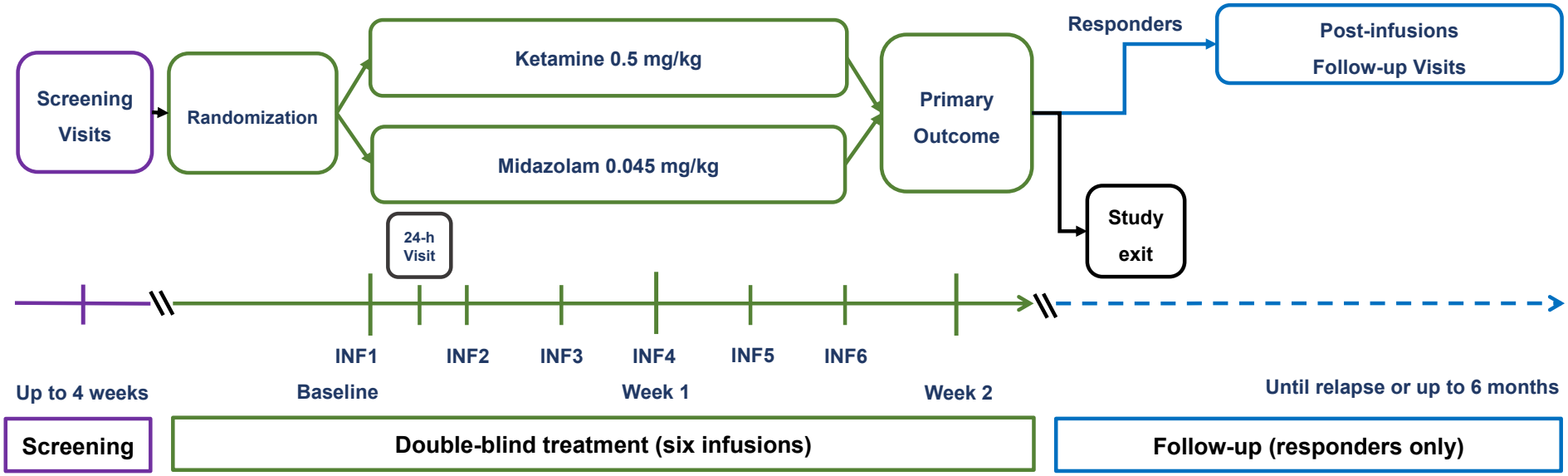
Online Supplement

Feder A, Costi S, Rutter SB et al: A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder.

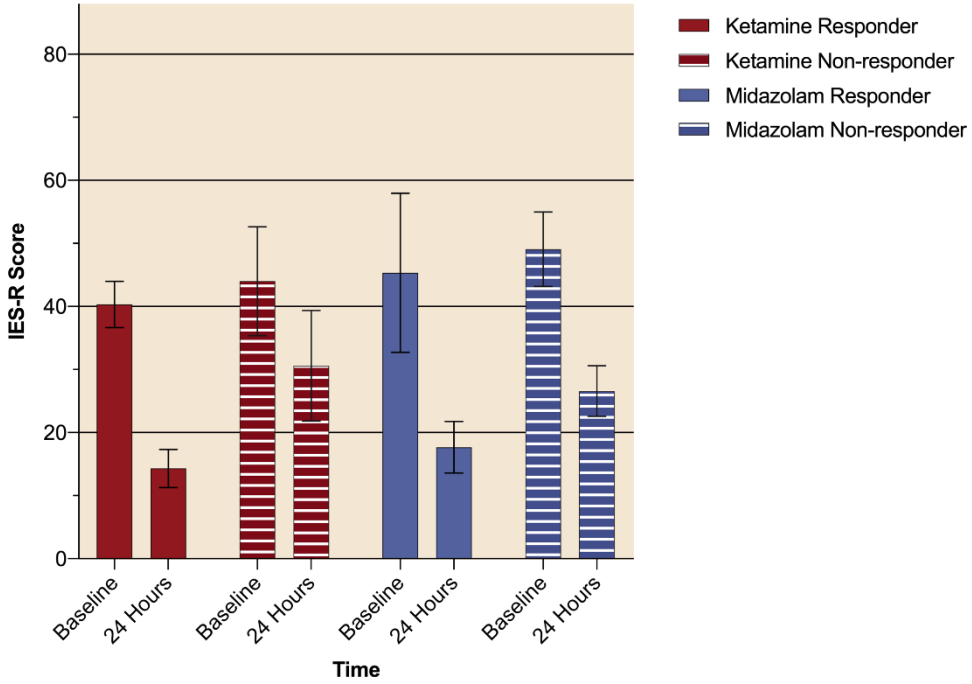
This supplementary material has been provided by the authors to give readers additional information about their work.

Figure S1. Study Flowchart



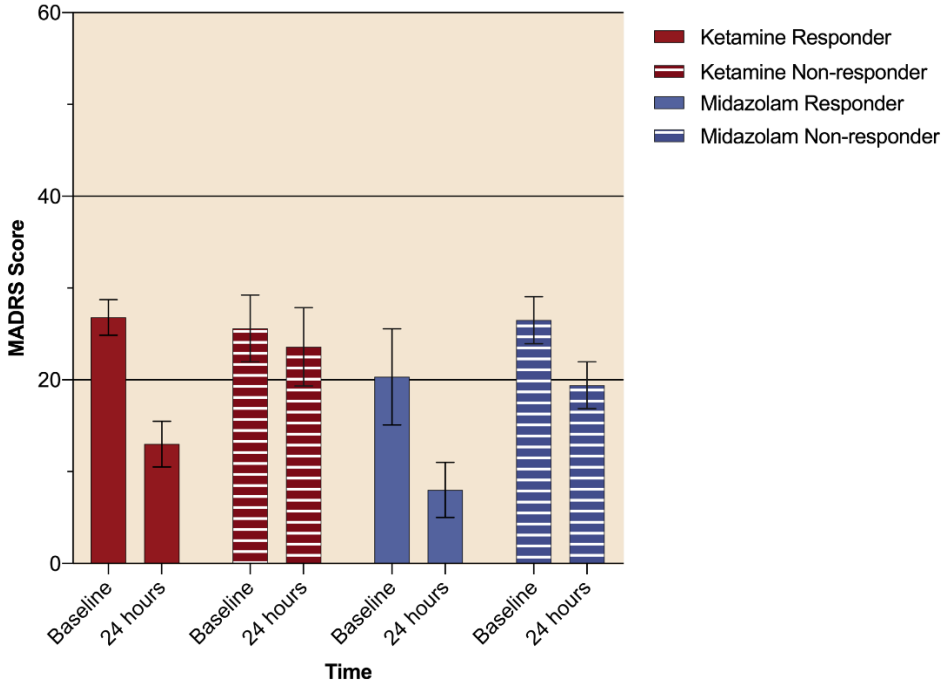
Graphical representation of study assessments; 24-h Visit, assessment 24 hours after the first infusion; INF, infusion.

Figure S2. Change in Overall PTSD Symptom Severity from Baseline to Twenty-Four Hours in the Ketamine and Midazolam Treatment Groups, by Responder and Non-responder Subgroups



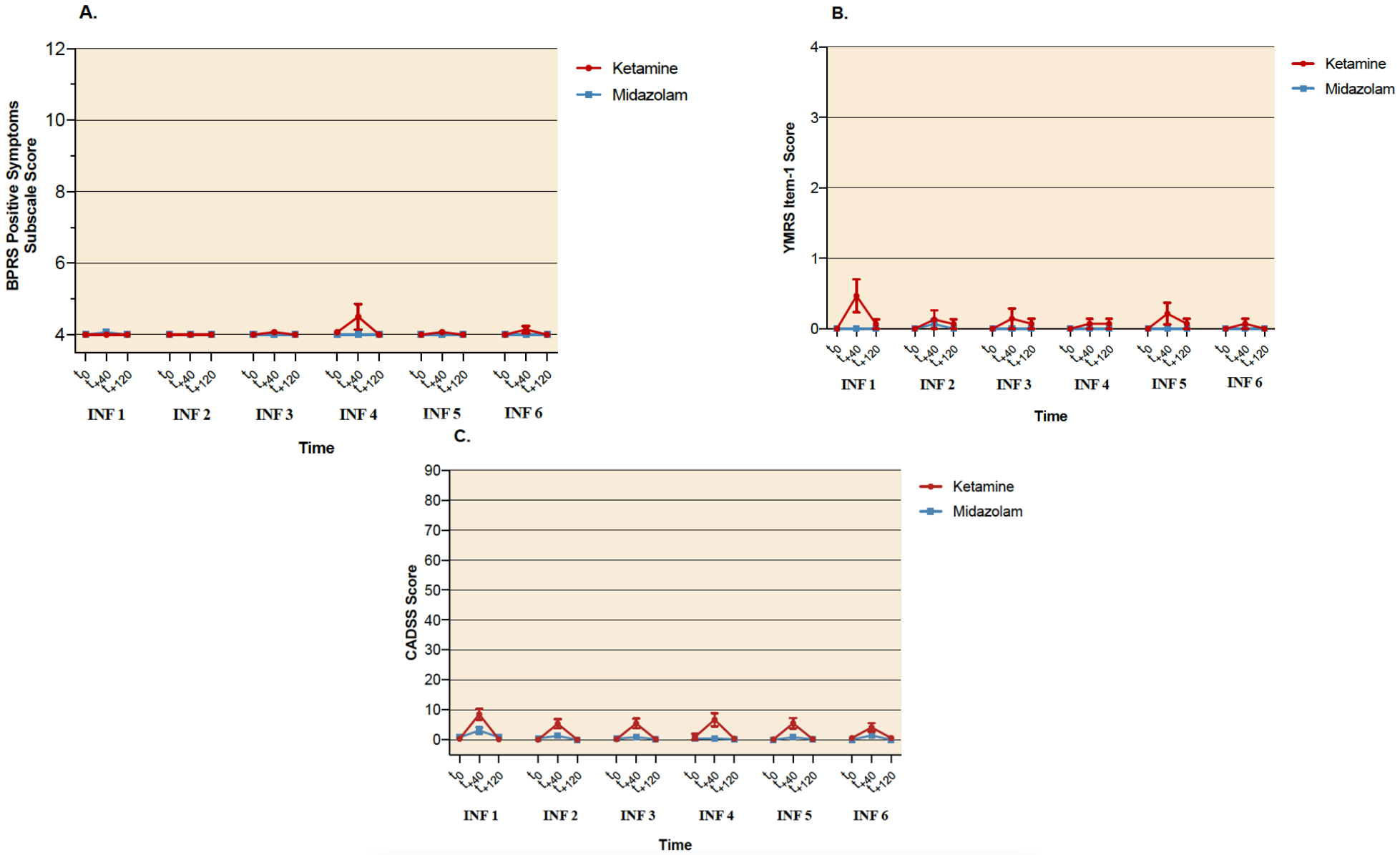
Mean change on the Impact of Event Scale - Revised (IES-R; 24 hours recollection time) scores during clinical trial of ketamine/midazolam in patients with chronic PTSD (n = 30) at 24 hours after infusion 1. Responders were defined as subjects who showed at least 30% symptom improvement at the primary outcome visit (approximately 2 weeks after the first infusion) compared to baseline, as assessed with the Clinician-Administered PTSD Scale (CAPS-5), past-week recall. Of the subjects randomized to ketamine, ten were deemed responders at the primary outcome visit. Of the subjects randomized to midazolam, three subjects were considered responders at the primary outcome visit. Error bars represent standard error of the mean (SEM).

Figure S3. Change in Overall Depressive Symptoms Severity from Baseline to Twenty-Four Hours in the Ketamine and Midazolam Treatment Groups, by Responder and Non-responder Subgroups



Mean change on Montgomery-Åsberg Depression Rating Scale (MADRS; 24 hours recollection time) scores during clinical trial of ketamine/midazolam in patients with chronic PTSD (n = 30) at 24 hours after infusion 1. Responders were defined as subjects who showed at least 30% symptom improvement at the primary outcome visit (approximately 2 weeks after the first infusion) compared to baseline, as assessed with the Clinician-Administered PTSD Scale (CAPS-5), past-week recall. Of the subjects randomized to ketamine, ten were deemed responders at the primary outcome visit. Of the subjects randomized to midazolam, three subjects were considered responders at the primary outcome visit. Error bars represent standard error of the mean (SEM).

Figure S4. Emergence of Psychotomimetic, Manic, and Dissociative Symptoms from Baseline to Discharge during Each of the Six Infusions



Change in the 4-item positive symptoms subscale of the Brief Psychiatric Rating Scale (BPRS), the Clinician-Administered Dissociative States Scale (CADSS), and the first item (elevated mood) of the Young Mania Rating Scale (YMRS-1) scores at each infusion day (n = 30). Error bars represent standard error of the mean (SEM). The rating scales were administered at pre-infusion baseline (t0), and 40 minutes (t+40), and 120 minutes (t+120) from infusion start.

Table S1. Concomitant Psychotherapy and Psychotropic Medications, by Participant

	Medication Name(s)		Concomitant Psychotherapy
Ketamine	*Stable Doses*	*PRN*	*Yes/No*
Participant A	Sertraline		No
Participant B	Sertraline		Yes
Participant C	Escitalopram		Yes
Participant D		Alprazolam	No
Participant E	Lithium	Alprazolam	Yes
Participant F	Fluoxetine, quetiapine	Lorazepam; Dextroamphetamine-amphetamine	Yes
Participant G	Bupropion		Yes
Participant H		Dextroamphetamine-amphetamine	No
Participant I	-	-	Yes
Participant J	-	-	Yes
Participant K	-	-	Yes
Participant L	-	-	Yes
Midazolam			
Participant M	Escitalopram, prazosin, risperidone		Yes
Participant N	Clonidine, fluoxetine, olanzapine		Yes
Participant O	Bupropion, escitalopram		Yes
Participant P	Bupropion XL, citalopram		Yes
Participant Q	Bupropion XL, clomipramine, guanfacine, methylphenidate		Yes
Participant R		Lorazepam	Yes
Participant S	-	-	Yes
Participant T	-	-	Yes

PRN, as needed. This table includes only participants who were taking psychotropic medications and/or were in ongoing psychotherapy during the course of the trial.

Table S2. Prior Treatment History

	No Prior Treatment		Psychotherapy Only		Pharmacotherapy Only		Both	
	n	%	n	%	n	%	n	%
Ketamine	4	26.7	2	13.3	0	0.0	9	60.0
Midazolam	2	13.3	2	13.3	0	0.0	11	73.3

Table S3. Results of Mixed Model Analyses for the Clinician-Administered PTSD Scale (CAPS-5) Total and Its Four Subscale Scores

		F Statistic	Degrees of freedom	*p* value
CAPS-5 Total				
	Treatment	4.34	1, 28	0.047
	Time	27.02	2, 55	<0.0001
	Treatment-by-time interaction	5.97	2, 55	0.0045
CAPS-5 Intrusion Subscale				
	Treatment	5.26	1, 28	0.03
	Time	16.52	2, 55	<0.0001
	Treatment-by-time interaction	3.77	2, 55	0.03
CAPS-5 Avoidance Subscale				
	Treatment	1.94	1, 28	0.17
	Time	30.37	2, 55	<0.0001
	Treatment-by-time interaction	12.29	2, 55	<0.0001
CAPS-5 Negative mood and cognitions Subscale				
	Treatment	2.36	1, 28	0.14
	Time	19.18	2, 55	<0.0001
	Treatment-by-time interaction	4.42	2, 55	0.02
CAPS-5 Arousal and reactivity Subscale				
	Treatment	2.81	1, 28	0.10
	Time	14.98	2, 55	<0.0001
	Treatment-by-time interaction	2.47	2, 55	0.09

Table S4. Side Effects on Infusion Days Covering the Periods from Infusion Start until Discharge to Home

Adverse Event *	Week 1								Week 2							
	Ketamine				Midazolam				Ketamine				Midazolam			
	Total		Distressing		Total		Distressing		Total		Distressing		Total		Distressing	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gastrointestinal			1	6.7			0	0			0	0			0	0
Diarrhea	0	0			1	6.7			0	0			0	0		
Constipation	0	0			0	0			0	0			0	0		
Dry mouth	0	0			0	0			2	13.3			0	0		
Nausea/vomiting	3	20			1	6.7			2	13.3			0	0		
Heart			0	0			0	0			0	0			0	0
Palpitation	1	6.7			1	6.7			0	0			1	6.7		
Dizziness on standing	0	0			1	6.7			0	0			0	0		
Chest pain	0	0			0	0			0	0			0	0		
Skin			0	0			0	0			0	0			0	0
Rash	0	0			0	0			1	6.7			0	0		
Increased perspiration	0	0			0	0			0	0			0	0		
Itching	0	0			0	0			0	0			0	0		
Dry skin	0	0			0	0			0	0			0	0		
Nervous System			2	13.3			0	0			1	6.7			0	0
Headache	4	26.7			2	13.3			3	20			2	13.3		
Tremors	0	0			1	6.7			0	0			0	0		
Poor concentration	0	0			0	0			0	0			0	0		
Dizziness	5	33.3			1	6.7			4	26.7			2	13.3		
Eyes/Ears			1	6.7			0	0			1	6.7			0	0
Blurred vision	6	40			0	0			8	53.3			0	0		
Ringing in ears	0	0			0	0			0	0			0	0		
Genital/Urinary			0	0			0	0			0	0			0	0
Difficulty urinating	0	0			0	0			0	0			0	0		
Painful urination	0	0			0	0			0	0			1	6.7		
Frequent urination	1	6.7			0	0			1	6.7			0	0		
Menstrual irregularity	0	0			0	0			0	0			0	0		

Sleep			0	0			0	0			0	0			0	0
Difficulty sleeping	0	0			0	0			0	0			0	0		
Sleeping too much	0	0			0	0			0	0			0	0		
Sexual Functioning			0	0			0	0			0	0			0	0
Loss of sexual desire	0	0			0	0			0	0			0	0		
Trouble achieving orgasm	0	0			0	0			0	0			0	0		
Trouble with erections	0	0			0	0			0	0			0	0		
Other			3	20			0	0			1	6.7			0	0
Anxiety	1	6.7			0	0			0	0			0	0		
Poor concentration	3	20			0	0			2	13.3			0	0		
General malaise	0	0			0	0			0	0			0	0		
Restlessness	0	0			0	0			0	0			0	0		
Fatigue	4	26.7			11	73.3			5	33.3			13	86.7		
Decreased energy	1	6.7			1	6.7			0	0			1	6.7		
Other, specify	11	73.3			6	40			8	53.3			5	33.3		

Numbers of patients who endorsed each symptom on the Patient-Rated Inventory of Side Effects (PRISE) from infusion start until they were ready for discharge to home, collapsed across assessments. Week 1 includes assessments administered on days of infusions 1-3. Week 2 includes assessments administered on days of infusions 4-6.

Table S5. Side Effects Covering the Periods after Discharge to Home until the Next Assessment

Adverse Event	Week 1								Week 2							
	Ketamine				Midazolam				Ketamine				Midazolam			
	Total		Distressing		Total		Distressing		Total		Distressing		Total		Distressing	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gastrointestinal			2	13.3			1	6.7			0	0			0	0
Diarrhea	3	20			1	6.7			0	0			2	13.3		
Constipation	0	0			0	0			0	0			0	0		
Dry mouth	0	0			0	0			0	0			0	0		
Nausea/vomiting	5	33.3			3	20			1	6.7			2	13.3		
Heart			1	6.7			0	0			0	0			0	0
Palpitation	0	0			1	6.7			0	0			0	0		
Dizziness on standing	1	6.7			1	6.7			0	0			0	0		
Chest pain	0	0			0	0			0	0			0	0		
Skin			0	0			0	0			0	0			0	0
Rash	0	0			0	0			1	6.7			0	0		
Increased perspiration	1	6.7			0	0			0	0			0	0		
Itching	0	0			0	0			0	0			1	6.7		
Dry skin	0	0			0	0			0	0			0	0		
Nervous System			0	0			0	0			0	0			0	0
Headache	5	33.3			3	20			2	13.3			1	6.7		
Tremors	0	0			0	0			0	0			1	6.7		
Poor concentration	0	0			0	0			0	0			0	0		
Dizziness	1	6.7			1	6.7			0	0			1	6.7		
Eyes/Ears			0	0			0	0			0	0			0	0
Blurred vision	1	6.7			0	0			0	0			0	0		
Ringing in ears	0	0			0	0			0	0			0	0		
Genital/Urinary			0	0			0	0			0	0			0	0
Difficulty urinating	0	0			0	0			1	6.7			1	6.7		
Painful urination	0	0			0	0			0	0			1	6.7		
Frequent urination	1	6.7			0	0			1	6.7			0	0		

Menstrual irregularity	0	0			0	0			0	0			0	0		
Sleep			1	6.7			0	0			0	0			0	0
Difficulty sleeping	2	13.3			0	0			1	6.7			0	0		
Sleeping too much	0	0			0	0			1	6.7			0	0		
Sexual Functioning			0	0			0	0			0	0			0	0
Loss of sexual desire	0	0			0	0			0	0			0	0		
Trouble achieving orgasm	0	0			0	0			0	0			0	0		
Trouble with erections	0	0			0	0			0	0			0	0		
Other			0	0			0	0			0	0			0	0
Anxiety	0	0			0	0			0	0			0	0		
Poor concentration	0	0			0	0			1	6.7			1	6.7		
General malaise	0	0			0	0			0	0			0	0		
Restlessness	0	0			0	0			0	0			0	0		
Fatigue	3	20			1	6.7			1	6.7			2	1.3		
Decreased energy	0	0			0	0			0	0			0	0		
Other, specify	4	26.7			3	20			6	40			5	33.3		

Numbers of patients who endorsed each symptom on the Patient-Rated Inventory of Side Effects (PRISE) during intervals between discharge to home post-infusion until the next assessment, collapsed across assessments. Week 1 includes assessments administered 24 hours after the first infusion, and prior to infusions 2 and 3. Week 2 includes assessments administered prior to infusions 4, 5 and 6, and at the primary outcome day.

Note: One participant in the ketamine group reported mild intermittent difficulty urinating with onset after the 4th infusion, resolving fully 2 weeks later. This participant again experienced this side effect when she received 3 open-label ketamine infusions following completion of this trial, again resolving fully but followed by a urinary tract infection, successfully treated with a 5-day course of antibiotics. Concomitantly with her open-label ketamine infusions, this patient had also started escitalopram.

Another participant in the ketamine group reported mild urinary frequency associated with mild pelvic pressure, with onset the morning of her 3rd infusion, with evidence of mild inflammation on urinalysis; both her symptoms and mild abnormality on urinalysis had resolved fully by her follow-up visit occurring 18 days from symptom onset.

Table S6. Changes on the Past-week C-SSRS from Baseline to 1-Week and 2-Week Time Points

	1 Week				2 Weeks			
	Ketamine (n=15)		Midazolam (n=15)		Ketamine (n=14)[a]		Midazolam (n=15)	
	n	%	n	%	n	%	n	%
No Change	9	60.0	14	93.3	8	53.3	13	86.7
Worsening (increase from baseline)	0	0.0	1[b]	6.7	0	0.0	2[b]	13.3
Improvement (decrease from baseline)	6	40.0	0	0.0	6	40.0	1	6.7

Note: On the past-week C-SSRS *at baseline*, in the ketamine group 5 (33.3%) patients answered positively on question 1 (wish to be dead), 2 (13.3%) on question 2 (non-specific suicidal ideation), and 1 (6.7%) on questions 3 (active suicidal ideation without intent) and 4 (active suicidal ideation with some intent, no plan; this patient contracted no harm). At baseline in the midazolam group, 2 (13.3%) patients answered positively on question 1, and none expressed any active suicidal ideation.

[a] One patient in the ketamine group was exited after two infusions.

[b] Worsening in the midazolam group: One patient, who answered negatively to all C-SSRS questions at baseline, answered positively to question 3 both at 1 week and 2 weeks. Another patient, who answered positively on question 1 at baseline and at 1 week, answered positively to question 2 at 2 weeks.

No suicidal behavior was present during the assessment period.

Box S1. Selected Quotes from Ketamine Responders, Obtained as Part of Clinical Assessment

Middle aged female, with a history of sexual assault as a young adult. During the study follow-up period (after all infusions), she reported:
"I don't feel my life is going to end anymore, it made it impossible to plan a future. I want a life now too." *After interacting with someone who had been harassing her recently:* "One huge thing I noticed that is different. Before I would have panicked. He's been very aggressive, I don't feel panicky or afraid".

Middle aged female, with a history of repeated sexual abuse during childhood. During the second week of infusions, she reported:
"I feel like a normal person. I seem like a normal person. My brain doesn't *(any longer)* let me envision or picture a thought of suicide". *Now, when she thinks about her past trauma,* "it doesn't make me feel weighed down". "I have to dig out the *(trauma)* memory as if from an attic". "Before, talking about it used to make me feel a terrible feeling".

Middle aged female, with a history of physical and emotional abuse in childhood, and sexual assault in adolescence; additional history of motor vehicle accident. During the study follow-up period, she reported:
"I've been OK." "I've been able to deal with *(the trauma memories)*. It's been a lot better. I don't feel tightness in my chest". *Her mood has been* "fine, sad a little bit, but I still feel like I'm handling everything in my life. I didn't have any panic like I used to".

Middle aged female, with a history of physical and emotional abuse and neglect in childhood. At the primary outcome assessment (2 weeks), she reported:
"I am feeling pretty good. Like a *(heavy)* blanket has been lifted off. (*The weight went down from)* 50 lbs to 15 lbs. I am able to talk about *(the trauma)* easier, I internalize things less".

Young adult female, who grew up in a physically abusive household, with a history of sexual assaults as an adolescent and young adult. At the primary outcome assessment (2 weeks), she reported:
Feeling "like I have energy and want to do things again. I felt safe and able to confront feelings *(about the trauma)* without problems. I could just feel it, and figure out what happened and why it happened." *This participant reported that during the infusions, she felt* "like I made peace, I could go past it, I could, can let it go. *(It's been a)* gradual acceptance. I haven't felt this safe in a long time".

Young adult female, with a history of repeated sexual abuse during childhood and sexual assault as a young adult. During the study follow-up period, she reported:
Things are "pretty good. No meltdowns, panic attacks, flashbacks. Sleep is more restful, improved quality. It's easier to breath slower and deeper". "More of a sense of inner peace, a bit more grounded. I feel a lot less despair. During infusions, my own experiences *(were)* less painful, *(I was)* able to fit *(them)* into a larger scope/world" *(perspective).*

Box S2. Integrity of the Blind

Participants were asked to guess whether they received ketamine or midazolam. Of 15 participants in the ketamine group, 15 provided guesses: 7 guessed correctly, 2 guessed incorrectly, and 6 changed their minds during the course of the study. Of 15 participants in the midazolam group, 14 provided guesses: 5 guessed correctly, 1 guessed incorrectly, and 8 changed their minds during the course of the study. The percentage of participants in each group who guessed correctly throughout the course of the study did not differ significantly between the two treatment groups: ketamine group 7/15 (46.7%), midazolam group 5/14 (35.7%), χ^2=4.89, p=0.55.