Progress in Neuropsychopharmacology & Biological Psychiatry 105 (2021) 110126

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

# Early symptomatic improvements as a predictor of response to repeated-dose intravenous ketamine: Results from the Canadian Rapid Treatment Center of Excellence

Orly Lipsitz[a,b], Roger S. McIntyre[a,b,c,d,*], Nelson B. Rodrigues[a,b], Tyler S. Kaster[d,h], Danielle S. Cha[a,b], Elisa Brietzke[j,k], Hartej Gill[a,b], Flora Nasri[a], Kangguang Lin[e,f], Mehala Subramaniapillai[a,b], Kevin Kratiuk[b], Kayla Teopiz[b], Leanna M.W. Lui[a], Yena Lee[a,b], Roger Ho[g], Margarita Shekotikhina[a,b,i], Rodrigo B. Mansur[a,d], Joshua D. Rosenblat[a,b,c,d]

[a] Mood Disorders Psychopharmacology Unit, Poul Hansen Family Centre for Depression, University Health Network, Toronto, ON, Canada
[b] Canadian Rapid Treatment Center of Excellence, Mississauga, ON, Canada
[c] Brain and Cognition Discovery Foundation, Canada
[d] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[e] Department of Affective Disorder, the Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou Huiai Hospital, Guangzhou Medical University, Guangzhou, China
[f] Laboratory of Emotion and Cognition, the Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou Huiai Hospital, Guangzhou Medical University, Guangzhou, China.
[g] Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[h] Centre for Addiction and Mental Health, Toronto, ON, Canada
[i] Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada
[j] Queen's University School of Medicine, Kingston, ON, Canada
[k] Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada

ARTICLE INFO

*Keywords:*
NMDA
Glutamate
Treatment-resistant depression
Major depressive disorder
Bipolar disorder
Antidepressant
Esketamine

ABSTRACT

*Background:* Early symptomatic improvement with monoamine-based antidepressants is predictive of treatment response. The objective of this study was to determine if early symptomatic improvements with intravenous (IV) ketamine predicted treatment response to an acute course of four infusions.

*Method:* 134 adults with treatment resistant depression (TRD) received four ketamine infusions over one to two weeks. Depressive symptoms were measured using the Quick Inventory for Depressive Symptomatology Self-Report$_{16}$ (QIDS-SR$_{16}$) at baseline and post-infusions 1, 2, 3, and 4. Early improvement was defined as ≥20% reduction in QIDS-SR$_{16}$ scores after the first or second infusion. Linear models were used to determine whether early improvement was associated with post-infusion 4 QIDS-SR$_{16}$ scores after controlling for baseline characteristics.

*Results:* Early improvement post-infusion 1 ($\beta = -3.52$, 95% BCa CI [−5.40, −1.78]) and 2 ($\beta = -3.16$, 95% BCa CI [−5.75, −1.59]) both significantly predicted QIDS-SR$_{16}$ scores post-infusion 4. Early improvers had significantly lower QIDS-SR$_{16}$ scores at post-infusion 4 (post-infusion 1 improvers: $M = 9.8$, $SD = 4.5$; post-infusion 2 improvers: $M = 10.6$, $SD = 5.7$) compared to non-early improvers (post-infusion 1 non-improvers: $M = 13.7$, $SD = 5.8$; post-infusion 2 non-improvers: $M = 14.1$, $SD = 5.3$) when controlling for baseline characteristics. The majority (58%) of individuals who did not improve post-infusions 1 or 2 still experienced an antidepressant response or partial response (≥20% reduction in QIDS-SR$_{16}$) post-infusion 4.

*Limitations:* This is a *post-hoc* analysis of an open-label study.

*Conclusion:* Early improvement was associated with greater antidepressant effects following a course of four ketamine infusions. However, individuals who did not show early improvements still had a high likelihood of experiencing clinically significant symptom reduction after the fourth infusion, suggesting that completing four infusions, regardless of early symptom changes, is appropriate and merited.

* Corresponding author at: University Health Network, 399 Bathurst Street, MP 9-325, Toronto, ON M5T 2S8, Canada.
*E-mail address:* roger.mcintyre@uhn.ca (R.S. McIntyre).

https://doi.org/10.1016/j.pnpbp.2020.110126
Received 10 July 2020; Received in revised form 17 September 2020; Accepted 2 October 2020
Available online 05 October 2020
0278-5846/ © 2020 Elsevier Inc. All rights reserved.

## 1. Introduction

Treatment-resistant depression (TRD), defined as insufficient response to at least two antidepressant treatments, is estimated to affect 20% of all individuals with depression, with an economic burden of $29–$48 billion in the United States (Mrazek et al., 2014). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported that one third of patients do not experience remission of depressive symptoms following four different treatment trials (Gaynes et al., 2009). Identification of factors that influence treatment response is beneficial to accelerate treatment selection and symptom relief, reduce exposure to ineffective treatments, and limit costs. Unnecessary duration of ineffective treatment trials can also prolong patients' feelings of hopelessness and suicidality, while simultaneously decreasing treatment adherence (Szegedi et al., 2009).

Individuals who experience early symptom improvement (i.e., within 2–4 weeks of an antidepressant trial) have been identified as a subpopulation of patients most likely to experience an antidepressant response and remission with the extended treatment trial (Kudlow et al., 2012; Stassen et al., 1996, 1999; Stassen and Angst, 1998; Szegedi et al., 2009; Szegedi et al., 2003). Identifying early improvement as a predictor of overall antidepressant response and characterizing the duration to improvement with an index dosage allows for additional treatment decisions to be made earlier on if patients do not exhibit improvements (e.g., dose increase, adjunctive medication, medication change, psychotherapy, electroconvulsive therapy).

Ketamine is a dissociative anesthetic and non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has demonstrated rapid and robust antidepressant effects in adults with depression, including TRD (Aan Het Rot et al., 2010; Coyle and Laws, 2015; Phillips et al., 2019; Rosenblat et al., 2019; Wilkinson et al., 2018). The overall safety and effectiveness of intravenous (IV) ketamine for TRD in a community-based clinical setting has been previously reported by our group (McIntyre et al., 2020b; Rodrigues et al., 2020). Following four ketamine infusions, 50% of participants were partial responders (≥ 25% reduction in symptoms, measured by Quick Inventory of Depressive Symptomatology Self-Report-16 [QIDS-$SR_{16}$]), 27% of participants responded to the treatment (≥ 50% reduction in QIDS-$SR_{16}$ score) and 13% achieved full remission (QIDS-$SR_{16}$ score ≤ 5) of depressive symptoms, in addition to a significant reduction in suicidal ideation (McIntyre et al., 2020b). However, similar to conventional antidepressants, possible predictors of response to ketamine have been insufficiently investigated. Amongst populations with TRD responding to IV ketamine, there are likely subpopulations with differential response trajectories. Shiroma et al. found that 92% of participants responded and 67% of participants remitted following repeated ketamine infusions, while only 25% and 8% responded and remitted respectively after the first infusion, indicating heterogeneity in time to response and remission (Shiroma et al., 2014).

As early symptom improvement with conventional antidepressant treatment has been identified as having strong predictive power of antidepressant response, it would be beneficial to identify whether early improvements with IV ketamine predict which patients will ultimately respond to repeat-dose ketamine infusions. Given that ketamine is associated with rapid antidepressant effects, the definition of early response would differ from conventional antidepressants. While there is no agreed upon definition for early response to ketamine, many patients are observed to have significant depressive symptom reduction after the first or second ketamine infusion (Shiroma et al., 2014), which may be a more reasonable definition for early response to ketamine specifically, as compared to the 2–4 week early response definition typically used for conventional antidepressants (Kudlow et al., 2012; Stassen et al., 1996, 1999; Stassen and Angst, 1998; Szegedi et al., 2009; Szegedi et al., 2003). Understanding if early response predicts treatment outcomes with ketamine would have important implications for proceeding with additional ketamine infusions when no improvements are observed after the first or second infusions. For example, if early non-response is strongly predictive of overall treatment non-response to ketamine, additional infusions may be considered futile for individuals who have shown no signs of improvement after two infusions. Conversely, if early non-responders are still likely to achieve clinically significant improvements with additional infusions, proceeding with subsequent infusions would be essential.

The primary objective of this study was to evaluate whether early clinically significant improvements following a single ketamine infusion and/or two ketamine infusions predicted reduction in depressive symptoms following repeat-dose IV ketamine treatment (i.e., response after full set of four infusions). The secondary objective of this study was to descriptively identify whether participants who did not exhibit improvements following 1–2 ketamine infusions ultimately responded to the treatment, in order to guide decision-making for patients who do not initially report symptomatic improvements with IV ketamine.

## 2. Method

The eligibility criteria and study procedure have been previously reported in detail (McIntyre et al., 2020a). Analysis of this data was approved by a community institutional review board and is registered at clinicaltrials.gov under the identifier NCT04209296. Briefly, between July 2018 to April 2020, 257 adults with treatment-resistant depression (TRD) and a primary diagnosis of a DSM-5-defined mood disorder (confirmed by a clinical interview) received acute IV ketamine treatment at the Canadian Rapid Treatment Center of Excellence (CRTCE). A small subset of participants did not have a primary diagnosis of a DSM-5 defined mood disorder but did meet criteria for TRD, and were therefore included in the analyses. The CRTCE is a community-based clinic and research center that specializes in the administration of IV ketamine for TRD. Treatment-resistance (Stage 2) was defined as an insufficient response to at least two adequate antidepressant trials (Thase and Rush, 1997). The safety and tolerability of IV ketamine by participants receiving treatment at CRTCE has been previously reported (Rodrigues et al., 2020). Fewer than 5% of participants withdrew from treatment due to tolerability issues. Overall, 44.3% of participants experienced treatment-emergent hypertension, and 12% of those cases required pharmacological intervention. Additionally, dissociation was reported following 36.5% of infusions. The Clinician-Administered Dissociative States Scale (CADSS) was administered 5–10 min after each infusion. Following the first infusion, participants reported an average CADSS score of 10.06 ($SE$ = 0.64). Dissociative symptoms attenuated by the fourth infusion, with participants reporting an average CADSS score of 7.32 ($SE$ = 0.63) post-infusion 4. Psychosis, mania, and new-onset suicidality were not reported by any participants with repeated ketamine infusions (Rodrigues et al., 2020).

Eligible participants received an acute course of ketamine treatment, consisting of four infusions over one-to-two weeks. All participants received a dose of 0.5 mg/kg of ketamine hydrochloride at infusions 1 and 2. Participants who did not experience sufficient response following the first two infusions (operationalized as a ≤ 20% reduction in QIDS-$SR_{16}$ (Rush et al., 2003) total score from baseline) were eligible to receive a dose increase to 0.75 mg/kg for infusions 3 and 4 (Cusin et al., 2017). Dose optimization eligibility was contingent on patient tolerability to the index dose and patient preference. All infusions were administered over a period of 40–45 min, and participants were monitored at the clinic for up to two hours following treatment.

### 2.1. Measurements

The QIDS-$SR_{16}$ is a 16-item self-report measure of depressive symptoms that is scored on a scale of 0 to 27, with 0 representing a complete absence of depressive symptoms and 27 representing the most severe symptoms. The QIDS-$SR_{16}$ was administered at baseline and

**Table 1**
Pretreatment demographic information of early improvers and non-early improvers.

| | Infusion 1 | | Infusion 2 | |
|---|---|---|---|---|
| | Non-early improver $n$ = 91 (67.9%) | Early improver $n$ = 43 (32.1%) | Non-early improver $n$ = 72 (53.7%) | Early improver $n$ = 62 (46.3%) |
| Primary Diagnosis | | | | |
| MDD | 73 | 36 | 59 | 50 |
| BD | 14 | 6 | 10 | 10 |
| PTSD | 4 | 1 | 3 | 2 |
| Age, *M* (SD) | 44.8 (13.9) | 48.0 (15.9) | 44.2 (14.0) | 47.6 (15.1) |
| Sex, n (%) | | | | |
| Male | 40 (44.0) | 20 (46.5) | 26 (36.1) | 34 (54.8) |
| Female | 51 (56.0) | 23 (53.5) | 46 (63.9) | 28 (45.2) |
| Baseline QIDS-$SR_{16}$, *M* (SD) | 18.1 (4.6) | 17.7 (4.9) | 18.3 (4.6) | 17.7 (4.8) |
| Baseline GAD-7, *M* (SD) | 14.1 (5.4) | 14.8 (5.2) | 14.2 (5.4) | 14.4 (5.3) |
| BMI, *M* (SD) | 28.3 (6.6) | 28.5 (5.8) | 27.7 (6.5) | 29.4 (6.2) |
| Lifetime antidepressants, *M* (SD) | 6.8 (4.3) | 6.0 (4.2) | 7.2 (4.5) | 5.8 (3.8) |
| Current antidepressants, *M* (SD) | 1.49 (1.4) | 1.33 (1.0) | 1.47 (1.1) | 1.41 (1.5) |

Abbreviations: MDD: Major depressive disorder; BD: Bipolar Disorder; PTSD: Post-traumatic stress disorder; QIDS-$SR_{16}$: Quick Inventory for Depressive Symptomatology Self-$Report_{16}$; GAD-7: General Anxiety Disorder-7; BMI: Body mass index.

post-infusions 1, 2, 3, and 4 to measure changes in depressive symptom severity. Post-infusion 1–3 assessments were completed on average two days after each infusion, and the post-infusion 4 assessment was completed 7–14 days after the fourth infusion, based on scheduling and participant availability. Symptoms of anxiety were also measured at baseline using the Generalized Anxiety Disorder-7 Scale (Spitzer et al., 2006).

The QIDS-$SR_{16}$ was used to identify participants who experienced early symptom improvements with IV ketamine and participants who responded to the acute course of treatment. Early improvement was defined as a 20% or greater decrease in QIDS-$SR_{16}$ score compared to baseline. Participants were grouped as either 'early improvers' or 'non-early improvers' following infusions 1, and 2, respectively, based on this criteria (Szegedi et al., 2009). The post-infusion 4 QIDS-$SR_{16}$ score was used as the continuous independent variable to measure treatment response.

### 2.2. Data analysis

Linear models were conducted in order to identify the effects of a priori selected demographic covariates on the dependent variable, post-infusion 4 QIDS-$SR_{16}$ score. Only variables that have previously demonstrated association with treatment response, or that have reasonable importance in association with antidepressant response, were selected (Thorpe, 2017). The included demographic variables were (1) sex, (2) age, (3) baseline depressive symptom severity, (4) baseline anxiety symptom severity, (5) body mass index (BMI), and (6) level of treatment resistance (number of lifetime antidepressant trials). Two primary models were conducted with post-infusion 1 improvement and post-infusion 2 improvement as the independent variables, respectively, in order to identify whether early symptomatic improvements were associated with overall treatment response following four ketamine infusions (i.e., post-infusion 4 QIDS-$SR_{16}$ score) after controlling for baseline demographics. Linear models were conducted with restricted maximum likelihood (REML) with the *lme4* package in R version 3.6.2. Figures were created using the *ggplot2* package.

### 2.3. Missing data

All participants with post-infusion 4 missing data were excluded from analyses due to the non-random nature of the missing data. Participants missing data on any other variables were included in the analyses, as less than 20% of data were missing. We used multiple imputation with the weighted nearest-neighbor method (k = 5) and bootstrapped coefficient estimates and bias-corrected and accelerated (BCa) confidence intervals (CI) to account for the uncertainty from imputation, using the R packages *boot* and *VIM*. The *moderndive* package was used to bootstrap descriptive statistics. All bootstrapping was conducted with 1000 resamples.

## 3. Results

In total, 257 participants received treatment at the CRTCE from July 2018 to March 2020 of the total 257 participants, 122 (47%) participants were missing post-infusion 4 QIDS-$SR_{16}$ data, collected at the post-acute treatment follow-up appointment. Data were missing due to patients being lost to follow-up, technical difficulties in recording data, and inability to complete scales at some visits (i.e., participants with follow-up telehealth appointments did not complete the QIDS-$SR_{16}$ as scales were only available for completion at in-person visits). Due to the non-random nature of the missing data, all participants with missing QIDS-$SR_{16}$ data at post-infusion 4 were excluded from analyses. One participant was excluded due to missing data at all infusions except for infusion 4. Therefore, a total of 134 participants were included in this study. Of note, completion of questionnaires was voluntary, as the results reported herein are from a community clinic sample rather than a prospective clinical trial. The clinic encourages use of measurement-based care and completion of scales (including the QIDS-$SR_{16}$) at all visits, however, due the voluntary nature of these measurements and the aforementioned reasons, a large proportion of patients do not complete scales at all visits, leading to a high degree of missing data. Detailed demographic information for the included sample is described in Table 1.

### 3.1. Excluded participants

Participants who were excluded from the analyses due to missing data did not differ from the included sample on baseline depression severity ($t(227) = 1.095$, $p = .275$), post-infusion 1 depression severity ($t(202) = 1.355$, $p = .177$), baseline anxiety severity ($t(225) = 0.820$, $p = .413$), level of treatment resistance ($t(254) = 0.267$, $p = .790$), age ($t(252) = 0.379$, $p = .705$), or sex ($\chi^2(1) = 0.117$, $p = .732$).

### 3.2. Early improvements as a predictor of response

Forty-three (32%) participants improved post-infusion 1 and 62 (46%) improved post-infusion 2. Of the 43 participants that reported improvements post-infusion 1, 36 (84%) also improved post-infusion 2. Treatment outcomes are reported in detail in Tables 2 and 3. Coefficient and bootstrapping bias estimates, standard errors, and 95% BCa CIs are

**Table 2**
Treatment outcomes for early improvers compared to non-early improvers. Majority of participants who did not experience early improvements still ultimately responded or partially responded to the full set of four ketamine infusions.

| | Infusion 1 | | Infusion 2 | |
|---|---|---|---|---|
| | Non-early improver n = 91 (67.9%) | Early improver n = 43 (32.1%) | Non-early improver n = 72 (53.7%) | Early improver n = 62 (46.3%) |
| Post-Infusion 4 QIDS-$SR_{16}$ Score, *M* (SD) | 13.7 (5.8) | 9.81 (4.5) | 14.1 (5.3) | 10.6 (5.7) |
| QIDS-$SR_{16}$ Change from Baseline, *M* (SD) | 4.4 (5.5) | 7.9 (4.6) | 4.1 (4.8) | 7.1 (5.7) |
| Response Rate (≥ 50% decrease), n (%) | 17 (18.7) | 17 (39.5) | 10 (13.9) | 24 (38.7) |
| Clinically Significant Improvements (≥ 20% decrease), n (%) | 53 (58.2) | 38 (88.4) | 42 (58.3) | 49 (79.0) |

Abbreviations: QIDS-$SR_{16}$: Quick Inventory for Depressive Symptomatology Self-$Report_{16}$.

reported in Table 4.

Of the included baseline characteristics, baseline depression severity (β = 0.64, 95% BCa CI [0.43–0.90]) and level of treatment resistance (β = 0.20, 95% BCa CI [0.01–0.40]) were significantly associated with post-infusion 4 QIDS-$SR_{16}$ scores when controlling for all other demographic variables. Participants with higher baseline depression severity had significantly higher post-infusion 4 QIDS-$SR_{16}$ scores, and participants with a greater number of lifetime antidepressant trials had significantly higher post-infusion 4 QIDS-$SR_{16}$ scores, after controlling for other baseline characteristics.

We then conducted two separate linear models to identify whether post-infusion 1 or post-infusion 2 improvement significantly predicted post-infusion 4 QIDS-$SR_{16}$ scores when controlling for the above demographic variables. Both post-infusion 1 (β = −3.52, 95% BCa CI [−5.40, −1.78]) and post-infusion 2 (β = −3.16, 95% BCa CI [−5.75, −1.59]) symptomatic improvements significantly predicted lower QIDS-$SR_{16}$ scores at post-infusion 4 compared to participants who did not improve at post-infusion 1 or post-infusion 2, respectively, when controlling for demographic variables. Figs. 1 and 2 illustrate treatment outcomes of participants who experienced early improvements compared to those who did not experience early improvements, controlling for baseline depression severity.

### 3.3. Early non-improvers

Ninety-one (68%) participants did not improve post-infusion 1, and 72 (54%) participants did not improve post-infusion 2. Sixty-five (71%) participants who did not improve post-infusion 1 also did not experience an improvement in symptoms following post-infusion 2. The remaining 26 (29%) participants who did not improve post-infusion 1 subsequently reported symptomatic improvements post-infusion 2. Seven participants who initially reported symptomatic improvements post-infusion 1 did not improve post-infusion 2 at a clinically important level compared to pretreatment.

Participants who did not improve post-infusion 1 and/or post-infusion 2 reported, on average, a baseline QIDS-$SR_{16}$ score of 18 (SD = 5), and at post-infusion 4 reported a QIDS-$SR_{16}$ score of 14 (post-infusion 1 SD = 6, post-infusion 2 SD = 5). Seventeen (19%) participants who did not improve post-infusion 1 and ten (14%) participants who did not improve post-infusion 2 ultimately responded to the treatment at post-infusion 4 (≥ 50% decrease in QIDS-$SR_{16}$ score compared to baseline). Seven (11%) participants who did not report improvement following both infusions 1 and 2 ultimately responded to IV ketamine post-infusion 4. However, 58% of early non-improvers still achieved clinically significant symptom reduction with > 20% reduction in QIDS-$SR_{16}$ scores from baseline to post-infusion 4.

## 4. Discussion

In a well-characterized sample of adults with TRD, we found that participants who experienced early symptomatic improvement following their first or second treatment reported significantly lower depression symptoms following four repeated ketamine infusions when compared to participants who did not show early signs of improvement following infusions 1 or 2, even when controlling for baseline symptom severity.

Notwithstanding the evidence for early improvement predicting later response, descriptive statistics showed that a subset of participants who did not show early improvements ultimately responded to the treatment, suggesting a delayed onset of ketamine's antidepressant effects in a subpopulation. It can be hypothesized that the overall response in these early non-responder was a function of the dose increase to 0.75 mg/kg at infusion 3, which underscores the importance of early dosing optimization (Cusin et al., 2017; Kudlow et al., 2014). Overall, these findings comport with Kelley et al., who described differential response trajectories using latent class analysis with conventional antidepressants. Their findings highlighted that some patients may display early response or remission, while others may exhibit a more delayed response, or no response at all to treatment (Kelley et al., 2018). Furthermore, 58% of non-early improvers experienced clinically significant symptom reduction with a partial or full antidepressant response following the full set of four infusions. Given the severity of treatment resistance in the included sample, this is a clinically meaningful improvement which demonstrates that patients who do not report early improvements following the first two ketamine infusions still have a relatively high likelihood of experiencing important symptom relief, and should not discontinue the treatment following two infusions.

To our knowledge, a similar analysis has not yet been completed with ketamine in adults with TRD. Robust and replicated evidence on monoamine-based antidepressants indicates that early improvement or non-improvement is a predictor of response or remission at a distal endpoint (i.e., week 6 and 8 of the antidepressant trial) (Szegedi et al.,

**Table 3**
Early response patterns of participants who ultimately reported clinically significant improvements following four intravenous ketamine infusions (≥20% reduction in QIDS-$SR_{16}$ score compared to baseline).

| | Clinically Significant Improvements (*N* = 87) | Non-Clinically Significant Improvements (*N* = 47) |
|---|---|---|
| Post-Infusion 1 Improver | 37 (42.53) | 6 (12.77) |
| Post-Infusion 1 Non-Improver | 50 (57.47) | 41 (87.23) |
| Post-Infusion 2 Improver | 45 (51.72) | 17 (36.17) |
| Post-Infusion 2 Non-Improver | 42 (48.28) | 30 (63.83) |

**Table 4**
Bootstrapped model estimates.

| Variable | Coefficient estimate | Bootstrapping bias estimate | SE | 95% BCa CI (LL, UL) |
|---|---|---|---|---|
| Demographics Model | | | | |
| Sex(female) | 0.78 | 0.02 | 0.93 | −0.93, 2.55 |
| Age | 0.02 | 0.00 | 0.03 | −0.04, 0.08 |
| Baseline QIDS-$SR_{16}$ | 0.64 | −0.02 | 0.12 | 0.43, 0.90 |
| Baseline GAD-7 | −0.14 | 0.02 | 0.09 | −0.34, 0.03 |
| Baseline BMI | 0.04 | −0.01 | 0.07 | −0.07, 0.21 |
| Lifetime Antidepressants | 0.20 | 0.00 | 0.10 | 0.01, 0.40 |
| Post-Infusion 1 Improvement | | | | |
| Early Improvement (yes) | −3.52 | 0.18 | 1.00 | −5.40, −1.78 |
| Post-Infusion 2 Improvement | | | | |
| Early Improvement (yes) | −3.16 | 0.58 | 1.05 | −5.75, −1.59 |

2009; Uher et al., 2010). The relevance of identifying temporality to response is that it has influenced current recommendations regarding treatment guidelines, specifically the appropriate time for dose optimization, antidepressant switches, and augmentation strategies. Therefore, it is pertinent to identify whether early improvement or non-improvement is indicative of overall response to treatment (Kennedy et al., 2016; McIntyre et al., 2017).

The mechanism of action of ketamine's antidepressant effects remains unclear. It has been hypothesized that NMDA-mediated disinhibition of GABAergic interneurons is involved in ketamine's antidepressant effects. However, additional research has suggested that NMDA receptor antagonism is not responsible for exerting antidepressant effects observed from ketamine, as other non-ketamine NMDA receptor antagonists have not demonstrated similar effects (Kishimoto et al., 2016; Newport et al., 2015; Zanos and Gould, 2018). These findings suggest that NMDA receptor antagonism is not independently responsible for producing antidepressant effects. In fact, current evidence suggests that increased and sustained activity at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors following ketamine administration is, at least in part, responsible for ketamine's antidepressant effects (Zanos et al., 2016). It is further speculated that the foregoing affects brain-derived neurotrophic factor (BDNF) synthesis and release, via the mammalian target of rapamycin (mTOR) pathway, which have shown deficits in murine models of MDD and are critical for synaptogenesis (Abelaira et al., 2014; Paul et al., 2014; Yang et al., 2013; Abdallah et al., 2016; Maeng et al., 2008; Muller et al., 2016; Zhou et al., 2014). Non-mutually exclusive hypotheses regarding the mechanism of action of ketamine include effects on opioidergic, inflammatory, and catecholaminergic systems (Cadeddu et al., 2016; Durieux, 1995; Welters et al., 2010). It could be conjectured that within populations of adults responsive to IV ketamine treatment, the critical mechanistic steps mediating symptom relief (e.g., synaptogenesis) may differ across subpopulations of responders at a cellular level and at a behavioural level.

Available evidence suggests that select dimensions/symptoms of depression may have differential response trajectories. For example, for some individuals, early improvement in cognition and/or cognitive emotional processing, as well as sleep, may occur prior to full symptom resolution (Godlewska and Harmer, 2020; Park et al., 2020; Park et al., 2018; Warren et al., 2015). The foregoing behavioural symptoms may mediate symptom relief, and it can be conjectured that participants with subdomain improvements that precede overall improvement show slower response to treatment. As such, future research should investigate whether improvements in these domains/symptoms mediate response to treatment in patients who do not exhibit early symptomatic improvement but do ultimately respond to repeated ketamine treatment.

The strengths of this study include using a large, well-characterized sample of participants with TRD. Participants were not excluded on the basis of suicidality and concomitant medications, which strengthens the

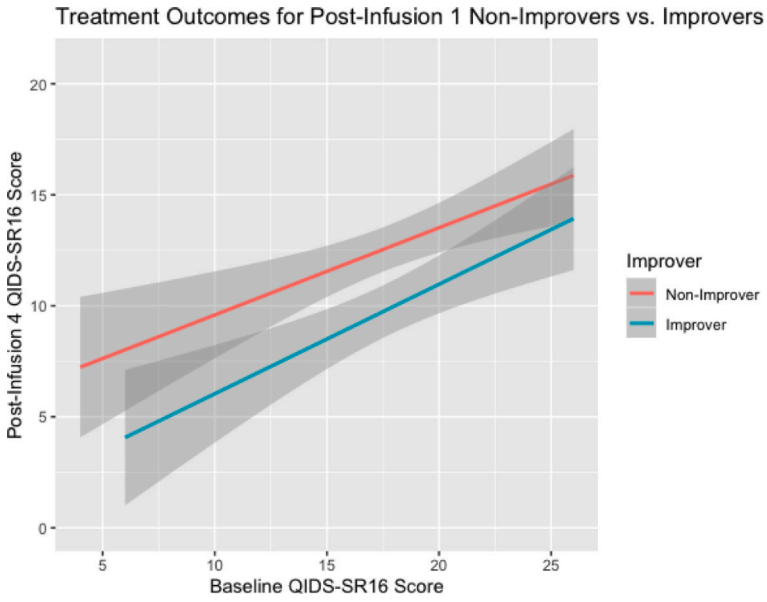


**Fig. 1.** Participants who improved post-infusion 1 reported lower QIDS-$SR_{16}$ scores after the full set of four treatments compared to participants with the same baseline depressive severity who did not improve post-infusion 1.
*Figures are based on non-bootstrapped imputed data.

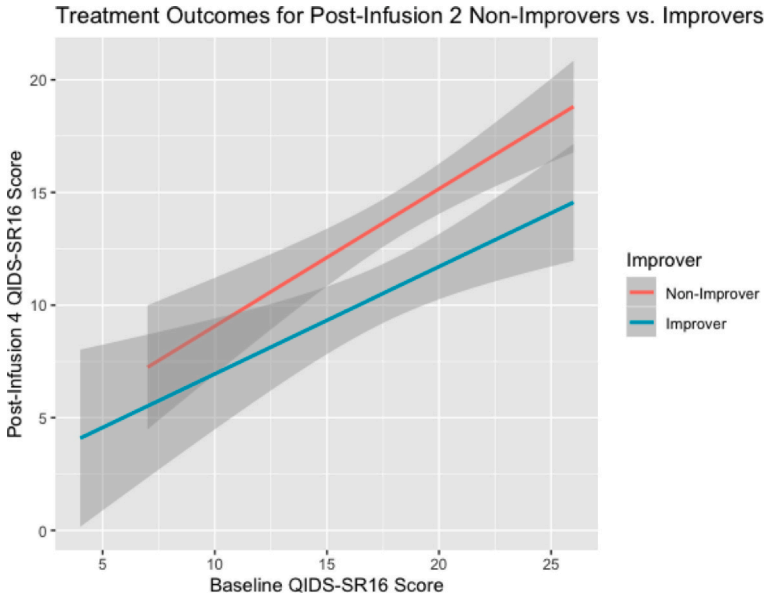


**Fig. 2.** Participants who improved post-infusion 2 reported lower QIDS-$SR_{16}$ scores following the full set of four infusions compared to participants with the same baseline depressive severity who did not improve post-infusion 2.
*Figures are based on non-bootstrapped imputed data.

external validity of this study to real-world patient populations. Additionally, subjective measures of symptomatic remission are more likely to predict behavioural improvements on domains such as cognition, compared to objective measures of remission (Sawada et al., 2019). The use of the subjective QIDS-$SR_{16}$ scale as the primary outcome strengthens the findings presented herein.

The limitations of this study should be considered when interpreting the findings. This was a *post-hoc* analysis of a naturalistic, observational study. As such, there was no control group to account for placebo and expectancy effects. Deviation from protocol and participant dropout resulted in a large amount of missing data. The missing data adds bias to the results of this study and its interpretability, as participant data were not missing at random. Variability between the fourth infusion and the completion of the post-infusion 4t assessment due to participant scheduling and availability also limits the interpretation of the findings (post-infusion 4 assessments were completed up to 14 days following the fourth infusion). It is possible that some participants did experience response or remission of symptoms post-infusion 4, but relapsed by the time the post-infusion 4 assessment was completed. In addition, we did not investigate the durability of the effect; we did not analyze whether participants with early or late improvements experienced a more lasting, longer-term symptom relief. Furthermore, we defined early response to IV ketamine based on expert clinician observations and by adapting findings from early response to conventional monoamine-based antidepressants. However, the definition of early response to ketamine treatment requires further investigation and consideration.

### 4.1. Conclusion

The need exists to identify persons more likely to respond to ketamine-based treatments due to the high cost of the treatment and the burden of multiple unsuccessful treatment trials. Our results suggest that early symptom improvement after the first or second infusion is associated with greater antidepressant effects following an acute course of four ketamine infusions. As with any treatment, it is critical to be able to inform patients who are not improving whether to continue with the treatment, optimize the dose, or switch to alternative treatments. Encouraging patients to continue with a futile treatment or, conversely, discontinuing a treatment early that may have been effective if continued longer, both have significant negative consequences.

While early improvement was associated with greater antidepressant effects with ketamine, patients who did not show signs of early improvement were still likely to benefit from additional infusions, as the majority of these patients (58%) still experienced clinically significant symptom reduction (e.g., partial or full response) to the full treatment course. As such, it is appropriate and worthwhile for patients with TRD to continue with the full course of ketamine treatment, even if the patient does not report improvements after the first two infusions. Future research is needed and merited to replicate our results and better characterize different response trajectories and biotypes that may predict anticipated time to antidepressant response to better inform treatment planning. Further, understanding how and *when* to integrate other treatments, such as other medications and psychotherapy, during the ketamine treatment course to optimize treatment outcomes is an important underexplored area of critical importance.

## Contributors

**Orly Lipsitz:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – reviewing & editing. **Roger S. McIntyre:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – reviewing & editing. **Nelson B. Rodrigues:** Conceptualization, Methodology, Writing – reviewing & editing. **Tyler S. Kaster:** Formal analysis, Writing – reviewing & editing. **Danielle S. Cha:** Writing – reviewing & editing. **Elisa Brietzke:** Writing – reviewing & editing. **Hartej Gill:** Writing – reviewing & editing. **Flora Nasri:** Writing – reviewing & editing. **Kangguang Lin:** Writing – reviewing & editing. **Mehala Subramaniapillai:** Methodology, Data curation, Project administration. **Kevin Kratiuk:** Methodology, Data curation, Project administration. **Kayla Teopiz:** Data curation. **Leanna M.W. Lui:** Writing – reviewing & editing. **Yena Lee:** Writing – reviewing & editing. **Roger Ho:** Writing – reviewing & editing. **Margarita Shekotikhina:** Writing – reviewing & editing. **Rodrigo B. Mansur:** Writing – reviewing & editing. **Joshua D. Rosenblat:** Formal analysis, Methodology, Supervision, Writing – original draft, Writing – reviewing & editing.

## Ethical statement

Analysis of this data was approved by a community Institutional

Review Board (IRB#00000971) and is registered at clinicaltrials.gov under the identifier NCT04209296.

## Declaration of Competing Interest

KK is the Vice President of Operations at the Canadian Rapid Treatment Center of Excellence (CRTCE). KK is a shareholder of Champignon Brands, which acquired the CRTCE in May 2020. RSM has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Allergan, Takeda, Neurocrine, Sunovion, Minerva, Intra-Cellular, and Abbvie. RSM is a shareholder and CEO of Champignon Brands, which acquired the Canadian Rapid Treatment Center of Excellence in May 2020.

JDR has received research grant support from the Canadian Cancer Society, Canadian Psychiatric Association, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from Allergan, Lundbeck and COMPASS. JDR is the medical director of a private clinic providing intravenous ketamine infusions and intranasal esketamine for depression.

EB has received research grant support from Queen's University (Research Establishment Grant, Centre for Neuroscience Studies and Department of Psychiatry) and from SEAMO. She has been received honorarium as speaker/member of advisory board from Daiichi-Sankyo. She does not have COI related to this study.

TSK has received research grant support from the American Psychiatric Association, Society of Biological Psychiatry, University of Toronto, and the Canadian Institute for Health Research Fellowship Award. He does not have COI related to this study.

## References


Aan Het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S., Mathew, S.J., 2010. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol. Psychiatry 67, 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038.

Abdallah, C.G., Adams, T.G., Kelmendi, B., Esterlis, I., Sanacora, G., Krystal, J.H., 2016. Ketamine's mechanism of action: a path to rapid-acting antidepressants. Depress. Anxiety 33, 689–697.

Abelaira, H.M., Réus, G.Z., Neotti, M.V., Quevedo, J., 2014. The role of mTOR in depression and antidepressant responses. Life Sci. 101, 10–14. https://doi.org/10.1016/j.lfs.2014.02.014.

Cadeddu, R., Jadzic, D., Carboni, E., 2016. Ketamine modulates catecholamine transmission in the bed nucleus of stria terminalis: the possible role of this region in the antidepressant effects of ketamine. Eur. Neuropsychopharmacol. https://doi.org/10.1016/j.euroneuro.2016.08.009.

Coyle, C.M., Laws, K.R., 2015. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum. Psychopharmacol. Clin. Exp. 30, 152–163.

Cusin, C., Ionescu, D.F., Pavone, K.J., Akeju, O., Cassano, P., Taylor, N., Eikermann, M., Durham, K., Swee, M.B., Chang, T., Dording, C., Soskin, D., Kelley, J., Mischoulon, D., Brown, E.N., Fava, M., 2017. Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. Aust. N. Z. J. Psychiatry 51, 55–64. https://doi.org/10.1177/0004867416631828.

Durieux, M.E., 1995. Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesth. Analg. 81, 57–62. https://doi.org/10.1097/00000539-199507000-00012.

Gaynes, B.N., Warden, D., Trivedi, M.H., Wisniewski, S.R., Fava, M., John Rush, A., 2009. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr. Serv. https://doi.org/10.1176/ps.2009.60.11.1439.

Godlewska, B.R., Harmer, C.J., 2020. Cognitive neuropsychological theory of antidepressant action: a modern-day approach to depression and its treatment. Psychopharmacology. https://doi.org/10.1007/s00213-019-05448-0.

Kelley, M.E., Dunlop, B.W., Nemeroff, C.B., Lori, A., Carrillo-Roa, T., Binder, E.B., Kutner, M.H., Rivera, V.A., Craighead, W.E., Mayberg, H.S., 2018. Response rate profiles for major depressive disorder: characterizing early response and longitudinal non-response. Depress. Anxiety 35, 992–1000. https://doi.org/10.1002/da.22832.

Kennedy, S.H., Lam, R.W., McIntyre, R.S., Tourjman, S.V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A.J., MacQueen, G.M., Others, 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can. J. Psychiatr. 61, 540–560.

Kishimoto, T., Chawla, J.M., Hagi, K., Zarate, C.A., Kane, J.M., Bauer, M., Correll, C.U., 2016. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. Psychol. Med. 46, 1459–1472.

Kudlow, P.A., Cha, D.S., McIntyre, R.S., 2012. Predicting treatment response in major depressive disorder: the impact of early symptomatic improvement. Can. J. Psychiatr. 57, 782–788. https://doi.org/10.1177/070674371205701211.

Kudlow, P.A., McIntyre, R.S., Lam, R.W., 2014. Early switching strategies in antidepressant non-responders: current evidence and future research directions. CNS Drugs 28, 601–609. https://doi.org/10.1007/s40263-014-0171-5.

Maeng, S., Zarate, C.A., Du, J., Schloesser, R.J., McCammon, J., Chen, G., Manji, H.K., 2008. Cellular mechanisms underlying the antidepressant effects of ketamine: role of α-Amino-3-Hydroxy-5-Methylisoxazole-4-propionic acid receptors. Biol. Psychiatry 63, 349–352. https://doi.org/10.1016/j.biopsych.2007.05.028.

McIntyre, R.S., Suppes, T., Tandon, R., Ostacher, M., 2017. Florida best practice psychotherapeutic medication guidelines for adults with major depressive disorder. J. Clin. Psychiatry. https://doi.org/10.4088/jcp.16cs10885.

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. 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. https://doi.org/10.1016/j.jad.2020.05.088.

Mrazek, D.A., Hornberger, J.C., Altar, C.A., Degtiar, I., 2014. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. PS 65, 977–987. https://doi.org/10.1176/appi.ps.201300059.

Muller, J., Pentyala, S., Dilger, J., Pentyala, S., 2016. Ketamine enantiomers in the rapid and sustained antidepressant effects. Ther. Adv. Psychopharmacol. 6, 185–192. https://doi.org/10.1177/2045125316631267.

Newport, D.J., Carpenter, L.L., McDonald, W.M., Potash, J.B., Tohen, M., Nemeroff, C.B., Others, 2015. APA Council of research task force on novel biomarkers and treatments. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am. J. Psychiatry 172, 950–966.

Park, C., Pan, Z., Brietzke, E., Subramaniapillai, M., Rosenblat, J.D., Zuckerman, H., Lee, Y., Fus, D., McIntyre, R.S., 2018. Predicting antidepressant response using early changes in cognition: a systematic review. Behav. Brain Res. 353, 154–160. https://doi.org/10.1016/j.bbr.2018.07.011.

Park, C., Zuckerman, H., Subramaniapillai, M., Mansur, R.B., Rosenblat, J.D., Cao, B., Iacobucci, M., Lee, Y., Levitan, R., Blumberger, D.M., McIntyre, R.S., 2020. Using early changes in cold cognition to predict response to vortioxetine in major depressive disorder. Psychiatry Res. 284, 112767. https://doi.org/10.1016/j.psychres.2020.112767.

Paul, R.K., Singh, N.S., Khadeer, M., Moaddel, R., Sanghvi, M., Green, C.E., O'Loughlin, K., Torjman, M.C., Bernier, M., Wainer, I.W., 2014. (R,S)-Ketamine Metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine increase the mammalian target of rapamycin function. Anesthesiology. https://doi.org/10.1097/aln.0000000000000285.

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, 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. 1–10. https://doi.org/10.1080/14740338.2020.1776699.

Rosenblat, J.D., Carvalho, A.F., Li, M., Lee, Y., Subramanieapillai, M., McIntyre, R.S., 2019. Oral ketamine for depression: a systematic review. J. Clin. Psychiatry 80. https://doi.org/10.4088/JCP.18r12475.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54, 573–583. https://doi.org/10.1016/S0006-3223(02)01866-8.

Sawada, K., Yoshida, K., Ozawa, C., Mizuno, Y., Rubinstein, E.B., Suzuki, T., Mimura, M., Uchida, H., 2019. Impact of subjective vs Objective Remission Status on Subjective Cognitive Impairments in Depression. J. Affect. Disord. 246, 99–104. https://doi.org/10.1016/j.jad.2018.12.049.

Shiroma, P.R., Johns, B., Kuskowski, M., Wels, J., Thuras, P., Albott, C.S., Lim, K.O., 2014. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord. 155, 123–129. https://doi.org/10.1016/j.jad.2013.10.036.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166, 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

Stassen, H., Angst, J., Delini-Stula, A., 1996. Delayed onset of action of antidepressant drugs? Survey of results of Zurich meta-analyses. Pharmacopsychiatry. https://doi.org/10.1055/s-2007-979551.

Stassen, H.H., Angst, J., 1998. Delayed onset of action of antidepressants. CNS Drugs 9, 177–184. https://doi.org/10.2165/00023210-199809030-00001.

Stassen, H.H., Angst, J., Delini-Stula, A., 1999. Fluoxetine versus moclobemide: cross-comparison between the time courses of improvement. Pharmacopsychiatry 32, 56–60. https://doi.org/10.1055/s-2007-979192.

Szegedi, A., Müller, M.J., Anghelescu, I., Klawe, C., Kohnen, R., Benkert, O., 2003. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J. Clin. Psychiatry. https://doi.org/10.4088/jcp.v64n0410.

Szegedi, A., Jansen, W.T., van Willigenburg, A.P.P., van der Meulen, E., Stassen, H.H., Thase, M.E., 2009. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J. Clin. Psychiatry 70, 344–353. https://doi.org/10.4088/jcp.07m03780.

Thase, M.E., Rush, A.J., 1997. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J. Clin. Psychiatry 58 (Suppl. 13), 23–29.

Thorpe, K.E., 2017. How to construct regression models for observational studies (and how NOT to do it!). Can. J. Anesth. 64, 461–470.

Uher, R., Muthén, B., Souery, D., Mors, O., Jaracz, J., Placentino, A., Petrovic, A., Zobel, A., Henigsberg, N., Rietschel, M., Aitchison, K.J., Farmer, A., McGuffin, P., 2010. Trajectories of change in depression severity during treatment with antidepressants. Psychol. Med. 40, 1367–1377. https://doi.org/10.1017/S0033291709991528.

Warren, M.B., Pringle, A., Harmer, C.J., 2015. A neurocognitive model for understanding treatment action in depression. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 370, 20140213. https://doi.org/10.1098/rstb.2014.0213.

Welters, I.D., Hafer, G., Menzebach, A., Mühling, J., Neuhäuser, C., Browning, P., Goumon, Y., 2010. Ketamine inhibits transcription factors activator protein 1 and nuclear factor-κB, Interleukin-8 production, as well as CD11b and CD16 expression: studies in human leukocytes and Leukocytic cell lines. Anesth. Analg. https://doi.org/10.1213/ane.0b013e3181c95cfa.

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, 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472.

Yang, C., Hu, Y.-M., Zhou, Z.-Q., Zhang, G.-F., Yang, J.-J., 2013. Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test. Ups. J. Med. Sci. 118, 3–8. https://doi.org/10.3109/03009734.2012.724118.

Zanos, P., Gould, T.D., 2018. Mechanisms of ketamine action as an antidepressant. Mol. Psychiatry 23, 801–811. https://doi.org/10.1038/mp.2017.255.

Zanos, P., Moaddel, R., Morris, P.J., Georgiou, P., Fischell, J., Elmer, G.I., Alkondon, M., Yuan, P., Pribut, H.J., Singh, N.S., Dossou, K.S.S., Fang, Y., Huang, X.-P., Mayo, C.L., Wainer, I.W., Albuquerque, E.X., Thompson, S.M., Thomas, C.J., Zarate Jr., C.A., Gould, T.D., 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533, 481–486. https://doi.org/10.1038/nature17998.

Zhou, W., Wang, N., Yang, C., Li, X.-M., Zhou, Z.-Q., Yang, J.-J., 2014. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur. Psychiatry 29, 419–423. https://doi.org/10.1016/j.eurpsy.2013.10.005.