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Supplementary Material

Article Title: The Effects of Ketamine on Cognition in Unipolar and Bipolar Depression: A Systematic Review

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Supplementary Table 1: Placebo-controlled trials of single-dose ketamine in healthy volunteers

Study	N	Route	Dose	Assessment time points	Results
[1]	34	IM	0·25 or 0·5 mg/kg bolus	10 min.	KET < PBO: immediate and delayed recall
[2]	19	IV	0·5 mg/kg/40 min.	During infusion	KET < PBO: verbal fluency, executive function, sustained attention; KET = PBO: global cognition
[3]	12	IM	10 or 25 mg/kg bolus	45 min.	KET < PBO: verbal learning and memory, parallel visual search, some measures of psychomotor performance; KET = PBO: simple attention, executive function
[4]	15	IV	0·12 mg/kg bolus + 0·65 mg/kg/h	During; 30, 60 min.	KET < PBO: free recall, recognition memory, attention
[5]	10	IV	0·12 mg/kg bolus + 0·65 mg/kg/h	0, 30 min.	KET < PBO: working and semantic memory
[6]	23	IV	0·26 mg/kg bolus + 0·65 mg/kg/h	During infusion	KET < PBO: executive function
[7]	20	IV	0·26 mg/kg bolus + 0·65 mg/kg/h	During infusion	KET < PBO: delayed recall, global cognition; KET = PBO: immediate recall, verbal fluency
[8]	15	IV	Max. 0·27 mg/kg bolus + 0·26 mg/kg/h	During infusion	KET < PBO: declarative memory; KET = PBO: selective and sustained attention, working memory, executive function
[9]	26	IV	0·5 mg/kg/h	During infusion	KET < PBO: episodic memory encoding; KET = PBO: episodic memory retrieval
[10]	18	IV	0·3 mg/kg/40 min + 0·05 mg/kg/10 min + 0·21 mg/kg/85 min	During infusion	KET = PBO: selective attention
[11]	20	IV	0·24 mg/kg bolus + 0·9 mg/kg/h	During infusion; 30 m	KET < PBO: cognitive control during infusion; KET = PBO: cognitive control 30 min. post-infusion
[12]	8	IV	0·5 mg/kg/h	During infusion	KET < PBO: reaction time
[13]	12	IV	Plasma level 50 or 100 ng/ml	During infusion	100 ng/ml KET < PBO: manipulation tasks of verbal working memory; KET = PBO: maintenance tasks of verbal working memory, and spatial working memory and planning
[14]	54	IV	0·4 or 0·8 mg/kg/80 min	During infusion; 3 d.	KET < PBO: episodic memory during infusion; KET = PBO: episodic memory at 3 d., semantic memory at both time points
[15]	54	IV	0·4 or 0·8 mg/kg/80 min	During infusion	KET < PBO: episodic, working, and recognition memory, procedural learning, and semantic processing; KET = PBO: attention, perceptual priming, executive function
[16]	12	IV	Plasma level 50 or 100 ng/ml	During infusion	KET < PBO: episodic memory encoding
[17]	41	IV	0·23 mg/kg bolus + 0·5 mg/kg/h	During infusion	KET < PBO: attention, delayed recall, working memory
[18]	13	IV	0·27 mg/kg/10 min. + 0·12 mg/kg/50 min.	During infusion; 3, 15, 30 min.	KET < PBO: delayed recall and reaction time during infusion; KET = PBO: delayed recall and reaction time at all post-infusion time points
[19]	12	IV	Plasma level 100 ng/ml	During infusion	KET < PBO: episodic recognition memory
[20]	18	IM	0·2 or 0·4 mg/kg bolus	Repeatedly up to 5 hr.	KET < PBO: encoding, working memory, psychomotor speed; KET = PBO: retrieval, attention, psychomotor accuracy, overall episodic memory
[21]	15	IV	8 mg bolus + 0·01 mg/kg/min	During infusion	KET < PBO: lexical and semantic verbal fluency; KET = PBO: phonological verbal fluency
[22]	37	IV	0.23 mg/kg bolus + 0.58 mg/kg/30 min + 0.29 mg/kg/64 min.	Immediately post-infusion	KET < PBO: reaction time, sustained attention, processing speed, working memory, executive function, verbal fluency, immediate and recognition recall; KET = PBO: motor speed, visual memory
[23]	18	IV	0.24 mg/kg bolus + 0.5 mg/kg/h	During infusion	KET = PBO: attention
[24]	20	IM	0.2 or 0.4 mg/kg bolus	5, 10, 125 min.	KET < PBO: working memory
[25]	44	IV	Plasma level 100 ng/ml	During infusion	KET < PBO: visual working memory
[26]	21	IV	Plasma level 100 ng/ml	5 d.	KET < PBO: memory
[27]	24	IN	84 mg	40 min; 2, 4, 6 hr.	KET < PBO: processing speed, attention, and visual, spatial, and working memory at 40 min. post-infusion; KET = PBO: processing speed, attention, and visual, spatial, and working memory at 2-6 hr.

mg/kg: milligram per kilogram; min.: minute; KET: ketamine; PBO: placebo; mg/kg/h: milligrams per kilograms per hour; d.: day; ng/ml: nanograms per millilitre; hr.: hour

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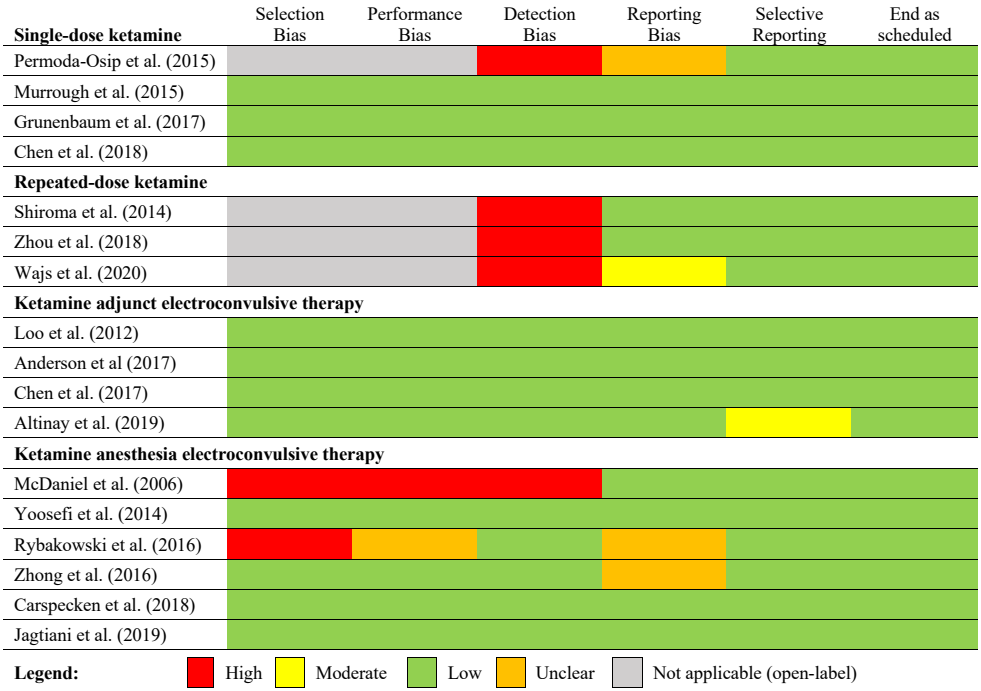
Supplementary Table 2. Cognitive tests and related cognitive domains measured in included studies

	Cognitive Test	Cognitive Domain Measured	Follow-up points
Single-dose ketamine studies			
Permoda-Osip et al. (2015)	Stroop test	Attention, executive function	Day 3
	Trails Making Test (TMT)	Processing speed (Part A), executive function (Part B)	
Murrough et al. (2015)	TMT-A, category fluency test, Brief Assessment of Cognition in Schizophrenia (BACS)– Symbol coding	Processing speed	Week 1
	Wechsler Memory Scale (WMS) – Spatial Span	Working Memory	
	Letter-Number Sequencing	Working Memory	
	Hopkins Verbal Learning Test (HVLT)	Verbal Memory	
	Brief Visuospatial Memory Test (BVMT)	Visual Memory	
	Neuropsychological Assessment Battery (NAB) – mazes	Problem Solving	
Grunenbaum et al. (2017)	Simple & Choice Reaction Time	Reaction time	Day 1
	TMT-A, Wechsler Adult Intelligence Scale (WAIS) – digit symbol coding, Stroop test	Processing speed	
	Continuous Performance Test (CPT) – identical pairs, Stroop test	Attention	
	Buschke Selective Reminding Test (SRT)	Global Memory	
	Brief Visual Retention Test (BVRT)	Visual memory	
	A not B test, N-back test	Working memory	
	Controlled Oral Word Association Test (COWAT)	Verbal fluency	
	Go/No-Go test, Time production test, Stroop test	Executive function	
Chen et al. (2018)	Working memory task	Working memory	Day 3, Week 2
	Go/No-Go test	Executive function	
Repeated-dose ketamine studies			
Shiroma et al. (2014)	Identification task	Attention	Week 1, 2, 3, 4
	N-back test	Working memory	
	Groton Maze Learning Test (GML)	Spatial memory	
	Groton Maze Chase Test, Detection task	Processing speed	
	Continuous Paired Associative Learning Task (CPAL), one card learning task, GML –delayed recall	Visual memory	
	International Shopping List Task (ISL)	Verbal memory	
	Set-shifting task	Executive function	
Zhou et al. (2018)	BACS – Symbol coding, category fluency, TMT Part A	Processing Speed	Day 1, day 14
	WMS – Spatial Span, Letter-Number Sequencing	Working memory	
	HVLT	Verbal memory	
	BVMT	Visual memory	
Wajs et al. (2020)	Simple Reaction Time – detection task	Processing speed	28 days after start of treatment; week 20, 32, and 44 follow-up
	Identification task	Attention	
	One card learning task	Visual memory	
	N-back test	Working memory	
	Groton Maze Learning Test	Spatial memory	
	HVLT	Verbal memory	
Ketamine adjunct to electroconvulsive therapy studies			
Loo et al. (2012)	Medical College of Georgia Complex Figures	Visuospatial function	Day 1-3, Month 1
	HVLT	Verbal memory	
	COWAT	Verbal fluency	
	Symbol Digit Modalities Test (SDMT), Woodcock Johnson Cross-Out Test	Processing speed	
	Autobiographical Memory Interview – Short form (AMI-SF)	Autobiographical memory	
Anderson et al. (2017)	HVLT	Verbal memory	After last session, month 1 and 4
	COWAT	Verbal fluency	
	AMI-SF	Autobiographical memory	
	Medical College of Georgia Complex Figures	Visuospatial function	
	WAIS – digit span	Attention, working memory	
Chen et al. (2017)	Wechsler Memory Scale-Chinese Revision (WMS-RC)	Global memory	Day 1
	Mini Mental State Exam (MMSE)	Global cognition	
Altinay et al. (2019)	Montreal Cognitive Assessment (MoCA)	Global cognition	After last session
	COWAT	Verbal fluency	

Ketamine anesthesia for electroconvulsive therapy studies			
McDaniel et al. (2006)	MMSE – Short term memory item	Short-term memory	≥2 days
Yoosefi et al. (2014)	MMSE	Global cognition	Day 3-7, Month 1
Rybakowski et al. (2016)	BVRT	Visual memory	Day 2-4
	Rey-Osterrieth complex figure test	Visuospatial function	
	WAIS – digit span	Attention, working memory	
	Rey Auditory Verbal Learning Test (RAVLT)	Verbal memory	
	Verbal fluency test	Verbal fluency	
	Stroop Test	Attention, executive function, processing speed	
Zhong et al. (2016)	Verbal fluency test	Verbal fluency	Day 2-3
	WAIS – Digit symbol coding, TMT Part A	Processing speed	
	WAIS – digit span	Attention, working memory	
	Wisconsin Card Sorting Test (WCST), TMT Part B	Executive function	
	Tower of Hanoi	Problem solving	
	Visual regeneration test	Visual memory	
Carspecken et al. (2018)	MoCA	Global cognition	Day 3
Jagtiani et al. (2019)	MMSE	Global cognition	Hour 6

Supplementary Table 3. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Criteria[42,43]



Appendix 1. Search Strategy

OVID (example for MEDLINE database):

1. exp Depressive Disorder, Major/
2. exp Bipolar Disorder/
3. exp Depressive Disorder, Treatment-Resistant/
4. bipolar disorder*.tw.
5. bipolar depression*.tw.
6. manic depressive disorder*.tw.
7. manic depression*.tw.
8. bipolar affective disorder*.tw.
9. affective disorder*.tw.
10. refractory depression*.tw.
11. therapy resistant depression*.tw.
12. treatment refractory depression*.tw.
13. refractory depressive disorder*.tw.
14. treatment resistant depressive disorder*.tw.
15. treatment resistant depression*.tw.
16. major depressive disorder*.tw.
17. depression*.tw.
18. depressive disorder*.tw.
19. depress*.tw.
20. mood disorder*.tw.
21. exp Ketamine/
22. ketamine*.tw.
23. ci 581*.tw.
24. calypsol*.tw.
25. calipsol*.tw.
26. kalipsol*.tw.
27. ketalar*.tw.
28. ketamine hydrochloride*.tw.
29. ketanset*.tw.
30. ketaset*.tw.
31. r ketamine*.tw.
32. arketamine*.tw.
33. s ketamine*.tw.
34. esketamine*.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
37. 35 or 36
38. limit 37 to human

Cochrane Library:

1. MeSH descriptor: [Depressive Disorder, Major] explode all trees
2. MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
3. MeSH descriptor: [Bipolar Disorder] explode all trees
4. (bipolar disorder*):ti,ab,kw
5. (bipolar depression*):ti,ab,kw
6. (manic depressive disorder*):ti,ab,kw
7. (manic depression*):ti,ab,kw
8. (bipolar affective disorder*):ti,ab,kw
9. (affective disorder*):ti,ab,kw
10. (refractory depression*):ti,ab,kw
11. (therapy resistant depression*):ti,ab,kw
12. (treatment refractory depression*):ti,ab,kw
13. (refractory depressive disorder*):ti,ab,kw
14. (treatment resistant depressive disorder*):ti,ab,kw
15. (treatment resistant depression*):ti,ab,kw
16. (major depressive disorder*):ti,ab,kw
17. (depression*):ti,ab,kw
18. (depressive disorder*):ti,ab,kw
19. (depress*):ti,ab,kw
20. (mood disorder*):ti,ab,kw
21. MeSH descriptor: [Ketamine] explode all trees
22. (ketamine*):ti,ab,kw
23. (ci 581*):ti,ab,kw
24. (calypsol*):ti,ab,kw
25. calipsol*):ti,ab,kw
26. (kalipsol*):ti,ab,kw
27. (ketalar*):ti,ab,kw
28. (ketamine hydrochloride*):ti,ab,kw
29. (ketanset*):ti,ab,kw
30. (ketaset*):ti,ab,kw
31. (r ketamine*):ti,ab,kw
32. (arketamine*):ti,ab,kw
33. (s ketamine*):ti,ab,kw
34. (esketamine*):ti,ab,kw
35. (#1)OR(#2)OR OR(#3) OR(#4) OR(#5) OR(#6) OR(#7) OR(#8) OR(#9) OR(#10) OR(#11) OR(#12) OR(#13) OR(#14) OR(#15) OR(#16) OR(#17) OR(#18) OR(#19) OR(#20)
36. (#21)OR(#22)OR OR(#23) OR(#24) OR(#25) OR(#26) OR(#27) OR(#28) OR(#29) OR(#30) OR(#31) OR(#32) OR(#33) OR(#34)

Clinical trial registries searched

1. Australian Clinical Trials
2. Clinicaltrials.gov
3. International Standard Randomised Controlled Trials Number (ISRCTN)
4. International Clinical Trials Registry Platform (ICTRP)
5. European Union Clinical Trials Register