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Supplementary Material

Article Title: Ketamine/Esketamine in Clinical Practice: Areas of Consensus and Non-consensus From an American Society of Clinical Psychopharmacology (ASCP) Delphi Panel Task Force

Authors: Gerard Sanacora, MD, PhD; Joseph F. Goldberg, MD, MS; Roger S. McIntyre, MD; Lisa Harding, MD; Michael Berk, PhD, MBBCh; Siegfried Kasper, MD; Cristina Cusin, MD; Sanjay J. Mathew, MD; James W. Murrough, MD, PhD; Dan V. Iosifescu, MD; Samuel T. Wilkinson, MD; Sandhya Prashad, MD; Eduard Vieta, MD, PhD; Joshua D. Rosenblat, MD; Elizabeth D. Ballard, PhD; Balwinder Singh, MD; Sagar V. Parikh, MD; Sara Costi, MD; Allan H. Young, MBChB; Rupert McShane, MD; Carlos A. Zarate, Jr, MD

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Supplementary Table 1. Indications and Contraindications

Statement	Strongly Disagree 1	Mod Disagree 2	Neither 3	Mod Agree 4	Strongly Agree 5	Median (IQR)	Confidence Low	Confidence Med	Confidence High	Consen-sus Agree-ment (95% CI)	Con-sen-sus
[1] - Ketamine/esketamine is a valuable and appropriate treatment option for patients with treatment resistant major depressive disorder.	0 (0%)	0 (0%)	1 (5%)	1 (5%)	18 (90%)	5 (0)	0 (0%)	2 (10%)	18 (90%)	18/20 (90%, 68-99%)	**Yes**
[2] - Ketamine/esketamine is a valuable and appropriate treatment option for patients with major depressive disorder who have not demonstrated treatment resistance.	3 (15%)	2 (10%)	8 (40%)	4 (20%)	3 (15%)	3 (2)	1 (5%)	11 (55%)	8 (40%)	7/20 (35%, 15-59%)	No
[3] – Ketamine/esketamine	0 (0%)	1 (5%)	0 (0%)	7 (35%)	12 (60%)	5 (1)	0 (0%)	9 (45%)	11 (55%)	19/20 (95%,	**Yes**

is primarily appropriate as an adjunctive treatment for major depression disorder (or TRD)				75-100%)	
[4] - Ketamine/esketamine is appropriate as monotherapy for major depression disorder (or TRD)	1 (5%) 1 (5%) 1 (5%) 14 (70%) 3 (15%)	4 (0)	1 (5%) 11 (55%) 8 (40%)	17/20 (85%, 62-97%)	**Yes**
[5] - Ketamine/esketamine is a valuable and appropriate treatment option for patients with major depressive disorder with psychotic features.	5 (25%) 5 (25%) 7 (35%) 2 (10%) 1 (5%)	3 (1)	4 (20%) 11 (55%) 5 (25%)	10/20 (50%, 27-73%) (DIS-AGREE)	No
[6] – Ketamine or esketamine should not be administered in patients with current psychotic symptoms.	1 (5%) 5 (25%) 2 (10%) 6 (30%) 6 (30%)	4 (3)	5 (25%) 9 (45%) 6 (30%)	12/20 (60%, 36-81%)	No
Round 2 revision:*					
[6a] - Ketamine or esketamine generally should not be administered in	1 (5%) 3 (14%) 5 (24%) 8 (38%) 4 (19%)	4 (1)		12/21 (54%, 34-78%)	No

patients with a history of psychosis					
[7] - Ketamine/esketamine is a valuable and appropriate treatment option for patients with bipolar disorder in a major depressive episode.	0 (0%) 0 (0%) 1 (5%) 11 (55%) 8 (40%)	5 (1)	3 (15) 10 (50%) 7 (35%)	19/20 (95%, 75-100%)	**Yes**
[8] – Ketamine/esketamine is a valuable and appropriate treatment for patients with bipolar disorder in a manic episode	16 (80%) 3 (15%) 1 (5%) 0 (0%) 0 (0%)	1 (1)	4 (20%) 8 (40%) 8 (40%)	19/20 (95%, 75-100%) (DIS-AGREE)	**Yes**
[9] - Ketamine/ esketamine is a valuable treatment option for depressed patients with significant suicidal ideation	0 (0%) 0 (0%) 1 (5%) 4 (20%) 15 (75%)	5 (1)	0 (0%) 5 (25%) 15 (75%)	19/20 (95%, 75-100%) (DIS-AGREE)	**Yes**
[10] - Ketamine/ esketamine can be useful in reducing suicidal behavior	0 (0%) 1 (5%) 4 (20%) 10 (50%) 5 (15%)	4 (2)	4 (20%) 10 (50%) 6 (30%)	15/20 (75%, 51-91%)	No
[11] - Ketamine/	0 (0%) 2 (10%) 6 (30%) 7 (35%) 1 (5%)[a]	4 (1)	6 (30%) 9 (45%) 5 (25%)	8/16 (50%,	No

esketamine is a valuable and appropriate treatment option for suicidal ideation not associated with major depressive disorder				25-75%)	
[12] - Ketamine is a valuable and appropriate treatment option for patients with a primary diagnosis of PTSD	0 (0%) 2 (10%) 5 (25%) 8 (60%) 1 (5%)[a]	4 (1)	5 (26%) 11 (58%) 3 (16%)[b]	9/16 (56%, 30-80%)	No
[13] - Ketamine is a valuable and appropriate treatment option for patients with a primary diagnosis of OCD	1 (5%) 4 (20%) 9 (40%) 6 (30%) 0 (0%)	3 (2)	8 (40%) 9 (45%) 3 (15%)	6/20 (30%, 12-54%)	No
[14] - Ketamine is a valuable and appropriate treatment option for patients with a primary diagnosis of anxiety disorder, such as GAD or panic disorder	3 (15%) 8 (40%) 6 (30%) 3 (15%) 0 (0%)	3 (1)	4 (21%) 12 (63%) 3 (16%)[b]	11/20 (55%, 32%-77%) (DIS-AGREE)	No
[15] - Ketamine/esketamine is a valuable and appropriate treatment	2 (10%) 3 (15%) 6 (30%) 9 (45%) 0 (0%)	3.5 (2)	1 (5%) 16 (80%) 3 (15%)	9/20 (45%, 23-68%)	No

for patients with mood disorders and a comorbid substance use disorder					
[16] - Ketamine or esketamine generally should be avoided in patients with active substance use disorders. **Round 2 revision:*** [16a] - Ketamine or esketamine generally should be avoided in patients with active substance use disorders.	1 (5%) 5 (25%) 1 (5%) 7 (35%) 6 (30%) 0 (0%) 3 (17%) 0 (0%) 8 (38%) 10 (48%)	4 (3) 5 (1)	0 (0%) 12 (60%) 8 (40%)	13/20 (65%, 41-85%) 18/21 (86%, 67-97%)	No **Yes**
[17] - Ketamine/esketamine is a valuable and appropriate treatment for patients with a primary diagnosis of substance use disorders in combination with psychosocial/behavioral interventions. **Round 2 revision:***	3 (15%) 8 (40%) 5 (25%) 3 (15%) 1 (5%) 3 (14%) 9 (43%) 4 (19%) 5 (24%) 0 (0%)	2 (1) 2 (1.5)	5 (25%) 13 (65%) 2 (10%)	11/20 (55%, 32-77%) (DIS-AGREE)	No No

[17a] - There is sufficient evidence to suggest ketamine/esketamine, in combination with psychosocial/behavioral interventions, is a valuable and appropriate treatment for patients with a primary diagnosis of substance use disorders in clinical settings				12/21 (57%, 34-78%) (DIS-AGREE)	
[18] - Ketamine/esketamine is a valuable and appropriate treatment for patients with borderline personality disorder (with or without comorbid MDD).	2 (10%) 8 (40%) 3 (15%) 5 (25%) 2 (10%)	3 (2)	4 (20%) 14 (70%) 2 (10%)	10/20 (50%, 27-73%) (DIS-AGREE)	No
[19] – Ketamine or esketamine should be avoided in patients with borderline personality disorder.	3 (15%) 8 (40%) 5 (25%) 3 (15%) 1 (5%)	2 (1)	5 (25%) 10 (50%) 5 (25%)	11/20 (55%, 32-77%) (DIS-AGREE)	No
[20] - Ketamine or esketamine should be avoided in patients with	1 (5%) 7 (35%) 8 (40%) 4 (20%) 0 (0%)	3 (2)	7 (35%) 12 (60%) 1 (5%)	8/20 (40%, 19%-	No

bipolar depression who have concurrent mixed features.					64%) (DIS-AGREE)	
[21] - Ketamine or esketamine generally should be avoided in patients with (unipolar) major depressive disorder with current mixed features	1 (5%)	13 (65%)	4 (20%)	2 (10%) 0 (0%)	2 (1)	7 (35%) 11 (55%) 2 (10%)	14/20 (70%, 46%-88%) (DIS-AGREE)	No
Round 2 revision:* [21a] - Ketamine or esketamine generally should be avoided in patients with (unipolar) major depressive disorder with current mixed features	1 (5%)	6 (29%)	7 (33%)	6 (29%) 1 (5%)	3 (2)		7/21 (33%, 15%-37%)	No
[22] - Ketamine or esketamine should be avoided in patients who have established but controlled cardiovascular disease	8 (40%)	10 (50%)	2 (10%)	0 (0%) 0 (0%)	2 (1)	2 (10%) 10 (50%) 8 (40%)	18/20 (90%, 68%-99%) (DIS-AGREE)	**Yes**

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"

[a] 4 abstaining respondents on Delphi item ratings

[b] 1 abstaining respondent on confidence ratings

Abbreviation: IQR=interquartile range

Supplementary Table 2. Dosing

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agree-ment, 95% CI)	Con-sen-sus
[23] - The starting dose for IV ketamine treatment should be 0.5 mg/kg/40 mins for all patients	0 (0%)	5 (25%)	1 (5%)	9 (45%)	5 (25%)	4 (3)	0 (0%)	9 (45%)	11 (55%)	14/20 (70%, 46-88%)	No
Round 2 revision*											
[23a] - The starting dose for IV ketamine treatment should generally be 0.5mg/kg/40mins for all patients	0 (0%)	0 (0%)	1 (6%)	9 (43%)	11 (52%)	5 (1)				20/21 (95%, 76-100%)	**Yes**
[24] - The preferred starting dose of IV ketamine should often be higher than 0.5 mg/kg/40 mins for patients with severe	5 (25%)	6 (39%)	5 (25%)	3 (15%)	1 (5%)	2.5 (1)	3 (15%)	10 (50%)	7 (35%)	11/20 (55%, 32-77%) (DIS-AGREE)	No

suicidal ideation or behavior.					
[25] - Based on your experience the starting dose should be modified in particular circumstances (i.e. low ≤18.5 or high BMI ≥30)	2 (10%) 3 (15%) 5 (26%) 7 (35%) 3 (15%)	3.5 (2)	3 (15%) 11 (55%) 6 (30%)	10/20 (50%, 27-73%)	No
[26] - Based on existing non-human toxicology data the FDA has determined a total 60 mg/day to be the upper limit of ketamine dosing in research studies. Based on your knowledge of the literature and personal experience, how strongly do you agree or disagree with this determination?	9 (45%) 5 (25%) 4 (20%) 2 (10%) 0 (0%)	2 (2)	4 (18%) 7 (35%) 8 (47%)[a]	14/20 (70%, 46-88%) (DIS-AGREE)	No
[27] - Dosing of IV ketamine higher than 0.5 mg/kg/40 mins is likely to achieve greater efficacy to treat major depression than limiting dosing to 0.5 mg/kg or under	0 (0%) 4 (20%) 1 (5%) 11 (55%) 4 (20%)	4 (2)	3 (15%) 12 (60%) 5 (25%)	15/20 (75%, 51-91%)	**Yes**

[28] - Dosing of IV ketamine should be flexible	0 (0%) 0 (0%) 1 (0%) 7 (39%) 12 (61%)	5 (1)	1 (5%) 12 (60%) 7 (35%)	19/20 (95%, 75-100%)	**Yes**
[29] - Dosing of IV ketamine higher than 0.75 mg/kg/40 mins is likely to achieve greater efficacy in treating major depression than limiting dosing to 0.75 mg/kg or under	1 (5%) 1 (5%) 8 (40%) 8 (40%) 2 (10%)	3.5 (1)	6 (30%) 8 (40%) 6 (30%)	10/20 (50%, 27-73%)	No
[30] - Dosing of IV ketamine higher than 1.00 mg/kg/40 mins is likely to achieve greater efficacy in treating major depression than limiting dosing to 1.0 mg/kg or under	3 (15%) 8 (40%) 4 (20%) 4 (20%) 1 (5%)	2.5 (2)	3 (15%) 12 (60%) 5 (25%)	11/20 (40%, 19-64%) (DIS-AGREE)	No
[31] - Dosing of IV ketamine higher than 2.00 mg/kg/40mins is likely to achieve greater efficacy in treating major depression than limiting dosing to 2.0 mg/kg or under	9 (45%) 9 (45%) 2 (10%) 0 (0%) 0 (0%)	2 (1)	5 (25%) 7 (35%) 8 (40%)	18/20 (90%, 68-99%) (DIS-AGREE)	**Yes**
[32] - Dosing of IV ketamine higher than 3.0 mg/kg/40mins is likely to achieve greater efficacy in treating	14 (70%) 4 (20%) 2 (10%) 0 (0%) 0 (0%)	1.5 (1)	7 (35%) 3 (15%) 10 (50%)	18/20 (90%, 68-99%)	**Yes**

major depression than limiting dosing to 3.0 mg/kg or under				(DIS-AGREE)	
New Round 2 Item:* [33] - The currently recommended dosing of IN esketamine as provided in the package insert starts at 56mg and may increase to 84mg in appropriate. This is an adequate and appropriate dosing range	0 (0%) 4 (19%) 2 (10%) 9 (43%) 6 (29%)	4 (2)		15/21 (71%, 48-89%)	No
[34] - Based on the same non-human toxicology data the FDA has also determined that 8 lifetime infusions is the maximum that can be provided in research studies. How strongly do you agree with this determination?	13 (68%) 4 (21%) 2 (11%) 0 (0%) 0 (0%) [b]	2 (1)	1 (5%) 10 (50%) 9 (45%)	17/19 (89%, 67-99%; (DIS-AGREE)	**Yes**
[35] - The available evidence and my experience best suggests a linear dose-response curve for IV Ketamine, limited only	2 (10%) 10 (50%) 5 (25%) 3 (15%) 0 (0%)	2.5 (1)	4 (20%) 10 (50%) 6 (30%)	12/20 (60%, 36-81%) (DIS-AGREE)	No

by risk of adverse events					
[36] - The available evidence and my experience best suggests a plateau in the dose-response curve for IV ketamine, where no further benefit is achieved with increased dosing	0 (0%) 3 (15%) 7 (35%) 6 (30%) 4 (20%)	3.5 (1)	6 (30%) 9 (45%) 5 (25%)	10/20 (50%, 27-73%)	No
[37] - The available evidence and my experience best suggests an inverted U-shaped dose-response curve for IV Ketamine where higher doses may actually reduce the clinical benefit to patients	0 (0%) 2 (10%) 5 (25%) 12 (60%) 1 (5%)	4 (1)	6 (30%) 10 (50%) 4 (20%)	13/20 (65%, 41-85%)	No
Round 2 revision:* [37a] - The available evidence and my personal experience best suggests an inverted U- shaped dose-response curve for	0 (0%) 2 (10%) 3 (14%) 11 (52%) 5 (24%)	4 (2)		16/21 (76%, 53-92%)	**Yes**

IV ketamine where higher doses may actually reduce the clinical benefit to patients.					
[38] - There remains insufficient data and documented real-world experience to truly know what the dose-response curve is for treatment with IV ketamine	0 (0%) 4 (20%) 2 (10%) 7 (35%) 7 (35%)	4 (2)	3 (15%) 9 (45%) 8 (40%)	14/20 (70%, 46-88%)	No
Round 2 revision:* [38a] - There remains insufficient data and documented real-world experience to truly know what the dose-response curve is for treatment with IV ketamine.	0 (0%) 3 (14%) 4 (19%) 7 (33%) 7 (33%)	4 (2)		14/21 (67%, 43-85%)	No
[39] - The induction of acute effects on perception, cognition, or dissociation are required to achieve maximal treatment response beyond the effects it may have on	4 (20%) 11 (55%) 2 (10%) 2 (10%) 1 (5%)	2 (1)	1 (5%) 11 (55%) 8 (40%)	15/20 (75%, 51-91%) (DIS-AGREE)	**Yes**

patient and clinician expectations					
[40] - Dosing of ketamine should be targeted to the induction of perceptual, cognitive and dissociative effects	6 (30%) 9 (45%) 3 (15%) 0 (0%) 2 (10%)	2 (2)	1 (5%) 10 (50%) 9 (45%)	15/20 (75%, 51-91%) (DIS-AGREE)	**Yes**
[41] - Dosing of ketamine should be targeted to minimize the induction of perceptual, cognitive and dissociative effects	2 (10%) 7 (35%) 8 (40%) 2 (10%) 1 (5%)	3 (1)	1 (5%) 12 (60%) 7 (35%)	9/20 (45%, 23-68%) (DIS-AGREE)	No
[42] - The induction phase for IV ketamine should be twice a week for 3-4 weeks	0 (0%) 1 (5%) 1 (5%) 13 (65%) 5 (25%)	4 (1)	0 (0%) 10 (50%) 10 (50%)	18/20 (90%, 68-99%)	**Yes**
[43] - The currently recommended dosing of IN esketamine as provided in the package insert starts at 56 mg and may increase to 84 mg in appropriate. This is an adequate and appropriate dosing range	0 (0%) 4 (20%) 3 (15%) 9 (45%) 4 (20%)	4 (2)	3 (15%) 8 (40%) 9 (45%)	13/20 (65%, 41-85%)	No
[44] - Older patients should typically be started at IN	0 (0%) 6 (30%) 5 (25%) 6 (30%) 3 (15%)	3.5 (2)	5 (25%) 11 (55%) 4 (20%)	9/20 (45%, 23-68%)	No

esketamine doses lower than 56 mg					
[45] - It would be best to be able to increase the dosing of IN esketamine above 84 mg for patients with limited response to 84 mg	0 (0%) 1 (5%) 10 (50%) 6 (30%) 3 (15%)	3.5 (1)	7 (30%) 11 (55%) 2 (10%)	9/20 (45%, 23-68%)	No
[46] - Guidance for IN esketamine suggests moving to a continuation phase where treatment frequency is reduced to no more than 1x/week after 4 weeks. Do you agree with this as guidance for IV ketamine?	0 (0%) 0 (0%) 2 (10%) 13 (65%) 5 (25%)	4 (4-5)	3 (15%) 13 (65%) 4 (20%)	18/10 (90%, 68-99%)	**Yes**
[47] - Guidance for IN esketamine suggests moving to a maintenance phase where attempts are made to further reduce the frequency of treatments and consider treatment discontinuation after week 8 of treatment. Do you agree with this	1 (5%) 4 (20%) 3 (15%) 7 (35%) 5 (25%)	4 (2)	2 (10%) 10 (50%) 8 (40%)	12/20 (60%, 36-81%)	No

as guidance for IV ketamine?					
[48] - After an initial response to ketamine/esketamine, it is reasonable to switch patients to dextromethorphan-bupropion as a maintenance treatment	3 (15%) 3 (15%) 11 (55%) 3 (15%) 0 (0%)	3 (0)	8 (40%) 7 (35%) 5 (25%)	6/20 (30%, 12-54%) (DIS-AGREE)	No
[49] - Long-term continued use of IV ketamine/IN esketamine is appropriate if the patient continues to experience benefit and is not experiencing concerning side effects	0 (0%) 0 (0%) 0 (0%) 8 (40%) 12 (60%)	5 (1)	2 (5%) 7 (35%) 11 (60%)	20/20 (100%, 83-100%)	**Yes**
[50] - Ketamine/esketamine treatments should be discontinued if the frequency cannot be reduced to below 1 time per month	9 (45%) 8 (40%) 2 (10%) 1 (5%) 0 (0%)	2 (1)	2 (5%) 7 (35%) 11 (60%)	17/20 (85%, 62-97%) (DIS-AGREE)	**Yes**
[51] - Ketamine/esketamine treatments should be discontinued if the frequency cannot be	4 (20%) 9 (45%) 5 (25%) 2 (10%) 0 (0%)	2 (1)	3 (15%) 9 (45%) 8 (40%)	13/20 (65%, 41-85%)	No

reduced to below 2 times per month				(DIS-AGREE)	
[52] - Ketamine/esketamine the treatments should be discontinued if the frequency cannot be reduced to below 1 time per week	1 (5%) 7 (35%) 4 (20%) 4 (20%) 4 (20%)	3 (2)	5 (25%) 9 (45%) 6 (30%)	8/20 (40%, 19-64%) (DIS-AGREE)	No
[53] - Ketamine/esketamine treatments should be discontinued if the frequency cannot be reduced to below 2 times per week	3 (15%) 2 (10%) 3 (15%) 5 (25%) 7 (35%)	4 (2)	3 (15%) 9 (45%) 8 (40%)	12/20 (60%, 36-81%)	No
[54] - It is best to use a symptom triggered (patients are re-treated only when symptoms seem to be increasing) approach to dosing in the maintenance period of treatment.	1 (5%) 4 (20%) 4 (20%) 9 (45%) 2 (10%)	4 (1)	4 (20%) 10 (50%) 6 (30%)	11/20 (55%, 32-77%)	No
[55] - It is best to use a maintenance dosing frequency that limits the number of treatments, but sustains the best level	0 (0%) 1 (5%) 0 (0%) 9 (45%) 10 (50%)	4.5 (1)	1 (5%) 8 (40%) 11 (55%)	19/20 (95%, 75-100%	**Yes**

of response without signs of worsening					

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"

[a] 1 abstaining respondent for confidence ratings;

[b] 1 abstaining respondent for Delphi item ratings

Abbreviation: IQR=interquartile range

Supplementary Table 3. IN Esketamine vs. IV Ketamine Comparisons

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agreement, 95% CI)	Consensus
[56] - In clinical practice, the magnitude of clinical benefit for IV ketamine versus IN esketamine for most major depressive disorder patients is roughly similar	1 (5%)	7 (35%)	2 (10%)	9 (45%)	1 (5%)	3.5 (2)	3 (15%)	13 (65%)	4 (20%)	10/20 (50%, 27-73%)	No
[57] - IN esketamine is a superior treatment to IV esketamine for major depression	7 (35%)	6 (30%)	6 (30%)	0 (0%)	1 (5%)	2.5 (2)	7 (35%)	5 (25%)	8 (40%)	13/20 (65%, 41-85%) (DIS-AGREE)	No
[58] - IV ketamine is a superior treatment to IN esketamine for major depression	0 (0%)	2 (10%)	4 (20%)	12 (60%)	2 (10%)	4 (1)	8 (40%)	8 (40%)	4 (20%)	14/20 (70%, 46-88%)	No
Round 2 revision:*											
[58a] - IV ketamine is a superior treatment to IN	0 (0%)	1 (5%)	7 (33%)	12 (57%)	1 (5%)	4 (1)				13/21 (62%, 38-82%)	No

esketamine for major depression					
Round 2 new item:* [59] - IN esketamine is a superior treatment to IV ketamine for major depression.	7 (33%) 9 (43%) 5 (24%) 0 (0%) 0 (0%)	2 (2)		16/21 (76%, 53%-92%) (DIS-AGREE)	**Yes**
[60] - The duration of benefit is similar between IV ketamine and IN esketamine	4 (20%) 4 (20%) 5 (25%) 7 (35%) 0 (0%)	3.5 (2)	4 (20%) 11 (55%) 5 (25%)	8/20 (40%, 19-64%) (DIS-AGREE)	No
[61] - IV ketamine has a longer duration of clinical benefit than IN esketamine	0 (0%) 5 (25%) 5 (25%) 4 (20%) 6 (30%)	3.5 (2)	5 (25%) 11 (55%) 4 (20%)	10/20 (50%, 27-73%)	No
[62] - IN esketamine has a longer duration of clinical benefit than IV ketamine	6 (30%) 4 (20%) 9 (45%) 1 (5%) 0 (0%)	3 (1)	7 (37%) 7 (37%) 5 (26%) [a]	10/20 (50%, 27-73%) (DIS-AGREE)	No
[63] - When administering IV ketamine, one should be following the instruction package for IN esketamine in regard to duration of observation	3 (15%) 5 (25%) 2 (10%) 8 (40%) 2 (10%)	3.5 (2)	0 (0%) 12 (60%) 8 (40%)	10/20 (50%, 27-73%)	No

period and VS monitoring					
[64] - After a successful acute response to IV ketamine, conversion to IN esketamine for maintenance treatment is feasible and usually comparably effective to maintenance IV ketamine for relapse prevention	0 (0%) 1 (5%) 12 (60%) 7 (35%) 0 (0%)	3.5 (1)	6 (30%) 11 (55%) 3 (15%)	7/20 (35%, 15-59%)	No

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"

[a] 1 abstaining respondent for confidence ratings

Abbreviation: IQR=interquartile range

Supplementary Table 4. Alternative Formulations

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agree-ment, 95% CI)	Con-sen-sus
[65] - Oral ketamine has robust demonstrated antidepressant properties	7 (35%)	7 (35%)	2 (10%)	3 (15%)	1 (5%)	2 (12)	2 (10%)	8 (40%)	10 (50%)	14/20 (70%, 46-88%) (DIS-AGREE)	No
Round 2 revision:*											
[65a] - Oral ketamine has demonstrated robust antidepressant properties suggesting it is appropriate for use in clinical practice	7 (33%)	8 (38%)	2 (10%)	4 (19%)	0 (0%)	2 (2)				15/21 (71%, 48-89%) (DIS-AGREE)	No
[66] - The prescribing of compounded oral ketamine lozenges to patients in between IV ketamine infusions for depression should be discouraged because there is not enough	1 (5%)	2 (10%)	2 (10%)	7 (35%)	8 (40%)	4 (2)	2 (10%)	9 (45%)	9 (45%)	15/20 (75%, 51-91%	**Yes**

evidence to suggest the benefits will outweigh the risks					
[67] - Oral ketamine provides a reasonable maintenance treatment for patients with a good response to either IV ketamine or IN esketamine	4 (20%) 6 (30%) 3 (15%) 7 (35%) 0 (0%)	3 (2)	4 (20%) 12 (60%) 4 (20%)	10/20 (50%, 27-73%) (DIS-AGREE)	No
[68] - IM ketamine is a reasonable formulation for the treatment of major depression	3 (15%) 4 (20%) 5 (25%) 8 (40%) 0 (0%)	3.5 (2)	8 (40%) 7 (35%) 5 (25%)	8/20 (40%, 19-64%)	No

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"
Abbreviation: IQR=interquartile range

Supplementary Table 5. Concomitant Therapies

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agreement, 95% CI)	Consensus
[69] - Clinicians should try to completely discontinue the use of benzodiazepines before initiating IV ketamine or IN esketamine treatments	3 (19%)	8 (50%)	3 (19%)	2 (13%)	0 (0%) [a]	2.5 (1)	3 (15%)	11 (55%)	6 (30%)	11/16 (69%, 41-89%) (DIS-AGREE)	No
[70] - Clinicians should try to avoid co-administering benzodiazepines shortly before or during IV ketamine or IN esketamine treatments	0 (0%)	4 (20%)	1 (5%)	10 (50%)	5 (25%)	4 (1)	3 (15%)	12 (60%)	5 (25%)	15/20 (75%, 51-91%)	**Yes**
[71] - Clinicians should try to avoid co-administering higher doses of benzodiazepines during ongoing IV ketamine or IN esketamine treatments, but use of	0 (0%)	1 (5%)	0 (0%)	9 (44%)	10 (50%)	4.5 (1)	1 (5%)	12 (60%)	7 (35%)	19/20 (95%, 75-100%)	**Yes**

lower doses and dosing separated by time from the IV ketamine or IN esketamine is acceptable					
[72] - In the clinic, co-administration of opioid antagonist (i.e. naltrexone, samidorphan) with IV ketamine or IN esketamine is likely to diminish antidepressant responsivity as suggested by theoretical mechanistic conflicts	1 (5%) 3 (15%) 10 (50%) 4 (20%) 2 (10%)	3 (1.5)	7 (35%) 12 (60%) 1 (5%)	6/20 (30%, 12-54%)	No
[73] - In the clinic, co-administration of lamotrigine with IV ketamine or IN esketamine is likely to diminish antidepressant responsivity as suggested by theoretical mechanistic conflicts	1 (5%) 8 (40%) 5 (25%) 5 (25%) 1 (5%)	3 (2)	7 (35%) 11 (55%) 2 (10%)	9/20 (45%, 23-68%) (DIS-AGREE)	No
[74] - In the clinic, co-administration of memantine with IV ketamine or IN esketamine is likely to diminish antidepressant responsivity or increase	1 (5%) 5 (25%) 11 (55%) 3 (15%) 0 (0%)	3 (1)	10 (50%) 10 (50%) 0 (0%)	6/20 (30%, 12-54%) (DIS-AGREE)	No

the likelihood of adverse events due to theoretical mechanistic conflicts					
[75] - It is generally not necessary to have patients refrain from taking usually-dosed stimulant medications on the day of ketamine/esketamine treatment	2 (10%) 4 (20%) 5 (25%) 6 (30%) 3 (15%)	3.5 (2)	8 (40%) 7 (35%) 5 (25%)	9/20 (45%, 23-68%)	No
[76] - Use of ketamine as general anesthesia during ECT for depression is likely to enhance ECT treatment outcomes for major depression	8 (40%) 9 (45%) 1 (5%) 2 (10%) 0 (0%)	2 (1)	2 (10%) 10 (50%) 8 (40%)	17/20 (85%, 62-97%) (DIS-AGREE)	**Yes**
[77] - Augmentation of IV ketamine or IN esketamine with dextromethorphan-bupropion (Auvelity®) is a potentially synergistic combination that offers conceptual advantages over purely monoaminergic antidepressants and can be used as an	0 (0%) 3 (15%) 8 (40%) 7 (35%) 2 (10%)	3.5 (1)	9 (45%) 8 (40%) 3 (15%)	9/20 (45%, 23-68%)	No

effective longer-term maintenance strategy to reduce the use of IV ketamine or IN esketamine					
[78] - Use of ketamine-assisted psychotherapy (defined as use of specific psychotherapeutic approaches within 2 hours of receiving the treatment) is likely to yield greater antidepressant efficacy than IV ketamine/IN esketamine alone (defined as the use of specific psychotherapeutic approaches within 2 hours of receiving the treatment)	2 (10%) 7 (35%) 6 (30%) 4 (20%) 1 (5%)	3 (2)	4 (20%) 10 (50%) 6 (30%)	9/20 (45%, 23-68%) (DIS-AGREE)	No

[a] 4 abstaining respondents for Delphi item ratings; Round 2 revisions of Round 1 items are designated with the letter "a"
Abbreviation: IQR=interquartile range

Supplementary Table 6. Issues Related to Treatment Access

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agree-ment, 95% CI)	Con-sen-sus
[79] - The current access to ketamine/esketamine is adequate in the US	8 (40%)	4 (20%)	5 (25%)	2 (10%)	1 (5%)	2 (1)	3 (15%)	5 (25%)	12 (60%)	12/20 (60%, 36-81%) (DIS-AGREE)	No
[80] - There are major barriers to patient access to ketamine/esketamine	1 (5%)	2 (10%)	1 (5%)	5 (25%)	11 (55%)	4.5 (1)	1 (5%)	10 (50%)	9(45%)	16/20 (80%, 56-94%)	**Yes**
[81] - A more relaxed access to ketamine would likely promote over-use	1 (5%)	0 (0%)	3 (15%)	12 (60%)	4 (20%)	4 (1)	4 (20%)	10 (50%)	6 (30%)	16/20 (80%, 56-94%)	**Yes**
[82] - The REMS represents a significant barrier to access for IN esketamine	0 (0%)	4 (20%)	4 (20%)	10 (50%)	2 (10%)	4 (1)	3 (15%)	11 (55%)	6 (30%)	12/20 (60%, 36-81%)	No
[83] - It is not appropriate to begin ketamine treatment at home	0 (0%)	0 (0%)	0 (0%)	5 (25%)	15 (75%)	5 (0)	1 (6%)	5 (28%)	12 (67%)	20/20 (100%, 81-100%)	**Yes**

[84] - It is reasonable to begin ketamine treatment at home with remote monitoring.	12 (67%) 4 (22%) 1 (6%) 0 (0%) 1 (6%)	1 (1)	2 (10%) 5 (25%) 13 (65%)	16/18 (89%, 65-99%) (DIS-AGREE)	**Yes**
[85] - At home treatment with ketamine (of any form) is reasonable if the patient has demonstrated adequate safety with previous treatments in a healthcare setting.	5 (25%) 4 (20%) 3 (15%) 6 (30%) 2 (10%)	3 (2)	1 (5%) 11 (55%) 8 (40%)	8/20 (40%, 19-64%) (DIS-AGREE)	No
[86] - It is almost never reasonable to provide at home treatments with ketamine (of any form) for the treatment of psychiatric disorders without the immediate presence of a health care professional on site.	2 (10%) 4 (20%) 0 (0%) 6 (30%) 8 (40%)	4 (3)	1 (5%) 10 (50%) 9 (45%)	14/20 (70%, 46-88%)	No
Round 2 Revision:*					
[86a] - It is almost never reasonable to provide at home treatments with ketamine (of any form) for the treatment of psychiatric disorders	2 (10%) 3 (14%) 3 (14%) 4 (19%) 9 (43%)	4 (2.5)		13/21 (62%, 38-82%)	No

without the presence of a health care professional on site					

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"
Abbreviation: IQR=interquartile range

Supplementary Table 7. Appropriate Laboratory and Other Safety Monitoring Before and During Treatment

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agree-ment, 95% CI)	Con-sen-sus
[87] - I have observed cases where patients have developed a new onset ketamine use disorder associated with clinical treatment with ketamine/esketamine treatments of any type.	7 (39%)	3 (11%)	2 (11%)	6 (28%)	2 (11%)	2.5 (2)	3 (15%)	7 (35%)	10 (50%)	10/20 (50%, 27-73%) (DIS-AGREE)	No
[88] - I have observed cases where patients have developed a new onset ketamine use disorder associated with clinical treatment with ketamine/esketamine treatments provided in line with the esketamine REMS or limited IV ketamine treatments provided under the	10 (50%)	5 (25%)	2 (10%)	2 (10%)	1 (5%)	2 (2)	3 (15%)	7 (35%)	10 (50%)	15/20 (50%; 0.51-0.91) (DIS-AGREE)	**Yes**

supervision in health care setting.					
[89] - Physical exams should routinely be completed prior to initiating treatment IV ketamine or IN esketamine	2 (10%) 6 (30%) 1 (5%) 5 (25%) 6 (30%)	4 (3)	1 (5%) 6 (30%) 13 (65%)	11/20 (55%, 32-77%)	No
[90] - Minimal laboratories (CBC, comprehensive metabolic profiles) should routinely be completed prior to initiating treatment IV ketamine or IN esketamine	2 (10%) 5 (25%) 2 (10%) 4 (20%) 7 (35%)	4 (3)	2 (10%) 8 (40%) 10 (50%)	11/20 (55%, 32-77%)	No
[91] - Electrocardiograms should be routinely completed prior to initiating treatment with IV ketamine or IN esketamine.	5 (25%) 2 (10%) 2 (10%) 7 (35%) 4 (20%)	4 (2.5)	1 (5%) 10 (50%) 9 (45%)	11/20 (55%, 32-77%)	No
[92] - Urine toxicology should be performed prior to initiating treatment to assess for substance use	3 (15%) 2 (10%) 1 (5%) 6 (30%) 8 (40%)	4 (3)	0 (0%) 7 (35%) 13 (65%)	14/20 (70%, 46-88%)	No
[93] - Laboratory assessments should be repeated on a regular	1 (5%) 6 (30%) 2 (10%) 8 (40%) 3 (15%)	4 (2)	2 (10%) 10 (50%) 8 (40%)	11/20 (55%,	No

basis with maintenance treatment				32-77%)	
[94] - Blood pressure should be measured prior to treatment and at scheduled intervals during the treatment session	1 (5%) 2 (10%) 0 (0%) 2 (10%) 15 (75%)	5 (3)	0 (0%) 2 (10%) 18 (90%)	17/20 (85%, (62-97%)	**Yes**
[95] - Tools measuring acute perceptual, cognitive and dissociative effects should be routinely employed during treatment sessions.	1 (5%) 5 (25%) 4 (20%) 6 (30%) 4 (20%)	3.5 (2)	1 (5%) 12 (60%) 7 (35%)	10/20 (50%, 27-73%)	No
[96] - Urine toxicology screens should be routinely performed on a regular basis during maintenance treatment with ketamine/esketamine.	3 (15%) 5 (25%) 3 (15%) 5 (25%) 4 (20%)	3 (2)	4 (20%) 9 (45%) 7 (35%)	9/20 (45%, 23-68%)	No
Round 2 revision:*					
[96a] - Urine toxicology should be performed prior to initiating treatment to assess for substance use.	2 (10%) 5 (24%) 2 (10%) 5 (24%) 7 (33%)	4 (3)		12/21 (57%, 34-78%)	No

[97] - Patients undergoing treatment with IV ketamine should have a mandatory minimum two hour observation period after each treatment, comparable to the FDA mandate for esketamine.	4 (20%) 7 (35%) 1 (5%) 6 (30%) 2 (10%)	2 (2)	0 (0%) 10 (50%) 10 (50%)	11/20 (55%, 32-77%) (DIS-AGREE)	No
[98] - Special care should be used when tapering or discontinuing the use of ketamine/esketamine because of a risk for increased suicidal ideation.	0 (0%) 1 (5%) 5 (25%) 7 (35%) 7 (35%)	4 (2)	3 (15%) 11 (55%) 6 (30%)	14/20 (70%; 46%-88%)	No
New Round 2 Item: [99] - Based on my combined reading of the literature and direct clinical experience, I believe there is a specific risk for increased suicidal ideation as a possible withdrawal phenomenon upon discontinuation of ketamine/esketamine	5 (24%) 10 (48%) 2 (10%) 1 (5%) 3 (14%)	2 (1.5)		15/21 (71%; 48-89%)	No

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"
Abbreviation: IQR=interquartile range

Supplementary Table 8. Parameters For Judging Improvement and Continued Treatment

Statement	Strongly Disagree	Mod Disagree	Neither	Mod Agree	Strongly Agree	Median (IQR)	Confidence Low	Confidence Med	Confidence High	N (% Agreement, 95% CI)	Consensus
[100] - Most patients who achieve a response to IV ketamine will show discernible signs of initial responsivity (e.g., at least a 20% improvement from baseline) after three initial infusions.	0 (0%)	4 (20%)	3 (15%)	8 (40%)	5 (25%)	4 (2)	4 (20%)	7 (35%)	9 (45%)	13/20 (65%, 41-85%)	No
Round 2 revision:*											
[100a] - Most patients who achieve a response to IV ketamine will show discernible signs of initial responsivity (e.g., at least a 20% improvement from baseline) after three initial infusions.	1 (5%)	0 (0%)	5 (24%)	8 (38%)	7 (33%)	4 (2)				15/21 (71%; 48%-89%)	No

[101] - It is reasonable to discontinue IV ketamine infusions for major depression if there has not been at least a 20% improvement from baseline after 3 initial infusions. **Round 2 revision:*** [101a] - As a general rule, it is reasonable to discontinue IV ketamine infusions for major depression if there has not been at least a 20% improvement from baseline after 3 initial infusions.	9 (45%) 4 (20%) 1 (5%) 4 (20%) 2 (10%) 6 (29%) 8 (38%) 1 (5%) 4 (19%) 2 (10%)	2 (2) 2 (2.5)	0 (0%) 9 (45%) 11(55%)	13/20 (65%, 41-85%) (DIS-AGREE) 14/21 (67%; 43%-85%) (DIS-AGREE)	No No
[102] - It is reasonable to discontinue IV ketamine infusions for major depression if there has not been at least a 50% improvement from baseline after 8 administrations	2 (10%) 5 (25%) 2 (10%) 8 (40%) 3 (15%)	4 (2)	0 (0%) 13 (65%) 7 (35%)	11/20 (55%, 32-77%)	No
[103] - It is reasonable to discontinue IV	1 (5%) 1 (5%) 1 (5%) 5 (25%) 12 (60%)	5 (1)	0 (0%) 9 (45%) 11 (55%)	17/20 (85%,	**Yes**

ketamine infusions for major depression if there has not been at least a 25% initial improvement from baseline after 8 administrations				62-97%)	
New Round 2 Item:* [104] - In general, ketamine/esketamine treatments should be discontinued if the frequency cannot be reduced to below 2 times per month.	4 (19%) 8 (38%) 3 (14%) 3 (14%) 3 (14%)	2 (2)		12/21 (57%; 34%-78%) (DIS-AGREE)	No
New Round 2 Item:* [105] - In general, ketamine/esketamine treatments should be discontinued if the frequency cannot be reduced to below 2 times per week unless there is a strong rationale.	0 (0%) 2 (10%) 2 (10%) 10 (48%) 7 (33%)	4 (1)		17/21 (**81%**; 58%-95%)	**Yes**

* Panelists' ratings of confidence in their responses for Round 2 items were not obtained; Round 2 revisions of Round 1 items are designated with the letter "a"
Abbreviation: IQR=interquartile range