Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response:

Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression

Mu-Hong Chen, MD, PhD[a,b,d]; Wei-Chen Lin, MD[a,b,d]; Hui-Ju Wu, BSN[b]; Ya-Mei Bai, MD, PhD[a,b]; Cheng-Ta Li, MD, PhD[a,b,d]; Shih-Jen Tsai, MD[a,b,d]; Chen-Jee Hong, MD[a,b,d]; Pei-Chi Tu, MD, PhD[a,b,c]; Chih-Ming Cheng, MD[a,b,d]; and Tung-Ping Su, MD[a,b,c,d,e,*]

ABSTRACT

Background: Studies have reported that ketamine potentially increases subjective happiness in healthy volunteers. However, whether ketamine-induced happiness can predict the treatment response of ketamine infusion among patients with treatment-resistant depression (TRD) remains unknown.

Methods: Between 2012 and 2015, 71 adult patients with TRD (based on *DSM-IV-TR* criteria) were enrolled and randomly assigned to receive a 40-minute ketamine (0.5 mg/kg or 0.2 mg/kg) or normal saline placebo infusion. Depressive symptoms were measured using the 17-item Hamilton Depression Rating Scale. Measurements were conducted prior to infusion, at 40 and 240 minutes postinfusion, and, sequentially, on days 2 to 7 and 14 postinfusion. The visual analog scale for happiness (VASH) was used to assess happiness during infusion. The positive symptoms subscale of the Brief Psychiatric Rating Scale (BPRS-P) was used to measure the potential psychotomimetic effects of ketamine.

Results: For both the 2-factor (ketamine vs placebo) and 3-factor (ketamine 0.5 mg/kg vs 0.2 mg/kg vs placebo) models, a generalized estimating equation model indicated that infusion response type (happiness vs nonhappiness) significantly ($P = .008$ vs $P = .002$) predicted the trajectory of depressive symptoms after infusion. Changes in VASH and BPRS-P measures were not associated with each other.

Conclusions: Subjective happiness during ketamine infusion predicted the antidepressant effect of both 0.5 mg/kg and 0.2 mg/kg ketamine infusion over time. Happiness during ketamine infusion, which was not related to the psychotomimetic effect of ketamine, may be associated with the reduction of depressive symptoms during the follow-up.

Trial Registration: UMIN Clinical Trials Registry registration number: UMIN000016985

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[a]Division of Psychiatry, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan

[b]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

[c]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan

[d]Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

[e]Department of Psychiatry, Cheng Hsin General Hospital, Taipei, Taiwan

**Corresponding author:* Tung-Ping Su, MD, Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Sec 2, Shih-Pai Rd, Beitou District, Taipei, 112, Taiwan (tomsu0402@gmail.com).

Treatment-resistant depression (TRD), defined as a major depressive disorder accompanied by lack of response to more than 2 adequate antidepressant trials, is commonly associated with functional impairment, poor quality of life and well-being, suicide ideation and attempts, self-injurious behavior, and a high relapse rate.[1] The Sequenced Treatment Alternatives to Relieve Depression study reported that up to 40% of patients with major depressive disorder met the TRD criteria and that over 33% of patients continued to have depression even after 4 trials of different antidepressant treatments—including combination therapy and augmentation therapy.[2]

In the 2010s, increasing evidence has supported the fast-acting and promising antidepressant effect of low-dose ketamine infusion in patients with TRD, with up to 65% and 50% of TRD patients reaching the response state after ketamine infusion in Western studies and in a Taiwanese study, respectively.[3–5] Several studies have investigated the clinical predictors of treatment response to ketamine infusion in patients with TRD, suggesting that a family history of an alcohol use disorder in a first-degree relative, nonmelancholic and melancholic-anxious features, moderate or severe anhedonia at baseline, and the absence of a prior suicide attempt predicted the likelihood of response.[6–9] However, only a few studies have examined the relationship between subjective psychological experience during ketamine infusion and the antidepressant response of ketamine infusion in patients with TRD.[6,10] Pennybaker et al[6] reported an association between dissociation during ketamine infusion and better antidepressant response. However, Luckenbaugh et al[11] reported that dissociative and psychotomimetic symptoms were not related to improvements in depressive symptoms at postinfusion. In addition, Aust et al[10] demonstrated that ketamine-induced anxiety during infusion had a negative effect on the antidepressant efficacy of ketamine.

In previous studies, the feeling of happiness during ketamine infusion has been rarely mentioned but often observed.[12] Gaydos et al[12] compared the performance in basic soldiering tasks among 48 healthy volunteers who received the standard battlefield analgesic (10 mg IM morphine) and 25 mg IM ketamine. They found that, relative to morphine and placebo administration,

Clinical Points

- Subjective feeling of happiness during infusion was associated with the antidepressant effect of both 0.5 mg/kg and 0.2 mg/kg ketamine infusions over time.
- Happiness during ketamine infusion was not related to the psychotomimetic effect of ketamine.
- The between-group significance of ketamine's antidepressant effect was noted only among patients with TRD who experienced happiness during infusion.

participants reported greater feelings of happiness—in addition to other symptoms such as dizziness and poor concentration—when given ketamine. Specifically, happiness is a subjective experience of positive affect and is often called subjective well-being or emotional well-being.[13] The lack of positive affect is likely to be more common and is usually seen in different stages of major depressive disorder, including the acute, chronic, and remitted phases.[14,15] Moreover, traditional antidepressants, such as selective serotonin reuptake inhibitors, are not effective in treating positive affect deficits.[14] Oren-Yagoda et al[16] determined that during a pharmacotherapy pretreatment and the administration of cognitive-behavioral therapy, compared with negative affect, positive affect was a much better predictor of depressive symptoms after treatment.

In this study, we reanalyzed data from the Adjunctive Ketamine Study of Taiwanese Patients with Treatment-Resistant Depression. That study involved 71 patients with TRD who were randomly administered 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, or a saline placebo. That study examined the outcomes of happiness and nonhappiness during infusion as well as the antidepressant effect of ketamine infusion during follow-up. We hypothesized that subjective ketamine-induced happiness was associated with a greater reduction of depressive symptoms at postinfusion.

METHODS

Inclusion Criteria and Study Procedure

The study design, patient enrollment, and clinical results of the current clinical trial study have been previously published.[4,17] Between 2012 and 2015, 71 adult patients with TRD with no history of major medical or neurologic diseases or alcohol or substance use disorders were enrolled in our study. Major depressive disorder was diagnosed based on the criteria of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*). Participants received 40-minute intravenous infusions and were randomly assigned to be administered 0.5 mg/kg of ketamine, 0.2 mg/kg of ketamine, or a saline placebo. Depressive symptoms were examined using a 17-item Hamilton Depression Rating Scale (HDRS). HDRS measurements were conducted prior to infusion; at 40, 80, 120, and 240 minutes postinfusion; and, sequentially, on days 2 to 7 and 14 postinfusion.[18] This study accorded with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. All participants gave their informed consent (clinical trial registration: UMIN Clinical Trials Registry; registration number: UMIN000016985).

Definition of Happiness During Infusion

The visual analog scale for happiness (VASH) was used for the assessment of happiness. The standard question for happiness evaluation was used in our study: Please rate your feeling of happiness (幸福 Xìngfú) from 0 (not at all) to 10 (very) now.[19] *Xìngfú* indicates the subjective feeling of well-being and happiness in Mandarin Chinese. VASH measurements were conducted prior to infusion, at 20 minutes during infusion, and at 40 minutes postinfusion. Subjective happiness at the moment was rated by every subject. Subjects whose VASH scores at either 20 minutes during infusion or 40 minutes postinfusion were higher than the baseline (prior to infusion) were defined as the happiness during infusion group, and subjects not in this group were defined as the nonhappiness during infusion group. In addition, to assess whether happiness during infusion was related to ketamine-related psychotomimetic symptoms, the positive symptoms subscale (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content, grandiosity, and disorientation) of the Brief Psychiatric Rating Scale (BPRS-P) was used to measure the potential ketamine-related psychotomimetic effects at 40 minutes postinfusion.[20] Furthermore, in order to clarify whether ketamine-related happiness may persist at postinfusion and to ensure that happiness was not just a byproduct of the side effects of ketamine,[21] VASH measurements of subjective happiness were assessed at 80 minutes, day 3, day 7, and day 14 postinfusion.

Statistical Methods

Continuous variables and nominal variables were analyzed using 1-way analysis of variance and Fisher χ^2 tests, respectively, to assess differences between the two subgroups (happiness during infusion vs nonhappiness during infusion) with respect to demographic and clinical data. A generalized estimating equation (GEE) model, with an autoregressive method for correlations of repeated measures for the same subject over time, was used to examine the effects of ketamine on reduction of HDRS scores during the study period. The GEE included between-patient factors, which comprised infusion type (0.5 mg/kg or 0.2 mg/kg ketamine or placebo) and infusion response type (happiness during infusion vs nonhappiness during infusion); a single within-patient factor, which was time (baseline, 40 and 240 minutes postinfusion, and days 2 to 7 and 14); and all possible interactions. Furthermore, stratified by treatment group, GEE models were used for further assessment of the effects of ketamine on depression symptoms and subjective happiness during the study period. These models included the infusion response type as a between-patient factor, time as a within-patient factor, and baseline depression score as

a between-patient predictor, in addition to all possible interactions. In addition, stratified by infusion response type, GEE models (with the autoregressive method for correlations of repeated measures for the same subject over time) were used to examine the effects of ketamine on depression symptoms during the study period. These models included the treatment group as a between-patient factor, time as a within-patient factor, and baseline depression score as a between-patient predictor, in addition to all possible interactions. Finally, a general linear model—adjusting for age, sex, treatment group, and baseline HDRS scores—was used to analyze the association between the changes in VASH and BPRS-P scores at 40 minutes postinfusion and the association between the changes in VASH scores at 40 minutes postinfusion and HDRS scores at each time point (baseline, 40 and 240 minutes, days 2 to 7 and 14). Finally, effect size of Cohen *d* was calculated to assess the predictive power of happiness vs nonhappiness during infusion for treatment response. A 2-tailed $P < .05$ was considered statistically significant. All data processing and statistical analyses were performed using SPSS, version 17 (SPSS Inc).

Table 1. Demographic Characteristics and Clinical Data Among Patients With Treatment-Resistant Depression

	All (N = 71)	Happiness During Infusion (n = 44)	Nonhappiness During Infusion (n = 27)	*P* Value
Age, mean (SD), y	47.38 (10.60)	46.45 (11.04)	48.89 (9.84)	.351
Sex, female, n (%)	53 (74.6)	30 (68.2)	23 (85.2)	.161
Education, mean (SD), y	12.30 (3.47)	12.36 (3.79)	12.19 (2.96)	.835
Duration of illness, mean (SD), y	11.26 (8.22)	11.34 (8.41)	11.13 (8.05)	.917
Treatment group, n (%)				.553
0.5 mg/kg ketamine	24 (33.8)	13 (29.5)	11 (40.7)	
0.2 mg/kg ketamine	23 (32.4)	16 (36.4)	7 (25.9)	
Normal saline placebo	24 (33.8)	15 (34.1)	9 (33.3)	
Visual analog scale of happiness, mean (SD), y				
Baseline	3.37 (2.57)	2.82 (1.91)	4.26 (3.26)	.021
20 min	4.80 (2.91)	5.80 (2.63)	3.19 (2.63)	< .001
40 min	5.03 (2.91)	6.00 (2.43)	3.44 (2.97)	< .001
BPRS-P, mean (SD), y				
Baseline	6.11 (0.55)	6.07 (0.45)	6.19 (0.68)	.387
40 min	6.15 (1.01)	6.00 (0.00)	6.41 (1.62)	.099
HDRS, mean (SD), y				
Baseline	23.13 (4.54)	23.25 (4.52)	22.93 (4.65)	.773
40 min	17.66 (6.96)	15.86 (6.49)	20.59 (6.81)	.005
240 min	16.28 (6.85)	14.98 (6.18)	18.41 (7.45)	.040
Day 2	15.34 (7.39)	13.93 (6.83)	17.63 (7.82)	.040
Day 3	15.56 (7.41)	14.30 (7.19)	17.63 (7.43)	.065
Day 4	15.54 (7.77)	14.30 (7.76)	17.56 (7.50)	.086
Day 5	15.90 (7.69)	14.52 (7.68)	18.15 (7.29)	.053
Day 6	16.28 (7.35)	15.05 (7.15)	18.30 (7.44)	.070
Day 7	17.18 (7.14)	15.57 (6.79)	19.81 (7.04)	.014
Day 14	17.31 (6.89)	16.34 (7.07)	18.89 (6.40)	.131
Responders, n (%)	23 (32.4)	18 (40.9)	5 (18.5)	.068

Abbreviations: BPRS-P = Brief Psychiatric Rating Scale positive symptoms subscale (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content, grandiosity, disorientation); HDRS = Hamilton Depression Rating Scale; TRD = treatment-resistant depression.

RESULTS

In total, 44 (62%) patients with TRD reported feelings of happiness during infusion (Table 1). Relative to the nonhappiness group, the happiness during infusion group had similar baseline scores for HDRS (23.25 ± 4.52 vs 22.93 ± 4.65, $P = .773$) and lower baseline scores for VASH (2.82 ± 1.91 vs 4.26 ± 3.26, $P = .021$) (Table 1).

For both the 2-factor (ketamine vs placebo) and 3-factor (ketamine 0.5 mg/kg vs 0.2 mg/kg vs placebo) models, GEE model results indicate that infusion response type (happiness vs nonhappiness) significantly ($P = .008$ for 2-factor model; $P = .002$ for 3-factor model) predicted the trajectory of depressive symptoms after infusion (Table 2). Effect size of infusion response type (happiness vs nonhappiness) for treatment response was 0.49, indicating a moderate predictive power. Stratified by treatment group, the feeling of happiness that occurred during ketamine (group effect: 0.5 mg/kg, $P = .001$; 0.2 mg/kg, $P = .018$), but not placebo ($P = .267$), infusion was related to the greater reduction of HDRS scores during follow-up (Figure 1). Furthermore, subjective happiness that occurred during ketamine infusion would persist up to day 14 postinfusion in both the 0.5 mg/kg ($P < .001$) and 0.2 mg/kg ($P = .002$) groups (Supplementary Figure 1).

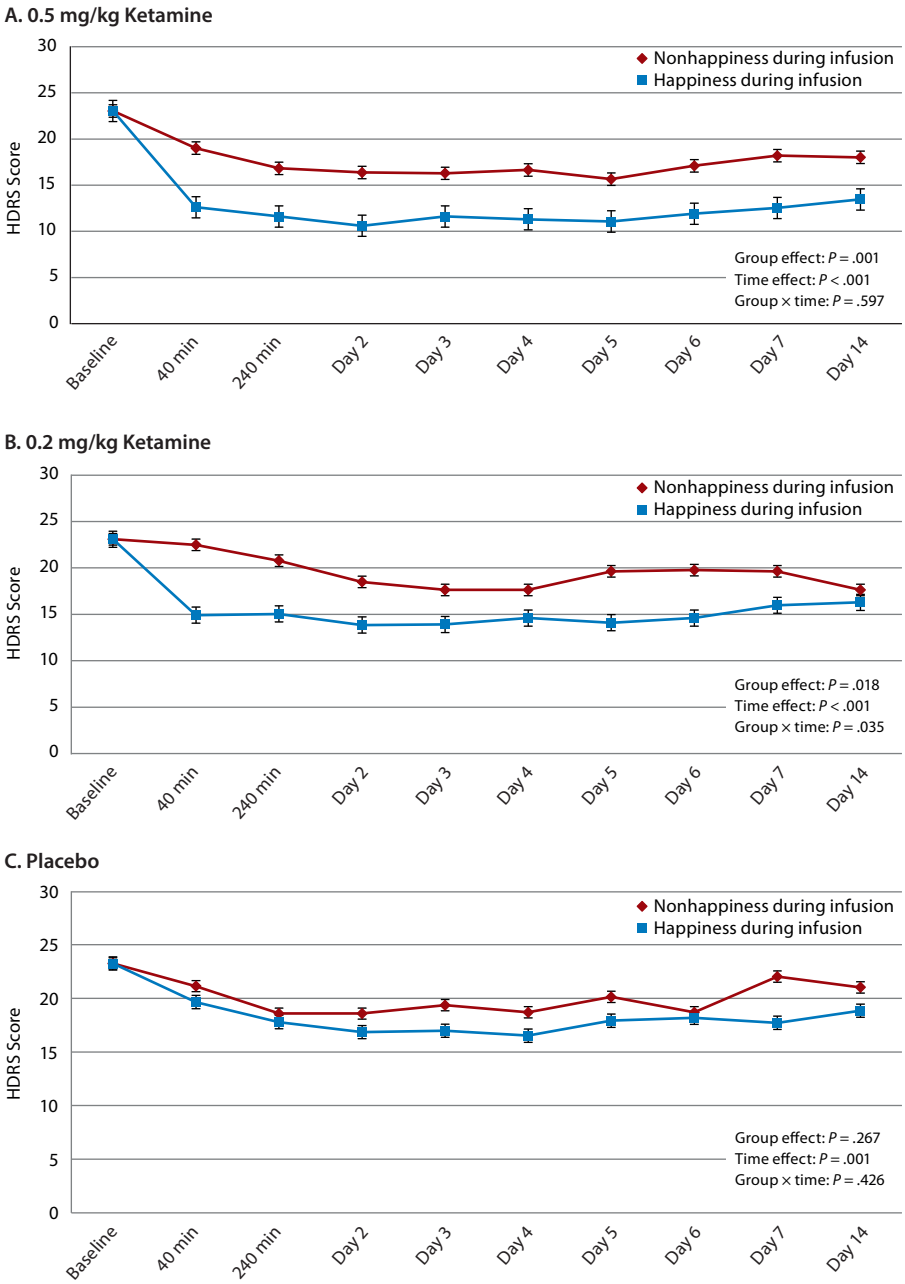
Table 2. Effect of Happiness vs Nonhappiness During Infusion and Treatment Group on Trajectory of Depressive Symptoms

	Depression (HDRS Score) Reduction			
	Two-Group (Ketamine vs Placebo) Comparison		Three-Group (0.5 mg/kg vs 0.2 mg/kg Ketamine vs Placebo) Comparison	
	df	*P* Value[a]	*df*	*P* Value[a]
Group	1	**.008**	2	**.002**
Happiness vs nonhappiness during infusion	1	**.001**	1	**< .001**
Time	8	**< .001**	8	**< .001**
Group × time	8	.102	16	**.003**
Group × happiness vs nonhappiness during infusion	1	.086	2	.143
Time × happiness vs nonhappiness during infusion	8	.536	8	.493

[a]Bold type indicates statistical significance.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

The dose-dependent effect of ketamine in the reduction of depressive symptoms was noted only in the happiness during infusion group ($P = .002$) and not in the nonhappiness during infusion group ($P = .341$) (Figure 2). In addition, changes in VASH and BPRS-P scores at 40 minutes postinfusion were not associated ($P > .05$). However, changes in VASH scores at 40 minutes postinfusion were significantly related to changes in HDRS scores at each time point from 40 minutes to day 7 (all $P < .05$).

Figure 1. Clinical Trajectory of Patients With TRD (Happiness vs. Nonhappiness During Infusion) After Ketamine/Placebo Infusion, Stratified by Treatment Group



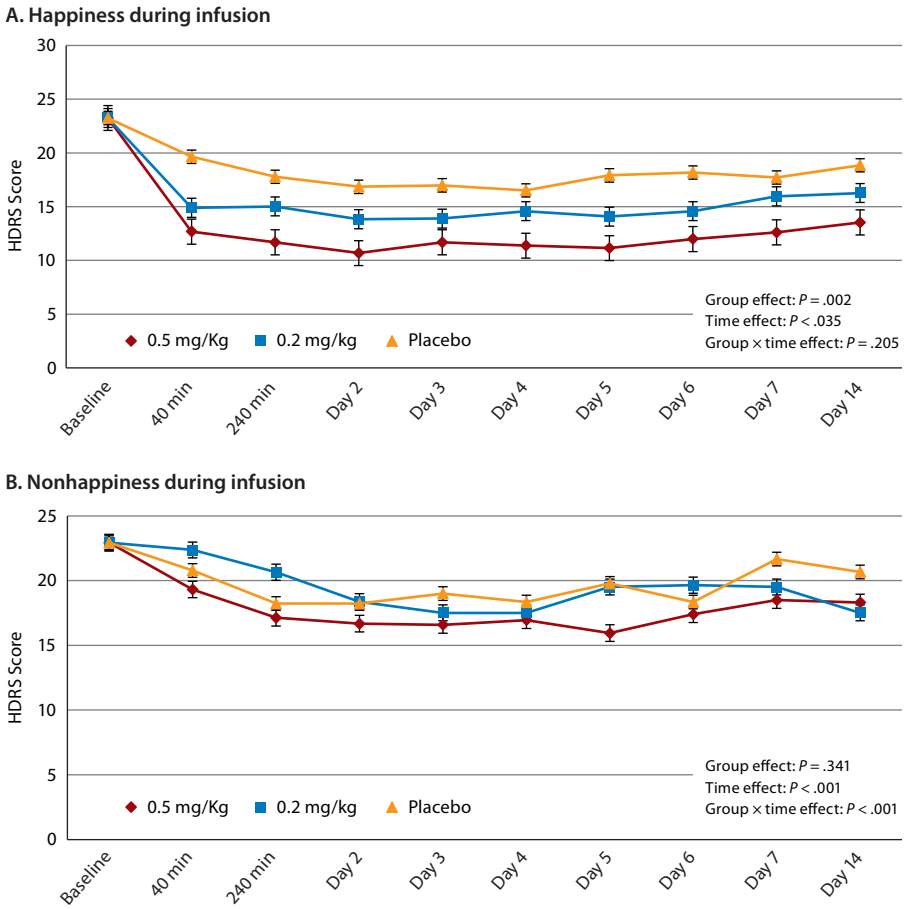
Abbreviations: TRD = treatment-resistant depression, HDRS = Hamilton Depression Rating Scale.

DISCUSSION

Our findings support the study's hypothesis that subjective happiness during ketamine infusion predicted the antidepressant effect of both 0.5 mg/kg and 0.2 mg/kg ketamine infusion over time. Happiness during ketamine infusion, which was not related to the psychotomimetic effect of ketamine, was significantly associated with the reduction of depressive symptoms during the follow-up. Furthermore, the between-group significance of ketamine's antidepressant effect was only noted among patients with TRD who experienced happiness during infusion.

As mentioned in the introduction, several clinical markers, such as features of melancholic and anxious distress, history of attempted suicide, and ketamine-induced anxiety during infusion, may negatively predict the treatment response of ketamine.[6–9] Our study is the first to suggest the positive role of subjective happiness during infusion in the antidepressant effect of low-dose ketamine infusion. Studies have reported the predictive role of positive affect, such as happiness or joy, in the therapeutic outcome of pharmacotherapy and nonpharmaceutical interventions for depression.[22–24] Gorwood et al[23] assessed the subjective feelings of joy and sadness during a 6-week antidepressant

Figure 2. Clinical Trajectory of Patients With TRD After Ketamine/Placebo Infusion, Stratified by Happiness vs Nonhappiness During Infusion



Abbreviations: TRD = treatment-resistant depression, HDRS = Hamilton Depression Rating Scale.

treatment among 2,049 adult outpatients with depression and found that an increase in joy at week 2 positively predicted treatment response and functional improvement at week 6. Suterwala et al[22] examined positive affect immediately after an acute exercise session, where the treatment response was a combination therapy of antidepressants and public-health-dose exercise; they discovered that positive affect after exercise significantly predicted the antidepressant response of the combination therapy. Geschwind et al[24] further discovered that early improvements in positive affect during the first week of antidepressant treatment predicted response and remission at week 6, with moderate to large effect sizes. Unlike the slow effect of traditional antidepressants on human affect, low-dose ketamine potentially induces positive affect (happiness) rapidly during infusion. The positive affect during infusion should be considered a clinical predictor of the antidepressant effect of ketamine.

The positron emission tomography (PET) results of our previous study may partially explain the mechanism underlying the predictive role of happiness during infusion in the antidepressant response of ketamine.[17] Li et al[17] examined glucose metabolism in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) prior to and immediately after a low-dose ketamine infusion, finding that both 0.5 mg/kg and 0.2 mg/kg ketamine infusions, but not a normal saline placebo infusion, resulted in increases in the glucose metabolism of the PFC and ACC. In the PFC, differences in glucose metabolism significantly predicted antidepressant responses 40 and 240 minutes after treatment.[17] Studies have demonstrated the crucial role of the PFC and ACC in the feeling of happiness.[25–28] A recent systematic review revealed that regardless of the neuroimaging technique used (PET and functional magnetic resonance imaging), activation in PFC and ACC was associated with the autobiographical recall of happy events.[27] Examining the influences of subjective happiness on emotion-related prefrontal activity using multichannel functional near-infrared spectroscopy (fNIRS), Oonishi et al[25] reported that subjects with a high subjective happiness score had a higher frequency of increased oxygenated hemoglobin in the left PFC when viewing pleasant pictures. Based on our hypothesis that the antidepressant effect of ketamine is driven by rapid activation in the PFC—which functions as a kindler and is followed by persistent increases in glucose metabolism in both the dorsal ACC and supplementary motor area—happiness during ketamine infusion can be regarded as a clinical phenomenon

involving rapid activation in the PFC.[29,30] Our study implies that the only people with TRD who respond to low-dose ketamine infusion are those who experience happiness during infusion and exhibit PFC activation.

This study has several limitations. First, we used only VASH for the assessment of happiness during infusion. This was because in the subanesthetic state, patients might be unable to complete a long questionnaire for happiness, such as rating their experience on a positive and negative affect scale. Further studies may be necessary for clearer measurements of the subjective emotional experience during infusion with respect to treatment response to ketamine. Second, our study was an add-on ketamine study because in severely depressed patients, it is arguably more ethical for the medications used in the study to be the same as those prescribed to them. Therefore, the feeling of happiness during infusion may be more appropriately explained by the add-on effect of a low-dose ketamine infusion. Third, further investigation is required to determine whether happiness during infusion is related to PFC activation. The fNIRS is a potential technique for the continual recording of brain function during ketamine infusion. Fourth, the subjective feelings during low-dose ketamine infusion may be quite different among individuals and between patients and healthy volunteers.[31] In our study, we found that subjective happiness during ketamine infusion was related to positive treatment responses among patients with TRD. As mentioned, subjective anxiety during infusion was associated with negative treatment responses among patients with TRD.[10] In addition, Gaydos et al[12] reported that healthy volunteers experienced the feelings of happiness during ketamine infusion, but Nugent et al[31] suggested the opposite finding that ketamine's effects in healthy subjects may represent a potential model for dysphoria. With regard to ketamine as a hallucinogen, the reason why different persons may experience different feelings during infusion would need further investigation. The conflicting results may remind clinicians to closely monitor patients' subjective feelings, such as happiness and anxiety, during ketamine infusion because these feelings may be associated with treatment responses.

In conclusion, happiness during ketamine infusion may predict the treatment response of low-dose ketamine infusion. The increase in subjective happiness during infusion was not related to the psychotomimetic effect of ketamine but was associated with the reduction in depressive symptoms during the follow-up. Further studies may be required to validate our findings and to investigate the neurobiological mechanism between ketamine-induced happiness and the antidepressant effect of ketamine infusion.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression (AKSTP-TRD)

Author(s): Mu-Hong Chen, MD, PhD; Wei-Chen Lin, MD; Hui-Ju Wu, BSN; Ya-Mei Bai, MD, PhD; Cheng-Ta Li, MD, PhD; Shih-Jen Tsai, MD; Chen-Jee Hong, MD; Pei-Chi Tu, MD, PhD; Chih-Ming Cheng, MD; and Tung-Ping Su, MD

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List of Supplementary Material for the article

1. **Figure 1** Happiness of Patients With TRD (Happiness vs. Nonhappiness During Infusion) During and After Ketamine Infusion

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Supplementary figure 1. Happiness of patients with TRD (happiness vs. non-happiness during infusion) during and after ketamine infusion.