et al., 2021). We find similar rates of response within our current dataset with 49 % reaching response at the end of induction. Additionally, in the current dataset 26 % of patients reported remission of their depression symptoms, compared to 29 %–30 % in previous studies that collectively span over 2000 patients. The similarities between these multiple studies highlight the reproducibility of KIT RWD and point towards a stable response across multiple patient populations.

Furthermore, we found that cumulative response rates reached 67 % of the sample early in the maintenance phase, due to delayed responders. Hull et al. (2022) and Oliver et al. (2022) also noted a population of late responders in their studies of real-world patients receiving sublingual ketamine and KIT, respectively. Over the years, studies have shown preferential outcomes with multiple infusions (Murrough et al., 2013; Phillips et al., 2019; Singh et al., 2016; Zheng et al., 2019) extending the standard induction phase up to 6 infusions. Our data supports the need for a tailored induction phase for some patients and predicting these late responders from clinical data should be investigated further.

4.2. Comorbid anxiety and depression

We found a strong relationship between baseline anxiety and depression, but we did not note any reduction in the efficacy of KIT for depression in patients with high GAD-7 scores at baseline. This complements previous studies wherein comorbid anxiety symptoms did not diminish the antidepressant effects of KIT in TRD patients given a single infusion of KIT up to 28 days post-infusion (Ionescu et al., 2015; Salloum et al., 2019). We found a concordant reduction in both symptoms with repeat infusions, which was sustained up to the first post-induction visit. These data hint at an additional treatment option for anxious depression, a condition for which classical antidepressants may have less efficacy (Fava et al., 2008).

4.3. Symptom reduction across multiple patient cohorts

Real-world observational data is confounded by two powerful but nonspecific therapeutic effects: first, patients may present for treatment during acute symptomatic flares, creating a sampling bias and subsequent false positive treatment effect known as “regression to the mean” (Bland and Altman, 1994); second, the effect of initiating any therapy may be associated with positive expectancy and improved mood ratings (Aday et al., 2022). We compared our KIT data to two external datasets to address these issues. To estimate regression to the mean, we compared KIT patients in this study to patients who did not receive ketamine in a similar real-world study (McInnes et al., 2022). Notably, this comparison dataset is subject to a similar dropout bias that we note for the present data; nonetheless, we found a clinically meaningful, significant benefit of KIT here. To estimate the effect of expectancy associated with beginning any new therapy, we also compared our data to outcomes derived from patients initiating SSRI or SNRI-class antidepressants which typically require at least 6–8 weeks to achieve full therapeutic efficacy (Henssler et al., 2018; Gaynes et al., 2009). At each timepoint (up to eight weeks) we again found a clinically and statistically significant benefit of KIT. Remarkably, we found that these two independently derived datasets showed very similar (and sizeable) nonspecific effects of simply engaging with therapy (Aday et al., 2022; Hengartner, 2020) and nonetheless support a ketamine-specific antidepressant effect, beyond concomitant antidepressants, in a real-world setting.

4.4. Limitations

Our analysis has several limitations. We employed stringent inclusion and exclusion criteria in order to analyze a set of patients with both baseline and outcomes data as well as a relatively homogenous number of induction phase treatments. Our resulting analysis represents 31 % of our initial sample, which does improve on prior work (McInnes et al., 2022) but nonetheless may result in upwardly biased response and remission estimates. Data missingness in retrospectively analyzed real-world samples is a problem for many of the studies published on

ketamine therapy to date, where 19 %–50 % of patients complete induction, irrespective of whether the delivery modality was via injection or oral dosing (Ahuja et al., 2022; Hassan et al., 2022; Hull et al., 2022; McIntyre et al., 2020b; Oliver et al., 2022). This relatively poor adherence is not unique to ketamine. Liberman et al. (2023) found that adherence to intranasal esketamine induction, defined as 8 treatment sessions within 4 weeks, was only 43 % in a sample of 308 real-world patients. Nonetheless data missingness precludes our ability to assess if patients dropped out due to intolerable side-effects during the induction phase or lack of perceived efficacy in the maintenance phase.

Like other real world studies of KIT, we cannot compare our measured efficacy with a placebo control. Use of a control group of individuals that were evaluated for ketamine therapy but did not receive it (McInnes et al., 2022), and a comparison with standard-of-care antidepressant efficacy partially mitigates this limitation. Additionally, this dataset contained few demographic features and limited medical history including lack of documentation of KIT side-effects, a down-side of many real-world studies of ketamine therapy similar to ours. It is crucial to assess the safety of administering ketamine infusions repeatedly in real-world populations to inform future studies. Prior research conducted by Rodrigues et al. (2020) and Ho and Zhang (2016) has addressed some of the concerns related to ketamine infusion safety in outpatients. Finally, there is likely to be an economic and racial selection bias for patients who are able to access KIT, as most community clinics are unable to have their services reimbursed by insurers, thus requiring out-of-pocket payment.

5. Summary

In summary, despite acknowledged limitations, we find further clinically meaningful real-world evidence that KIT is an effective treatment for symptoms of depression and anxiety when given as a series of infusions.

Author statement

On behalf of all the authors I certify that all authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

L. Alison McInnes MD, MS

Declaration of competing interest

Drs Hietamies and Klise have no conflicts of interest or disclosures to report. Dr. Worley is an employee of Osmind. Jimmy Qian is an employee of Osmind. Dr. McInnes is an employee of Osmind and a scientific advisor for Clexio Biosciences Ltd. Dr. Williams is a scientific advisor for One Mind Psyberguide and declares US Pants. App. 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data. Dr. Heifets is a scientific advisor for Osmind and Journey Clinical and is also a consultant for Clairvoyant Therapeutics and Vine Ventures Dr. Levine was Founder, president, and shareholder of Actify Neurotherapies (ceased operations March 2020). He is currently employed by Compass Pathways LLC.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.04.141.

References

Aday, J.S., Heifets, B.D., Pratscher, S.D., Bradley, E., Rosen, R., Woolley, J.D., 2022. Great expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. Psychopharmacology 239 (6), 1989–2010. https://doi.org/10.1007/s00213-022-06123-7.

Ahuja, S., Brendle, M., Smart, L., Moore, C., Thielking, P., Robison, R., 2022. Real-world depression, anxiety and safety outcomes of intramuscular ketamine treatment: a retrospective descriptive cohort study. BMC Psychiatry 22 (1), 634. https://doi.org/10.1186/s12888-022-04268-5.

Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M.Y., Rodrigues, N.B., Ceban, F., Di Vincenzo, J.D., Meshkat, S., Ho, R.C.M., Gill, H., Teopiz, K.M., Cao, B., Lee, Y., McIntyre, R.S., Rosenblat, J.D., 2022. Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. J. Psychiatr. Res. 151, 693–709. https://doi.org/10.1016/j.jpsychires.2022.04.037.

Ballard, E.D., Ionescu, D.F., Vande Voort, Niciu, M.J., Richards, E.M., Luckenbaugh, D. A., Brutsché, N.E., Ameli, R., Furey, M.L., Zarate Jr., C.A., 2014. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J. Psychiatr. Res. 58, 161–166. https://doi.org/10.1016/j.jpsychires.2014.07.027.

Bland, J.M., Altman, D.G., 1994. Regression towards the mean. BMJ (Clinical research ed.) 308 (6942), 1499. https://doi.org/10.1136/bmj.308.6942.1499.

Cohen, J., 2013 May 13. Statistical Power Analysis for the Behavioral Sciences. Routledge.

Fava, M., Rush, A.J., Alpert, J.E., Balasubramani, G.K., Wisniewski, S.R., Carmin, C.N., Biggs, M.M., Zisook, S., Leuchter, A., Howland, R., Warden, D., Trivedi, M.H., 2008. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am. J. Psychiatry 165 (3), 342–351. https://doi.org/10.1176/appi.ajp.2007.06111868.

Gaynes, B.N., Warden, D., Trivedi, M.H., Wisniewski, S.R., Fava, M., Rush, A.J., 2009. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. In: Psychiatric Services (Washington, D.C.), vol. 60(11), pp. 1439–1445. https://doi.org/10.1176/ps.2009.60.11.1439.

Hassan, K., Struthers, W.M., Sankarabhotla, A., Davis, P., 2022. Safety, effectiveness and tolerability of sublingual ketamine in depression and anxiety: A retrospective study of off-label, at-home use. Front. Psychiatry 13, 992624. https://doi.org/10.3389/fpsyt.2022.992624.

Hengartner, M.P., 2020. Is there a genuine placebo effect in acute depression treatments? A reassessment of regression to the mean and spontaneous remission. BMJ Evidence-based Med. 25 (2), 46–48. https://doi.org/10.1136/bmjebm-2019-111161.

Henssler, J., Kurschus, M., Franklin, J., Bschor, T., Baethge, C., 2018. Trajectories of acute antidepressant efficacy: how long to wait for response? A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. J. Clin. Psychiatry 79 (3), 17r11470. https://doi.org/10.4088/JCP.17r11470.

Ho, R., Zhang, M., 2016. Ketamine as a rapid antidepressant: the debate and implications. BJPsych Adv. 22 (4), 222–233. https://doi.org/10.1192/apt.bp.114.014274.

Hull, T.D., Malgaroli, M., Gazzaley, A., Akiki, T.J., Madan, A., Vando, L., Arden, K., Swain, J., Klotz, M., Paleos, C., 2022. At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: findings from a large, prospective, open-label effectiveness trial. J. Affect. Disord. 314, 59–67. https://doi.org/10.1016/j.jad.2022.07.004.

Ionescu, D.F., Luckenbaugh, D.A., Niciu, M.J., Richards, E.M., Zarate Jr., C.A., 2015. A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. Bipolar Disord. 17 (4), 438–443. https://doi.org/10.1111/bdi.12277.

Kryst, J., Kawalec, P., Mitoraj, A.M., Pilc, A., Lasoń, W., Brzostek, T., 2020. Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacol. Rep. 72 (3), 543–562. https://doi.org/10.1007/s43440-020-00097-z.

Liberman, J., Pesa, J., Rui, P., Joshi, K., Harding, L., 2023. Social determinants and distance from certified treatment centers are associated with initiation of esketamine nasal spray among patients with challenging-to-treat major depressive disorder. Medicine 102 (7), e32895. https://doi.org/10.1097/MD.0000000000032895.

McInnes, L.A., Qian, J.J., Gargeya, R.S., DeBattista, C., Heifets, B.D., 2022. A retrospective analysis of ketamine intravenous therapy for depression in real-world care settings. J. Affect. Disord. 301, 486–495. https://doi.org/10.1016/j.jad.2021.12.097.

McIntyre, R.S., Lipsitz, O., Rodrigues, N.B., Lee, Y., Cha, D.S., Vinberg, M., Lin, K., Malhi, G.S., Subramaniapillai, M., Kratiuk, K., Fagiolini, A., Gill, H., Nasri, F., Mansur, R.B., Suppes, T., Ho, R., Rosenblat, J.D., 2020a. The effectiveness of ketamine on anxiety, irritability, and agitation: implications for treating mixed features in adults with major depressive or bipolar disorder. Bipolar Disord. 22 (8), 831–840. https://doi.org/10.1111/bdi.12941.

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., 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., 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 178 (5), 383–399. https://doi.org/10.1176/appi.ajp.2020.20081251.

Murrough, J.W., Perez, A.M., Pillemer, S., Stern, J., Parides, M.K., aan het Rot, M., Collins, K.A., Mathew, S.J., Charney, D.S., Iosifescu, D.V., 2013. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol. Psychiatry 74 (4), 250–256. https://doi.org/10.1016/j.biopsych.2012.06.022.

Murrough, J.W., Soleimani, L., DeWilde, K.E., Collins, K.A., Lapidus, K.A., Iacoviello, B. M., Lener, M., Kautz, M., Kim, J., Stern, J.B., Price, R.B., Perez, A.M., Brallier, J.W., Rodriguez, G.J., Goodman, W.K., Iosifescu, D.V., Charney, D.S., 2015. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol. Med. 45 (16), 3571–3580. https://doi.org/10.1017/S0033291715001506.

Nikayin, S., Murphy, E., Krystal, J.H., Wilkinson, S.T., 2022. Long-term safety of ketamine and esketamine in treatment of depression. Expert Opin. Drug Saf. 21 (6), 777–787. https://doi.org/10.1080/14740338.2022.2066651.

Oliver, P.A., Snyder, A.D., Feinn, R., Malov, S., McDiarmid, G., Arias, A.J., 2022. Clinical effectiveness of intravenous racemic ketamine infusions in a large community sample of patients with treatment-resistant depression, suicidal ideation, and generalized anxiety symptoms: a retrospective chart review. J. Clin. Psychiatry 83 (6), 21m14336. https://doi.org/10.4088/JCP.21m14336.

Phillips, J.L., Norris, S., Talbot, J., Birmingham, M., Hatchard, T., Ortiz, A., Owoeye, O., Batten, L.A., Blier, P., 2019. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. Am. J. Psychiatry 176 (5), 401–409. https://doi.org/10.1176/appi.ajp.2018.18070834.

Rodrigues, N.B., McIntyre, R.S., Lipsitz, O., Lee, Y., Cha, D.S., Nasri, F., Gill, H., Lui, L.M. W., Subramaniapillai, M., Kratiuk, K., Lin, K., Ho, R., Mansur, R.B., Rosenblat, J.D., 2020. Safety and tolerability of IV ketamine in adults with major depressive or bipolar disorder: results from the Canadian rapid treatment center of excellence. Expert Opin. Drug Saf. 19 (8), 1031–1040. https://doi.org/10.1080/14740338.2020.1776699.

Salloum, N.C., Fava, M., Freeman, M.P., Flynn, M., Hoeppner, B., Hock, R.S., Cusin, C., Iosifescu, D.V., Trivedi, M.H., Sanacora, G., Mathew, S.J., Debattista, C., Ionescu, D. F., Papakostas, G.I., 2019. Efficacy of intravenous ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression. Depression Anxiety 36 (3), 235–243. https://doi.org/10.1002/da.22875.

Singh, J.B., Fedgchin, M., Daly, E.J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J.W., Sanacora, G., Shelton, R.C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W.C., Van Nueten, L., 2016. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am. J. Psychiatry 173 (8), 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037.

Wilkinson, S.T., Ballard, E.D., Bloch, M.H., Mathew, S.J., Murrough, J.W., Feder, A., Sos, P., Wang, G., Zarate Jr., C.A., Sanacora, G., 2018. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data Meta-analysis. Am. J. Psychiatry 175 (2), 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472.

Williams, L.M., Rush, A.J., Koslow, S.H., Wisniewski, S.R., Cooper, N.J., Nemeroff, C.B., Schatzberg, A.F., Gordon, E., 2011. International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials 12, 4. https://doi.org/10.1186/1745-6215-12-4.

Yavi, M., Lee, H., Henter, I.D., Park, L.T., Zarate Jr., C.A., 2022. Ketamine treatment for depression: a review. Discover mental health 2 (1), 9. https://doi.org/10.1007/s44192-022-00012-3.

Zheng, W., Zhou, Y.L., Liu, W.J., Wang, C.Y., Zhan, Y.N., Li, H.Q., Chen, L.J., Li, M.D., Ning, Y.P., 2019. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. J. Psychopharmacol. (Oxford, England) 33 (4), 494–501. https://doi.org/10.1177/0269881119827811.