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Ketamine metabolite pilot study in a suicidal depression trial

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ABSTRACT

Ketamine shows promise as a rapidly-acting treatment for depression and suicidal ideation, but side effects and abuse potential limit its use. Understanding its mechanism of action could help develop analogous but safer drugs. This *post hoc* study explored relationships of ketamine and metabolites, including hydroxynorketamine enantiomers, *(2S,6S)*- and *(2R,6R)*-HNK, to clinical response in a subgroup from a published trial in suicidal depression. Depressed adults with clinically significant suicidal ideation were randomized to double-blind infusion of sub-anesthetic ketamine or midazolam. Ketamine and metabolites were measured after infusion (N = 53). Plasma *(2R,6R)*-HNK was associated with change (higher levels correlated with less clinical improvement) from baseline to 24 h post-infusion of depression (HDRS-24: Spearman r = 0.37, p = 0.009) and suicidal thoughts (SSI: Spearman r = 0.29, p = 0.041). There were similar correlations with weekly follow-up clinical rating scores for both HNK enantiomers and dehydronorketamine (DHNK). Ketamine and norketamine were not associated with change in depression or suicidal ideation (unadjusted p > 0.28).

1. Introduction

Despite modest advantages over placebo, slow onset of action, and troubling side effects like sexual dysfunction, antidepressants are the third most-prescribed drug class in U.S. medical office visits (Cipriani et al., 2018; Mann et al., 2005; Pratt et al.2017). This likely relates to the fact that depression is among the most disabling of human maladies (WHO, 2017). It remits with antidepressant treatment in a third or fewer patients and a minority experience even 50% improvement with a first-line drug (Trivedi et al., 2006). An estimated 30–50% of patients don't respond sufficiently to current therapies – termed treatment resistant depression (TRD) (Akil et al., 2018; Fava and Davidson, 1996). Because depression is the major contributor to suicidal states, shortcomings of treatment may factor in the more than 30% increase from 1999 to 2017 in US suicide rates (Hedegaard et al., 2018; Mann et al., 2005). The level of interest in ketamine treatment for depression is further evidence of the need for antidepressants that work more quickly, effectively, with fewer side effects, and for more patients.

Clinical trials (Grunebaum et al., 2017, 2018; Milak et al., 2016; Murrough et al., 2013) show relief of depressive symptoms including suicidal thoughts within hours of treatment with sub-anesthetic ketamine, a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist approved in 1970 as an anesthetic (reviewed in (Newport et al., 2015)). We found that ketamine reduced suicidal thoughts within hours in suicidal depressed patients (N = 80) and the improvement appeared to persist for up to six weeks with optimized, standard pharmacotherapy (Grunebaum et al., 2018). Only about one-third of ketamine's effect on suicidal ideation was explained by its overall antidepressant effect (Grunebaum et al., 2018). There is no current approved treatment for rapid relief of suicidal thoughts in depressed patients.

Despite recent FDA approval of intra-nasal *(S)*-ketamine for treatment resistant depression, its dissociative effects, addictive potential and lack of long-term safety data on potential toxicity such as cystitis (Jhang et al., 2015) and white matter damage (Edward Roberts et al., 2014), limit its use (Caddy et al., 2015; Newport et al., 2015; Sanacora et al., 2017). It targets multiple receptors (NMDA, nicotinic, dopaminergic, opioid), and neurotransmitter systems (glutamate, GABA, serotonin) all of which could contribute to its clinical effects (Gupta et al., 2011; Morgan and Curran, 2006; Williams et al., 2018). Elucidating ketamine's antidepressant and anti-suicidal ideation mechanisms of action could aid development of safer alternatives. Pre-clinical research

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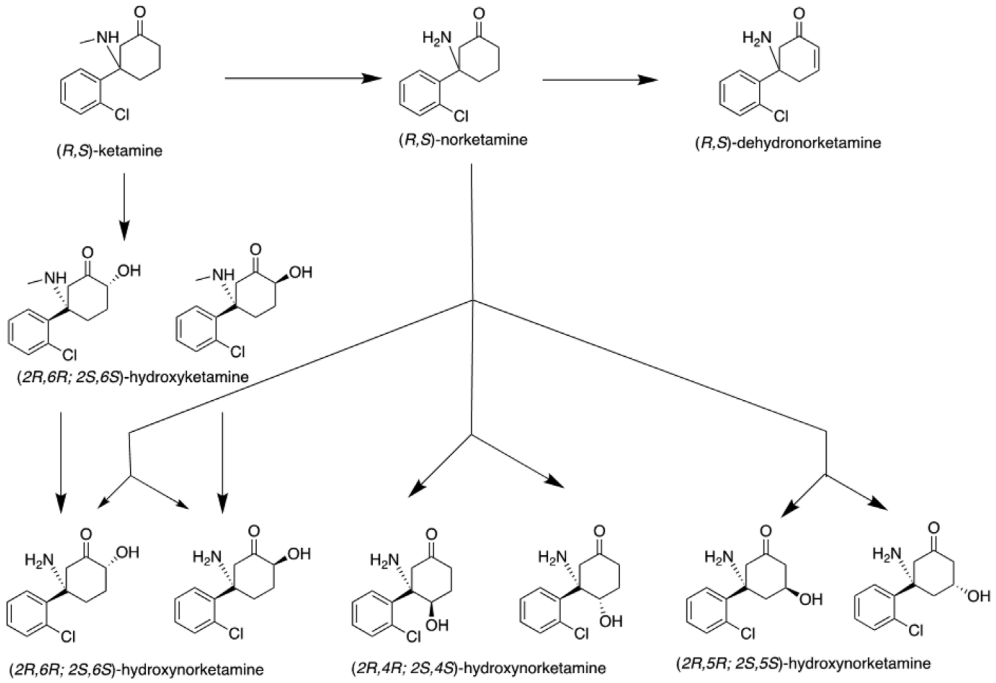

Fig. 1. Major metabolic pathways of ketamine (Zanos et al., 2018; Zarate et al., 2012).

suggests that ketamine's antidepressant mechanism of action may involve blockade of ionotropic NMDA receptors, enhanced transmission via α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) (Machado-Vieira et al., 2009; Maeng et al., 2008; Trullas and Skolnick, 1990), and trophic effects via mechanistic target of rapamycin (mTOR) and brain derived neurotrophic factor (BDNF) stimulating or maintaining dendritic spinogenesis (Ardalan et al., 2017; Autry et al., 2011; Duman and Duman, 2015; Li et al., 2010; Moda-Sava et al., 2019).

There is debate in pre-clinical literature on whether specific (*R*)- or (*S*)- enantiomers of ketamine or its metabolites - especially *(2R,6R)*-hydroxynorketamine (HNK) - may have antidepressant effects but with less potential toxicity and side effects. Ketamine is rapidly metabolized by liver enzymes to norketamine and hydroxyketamines, and then to the secondary metabolites dehydronorketamine and HNKs (Fig. 1) (Zanos et al., 2018; Zarate et al., 2012). The *(2S,6S)*- and *(2R,6R)*-HNK metabolites of, respectively, (*S*)-ketamine and (*R*)-ketamine, do not inhibit NMDARs at antidepressant-relevant concentrations, but demonstrate antidepressant-like effects in pre-clinical studies (Zanos et al., 2018). One group found *(2R,6R)*-HNK had antidepressant-related effects in mice associated with NMDA-independent AMPAR activation and without side effects seen in mice given racemic ketamine at pharmacologically relevant doses (Zanos et al., 2016). Another group using a learned helplessness model in rats found an antidepressant effect of *(R)*-ketamine but not *(2R,6R)*-HNK (Shirayama and Hashimoto, 2018). Adding complexity, *(2S,6S)*–HNK upregulates mTOR in rats (Li et al., 2010; Paul et al., 2014).

There are limited human data to add perspective. A study of ketamine metabolites after a 40-min infusion in 45 patients with a unipolar major depressive episode and 22 with bipolar depression did not report results for individual HNK enantiomers (Zarate et al., 2012). To our knowledge there is no published data on each enantiomer's antidepressant and anti-suicidal ideation effects in humans. We conducted a *post hoc* pilot study of ketamine, and its metabolites norketamine (NK), dehydronorketamine (DHNK), *(2S,6S)*–HNK, and *(2R,6R)*-HNK in a subgroup (N = 53) of a published clinical trial in suicidal depression (Grunebaum et al., 2018). We explored relationships with clinical response, and hypothesized that plasma *(2R,6R)*-HNK would correlate with improvement in depression and suicidal ideation.

2. Method

2.1. Participants

Detailed trial methods, CONSORT material, and clinical results are published (Grunebaum et al., 2018). Adults (N = 80) with current major depressive disorder (MDD) and a score ≥4 on the Beck Scale for Suicidal Ideation (SSI), of whom 54% (N = 43) were taking antidepressant medication, were randomly assigned to double-blind ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg) in 100 mL normal saline infused intravenously over 40 min. The primary outcome was the SSI score at 24 h post-infusion. Non-responders were un-blinded and if they had received midazolam were offered a second infusion the following day with open label ketamine. Other outcomes included global depressive symptoms and adverse effects. The main results at 24 h were greater reduction with ketamine compared to midazolam in SSI (95% CI = 2.33, 7.59; Cohen's d = 0.75), and Profile of Mood States (POMS) depression score (95% CI = 1.36, 13.94) (Grunebaum et al., 2018). The protocol was approved by the NYSPI IRB, and written informed consent was obtained from all participants.

2.2. Clinical measures

Raters were PhD or masters level psychologists. Axis I and II diagnoses were made using the Structured Clinical Interview for DSM-IV (First et al., 1994, 1996), in a weekly consensus conference of psychologists and psychiatrists. Raters participated in weekly reliability monitoring. Instruments included the clinician-rated SSI(Beck et al., 1979) to assess suicidal ideation with 19 items scaled 0 (least severe) to 2 (most severe) and total from 0 to 38 (Beck et al., 1979). It was assessed at screening, baseline (day before infusion), 230 min post-infusion, 24 h post-infusion (day1), and weeks 1–6 of follow-up. Response was defined as at least 50% reduction in SSI from baseline to day1 *and* day1 score < 4 (i.e. the subject would no longer be study-eligible). Depressive symptoms were assessed with the 24-item Hamilton Depression Rating Scale (HDRS-24) (Hamilton, 1960), Profile of Mood

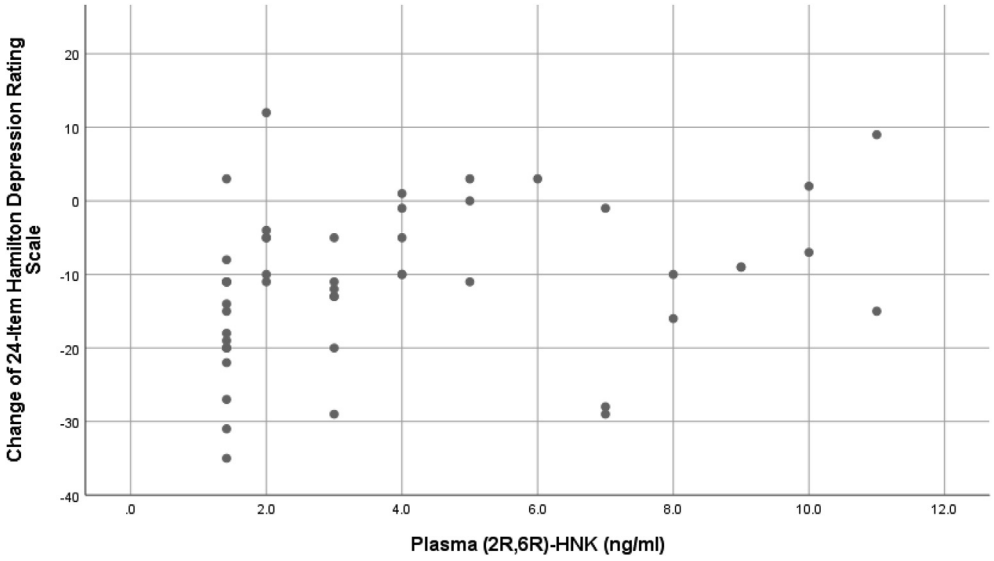

Fig. 2. Scatterplot of change in 24-item Hamilton Depression Rating Scale (24 h post-infusion score minus pre-infusion score) vs. plasma *(2R,6R)*-HNK (ng/ml)*.
*Higher post-infusion plasma *(2R,6R)*-HNK correlated inversely with improvement in depressive symptoms from pre-to 24 h post-infusion (Spearman rank correlation r = 0.37, p = 0.009).

States (POMS)(McNair et al., 1981), and anxiety was measured with a 5-level Likert scale asking patients to self-rate from 0 (not at all) to 4 (extremely anxious). Medication side effects were measured with the Clinician-Administered Dissociative States Scale (CADSS)(Bremner et al., 1998), and positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS)(Overall and Gorham, 1962).

2.3. Ketamine and metabolite levels

The pilot study of plasma ketamine (KET) and its metabolites norketamine (NK), dehydronorketamine (DHNK), and (*2S,6S*)- and (*2R,6R*)-hydroxynorketamine (HNK), immediately post-infusion, was initiated at approximately the midpoint of the parent trial (N = 80) and included all subsequent participants (N = 53). Plasma KET, NK, and DHNK were quantified using liquid/liquid extraction followed by validated HPLC separation and UV detection at 210 nm. HNK enantiomers *(2S,6S)*–HNK and *(2R,6R)*-HNK were quantified using a validated modified LC-MS method (Hasan et al., 2017).

2.4. Statistical analysis

SAS version 9.4 (SAS Institute, Cary, N.C.) and SPSS 25 (IBM, Armonk, NY) were used for analyses. Histograms and pairwise scatterplots of biomarkers and clinical outcomes were inspected for outliers and inconsistent values. The distribution of several biomarkers was skewed, and/or had outliers, which is reflected in the choice of analytic method. Imputation of square root(2) was used for the 15 (28%) non-zero *(2R,6R)*-HNK enantiomer levels that were below the detection threshold. Wilcoxon signed rank test (paired) was used to compare plasma levels of the *(2S,6S)*- versus *(2R,6R)*-HNK enantiomers. Spearman correlation coefficients were used to test for associations of plasma KET, NK, DHNK, *(2S,6S)*–HNK and *(2R,6R)*-HNK with change from pre-to 24 h post-infusion and weeks 1–6 of follow-up clinical treatment, in SSI, HDRS-24 and POMS. Pre-clinical data suggests a greater antidepressant-like effect of ketamine in female compared to male mice in association with higher brain levels of (2*S*,6*S*;2*R*,6*R*)-HNK but not KET or NK (Zanos et al., 2016), so we explored this by testing models of change in SSI or HDRS-24 score from baseline to 24 h post-infusion with *(2R,6R)*-HNK level, sex, and the interaction of these as predictor variables. Since this was an exploratory pilot study, we did not correct for multiple comparisons.

3. Results

3.1. Associations with 24 h post-infusion ratings

(2R,6R)-HNK levels were missing for 5 (9%) subjects and *(2S,6S)*–HNK levels were missing for 8 (15%). The distribution of *(2R,6R)*-HNK levels was not associated with infusion type (randomized *vs.* open) (Wilcoxon W = 604.0, p = 0.737), and the same was found for *(2S,6S)*–HNK (Wilcoxon W = 507.0, p = 0.617). Thus randomized and open ketamine infusion data were pooled. The interaction of sex with *(2R,6R)*-HNK was not associated with change from baseline to 24 h post-infusion in SSI (p = 0.931) or HDRS-24 (p = 0.413).

Change in SSI score from pre-to 24 h post-infusion was not correlated with post-infusion plasma KET (Spearman r = 0.12, p = 0.382, N = 53), NK (Spearman r = 0.06, p = 0.672, N = 53), or DHNK (Spearman r = 0.05, p = 0.739, N = 53) (ng/ml). Change in HDRS-24 from pre-to 24 h post-infusion also did not correlate with post-infusion plasma KET (Spearman r = −0.07, p = 0.636, N = 53), NK (Spearman r = −0.09, p = 0.501, p = 53), or DHNK (Spearman r = 0.06, p = 0.645, N = 53).

Plasma levels (ng/ml) of *(2S,6S)*–HNK (N = 45; Mean (SD) = 20.8(9.9); Median = 20.0, Range 6.0–52.0) were higher compared with *(2R,6R)*-HNK (N = 48; Mean(SD) = 4.0(2.9); Median = 3.0, Range 1.4–11.0; Wilcoxon signed rank p < 0.001), although levels of the two enantiomers were moderately correlated (N = 45, Spearman r = 0.52, p < 0.001). Baseline psychotropic medication status (taking *vs.* not) was not associated with *(2R,6R)*-HNK level (Mann-Whitney U = 240.0, p = 0.362), but *(2S,6S)*–HNK levels were higher in subjects taking psychiatric medications (Mean = 23.1 ng/ml; SD = 10.1) compared to those off meds (Mean = 13.9 ng/ml; SD = 5.4) (Mann-Whitney U = 293.0, p = 0.004).

Higher post-infusion plasma level of the *(2R,6R)*-HNK enantiomer correlated inversely with improvement in depressive symptoms from pre-to 24 h post-infusion using the HDRS-24 (Spearman r = 0.37, p = 0.009) (Fig. 2). Similarly, post-infusion *(2R,6R)*-HNK plasma level correlated inversely with improvement in suicidal ideation (SSI score) from pre-to 24 h post-infusion (Spearman r = 0.29, p = 0.041)(Fig. 3).

The *(2S,6S)*–HNK enantiomer was not associated with pre-to 24 h post-infusion change in SSI (Spearman r = 0.08, p = 0.597) or HDRS-24 scores (Spearman r = 0.12, p = 0.450). In separate models adjusting for baseline medication status, plasma *(2S,6S)*–HNK was not associated with change in SSI (β = 0.19, t = 1.21, p = 0.235) or HDRS-24 (β = 0.26, t = 1.59, p = 0.119).

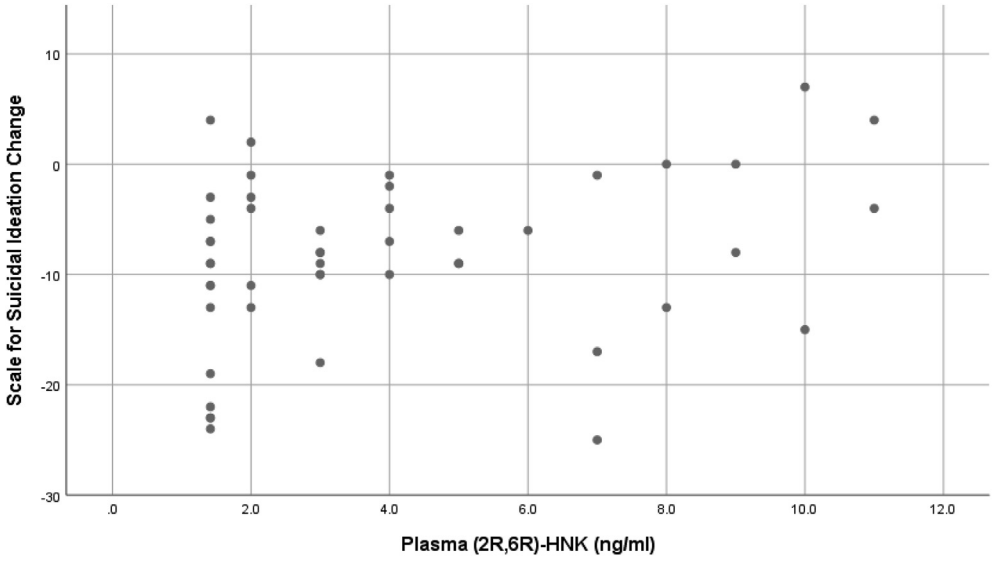

Fig. 3. Scatterplot of change in Beck Scale for Suicidal Ideation (24 h post-infusion score minus pre-infusion score) vs. plasma *(2R,6R)*-HNK (ng/ml)*.
*Higher post-infusion plasma *(2R,6R)*-HNK correlated inversely with improvement in suicidal ideation from pre-to 24 h post-infusion (Spearman rank correlation r = 0.29, p = 0.041).

POMS and adverse effect rating scales were only administered for the randomized infusion. In this smaller subgroup, plasma KET correlated inversely with improvement from pre-to 24 h post-infusion in the POMS Depression subscale (Spearman r = 0.41, p = 0.025, N = 29). Plasma NK correlated positively with dissociative symptoms on the CADSS immediately post-infusion (N = 28, Spearman r = 0.44, p = 0.019) and at day 1 (N = 26, Spearman r = 0.56, p = 0.003), and with anxiety at day 1 at a marginally significant level (N = 28, Spearman r = 0.37, p = 0.050).

3.2. Associations with weeks 1–6 follow-up ratings

Higher DHNK correlated with less decrease in SSI score from baseline to weeks 2, 3, 4, and 6 of follow-up clinical treatment (N ranged from 43 to 50, Spearman r ranged from 0.29 to 0.33, p values ranged from 0.026 to 0.044). DHNK was not associated with change in HDRS-24 from baseline to follow-up.

Levels of *(2S,6S)*–HNK were associated with less decrease in SSI score from baseline to follow-up weeks 3 (N = 38, Spearman r = 0.36, p = 0.027) and 4 (N = 37, Spearman r = 0.37, p = 0.026). Levels of *(2S,6S)*–HNK correlated with less decrease in HDRS-24 from baseline to weeks 1 (N = 41, Spearman r = 0.37, p = 0.019) and 3 (N = 38, Spearman r = 0.38, p = 0.018).

The *(2R,6R)*-HNK enantiomer was associated with less decrease in SSI score from baseline to follow-up weeks 1–4 and 6 (N ranged from 39 to 45, Spearman r ranged from 0.30 to 0.41, p ranged from 0.008 to 0.039). Levels of this enantiomer were associated with less decrease from baseline to weeks 1,2,4, and 5 in HDRS-24 (N ranged from 37 to 45, Spearman r ranged from 0.33 to 0.39, p ranged from 0.009 to 0.044). There were no other statistically significant associations of ketamine or metabolites with clinical response.

4. Discussion

The main finding of this pilot study is the inverse association of post-infusion plasma *(2R,6R)*-HNK with clinical improvement from pre-to 24 h post-infusion in suicidal ideation, and separately, global depressive symptoms. There were similar correlations with change in SSI and HDRS-24 from baseline to follow-up timepoints. Our results contrast with a report that *(2R,6R)*-HNK had antidepressant-related effects in mice (Zanos et al., 2016), although another study did not find this association in rats (Shirayama and Hashimoto, 2018). This subject remains controversial in the pre-clinical literature. We found correlations of DHNK with less improvement in SSI and of *(2S,6S)*–HNK with less improvement in SSI and HDRS-24 from baseline to follow-up timepoints. To our knowledge, these are the first clinical trial data published on relationships of the individual (2*S*,6*S*)- and (2*R*,6*R*)-HNK enantiomers to antidepressant and anti-suicidal ideation response in humans.

Given pre-clinical evidence of antidepressant-like effects of *(2R,6R)*-HNK (Zanos et al., 2016), the inverse association with clinical improvement that we found in a human trial is counter-intuitive. A plausible explanation is if less ketamine metabolism and higher parent compound levels correlated with clinical improvement, as our group found with NK – precursor to HNK – in a prior study (Milak et al., 2016). However, the current study, with a sample more than fourfold larger, did not find KET or NK levels to be associated with change in SSI or HDRS-24 scores. The lack of these associations is consistent with a study of ketamine and metabolite levels in 45 MDD and 22 BD patients (Zarate et al., 2012). Our results should not be interpreted to mean that *(2R,6R)*-HNK does not have antidepressant effects as sample timing, assay sensitivity, and dosing may all have contributed. An association of clinical improvement with more rapid absorption of *(2R,6R)*-HNK into brain, resulting in lower plasma levels, is an alternative explanation requiring further research. The fact that subjects continued current medications at stable doses may have influenced our results, but *(2R,6R)*-HNK level was not associated with subjects' baseline psychotropic medication status (taking *vs.* not), so this seems unlikely.

Pre-clinical evidence shows higher brain levels of KET and NK in female rats (Saland and Kabbaj, 2018) and of (2S,6S; 2R,6R)-HNK in female mice, as compared to males (Zanos et al., 2016). A human study also found higher (2S,6S; 2R,6R)-HNK and DHNK levels in women compared to men (Zarate et al., 2012). We did not find an interaction of sex with *(2R,6R)*-HNK in terms of effect on clinical response at 24 h post-infusion.

Our finding that *(2S,6S)*–HNK levels were higher than those of the *(2R,6R)*- enantiomer, is consistent with pre-clinical data (Moaddel et al., 2015). Unlike the *(2R,6R)*- enantiomer, the distribution of plasma *(2S,6S)*–HNK was associated with baseline medication status, but it did not correlate with change in depressive symptoms or suicidal ideation after adjusting for the potential confound.

Our finding that NK levels correlated positively with dissociative side effects is consistent with a prior study that found DHNK correlated inversely with these adverse effects since NK is a precursor to DHNK (Zarate et al., 2012).

The main limitation of this *post hoc* study is that it was added after the parent trial was underway, and therefore involved a subgroup. However, this seems an unlikely source of bias since the study included

all subsequent participants, comprising more than half of the parent trial sample. The substantial number of *(2R,6R)*-HNK enantiomer levels that were non-zero yet below the detection limit, appeared influential on the result, however non-parametric Spearman rank correlation takes this into account. The latter may partly explain why the *2R,6R* enantiomer was more correlated with symptom change compared to the *2S,6S* enantiomer. It is possible that any monotonic association here may be restricted to a very small range of the biomarker, after which there is a saturation effect. Of note, *(2R,6R)*-HNK was associated with antidepressant-like effects in mice at time points after its brain concentration was below detectable levels (Zanos et al., 2016). HDRS-24 and SSI scores before *open* ketamine infusion were less severe than before the *randomized* ketamine infusion, but improvement after both infusion types was similar (Grunebaum et al., 2018). The distributions of both HNK enantiomers were not associated with infusion type, suggesting that pooling the plasma ketamine data from randomized and open infusions was reasonable. Measurement of ketamine and metabolites at a single time point immediately post-infusion is a limitation, however, published data show that KET, NK, DHNK, 2*S*,6*S*- and 2*R*,6*R*–HNK are present at significant levels during the first 230 min post-infusion (Zarate et al., 2012).

In contrast to results from a pre-clinical study in mice (Zanos et al., 2016), our findings suggest that higher *(2R,6R)*-HNK plasma level is associated with less improvement in depression and suicidal thoughts in suicidal depressed persons. These preliminary findings need replication, but at minimum do not suggest a robust benefit of *(2R,6R)*-HNK for depression or suicidal ideation. They also raise questions about potential differences in response to ketamine and its metabolites in rodent models of depression versus in the human illness.

Conflicts of interest

Drs. Mann and Burke receive royalties for commercial use of the Columbia Suicide Severity Rating Scale which was not used in this work. Dr. Galfalvy's family owns stock in Illumina, Inc. Dr. Suckow owns stock in Johnson & Johnson. The other authors report no financial relationships with commercial interests.

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