

Online Supplemental Table 1 – Representative List of NMDA Receptor Antagonists

Competitive Inhibition		Non-Competitive Inhibition			
Glutamate Receptor Antagonist	Glycine Receptor Antagonist	Antagonists at Allosteric Sites	Ion Channel Blockers		
AP5 ¹	D-Cycloserine ³	Dexanabinol (HU-211)	Amantadine	Ethanol	Magnesium
AP7 ²	Rapastinel (GLYX-13) ³	EVT101	Atomoxetine	Gacyclidine	Memantine
Midafotel (CPPene)	Lacosamide	Ifenprodil	Chloroform	Ibogaine	Methoxetamine
Selfotel (CGS-19755)	L-Phenylalanine	Ketamine ⁴	Dextromethorphan	Ketamine	Nitrous Oxide
		MK-0657 (CERC 301)	Dextrorphan	Lanicemine (AZD6765)	Phencyclidine (PCP)
		Traxoprodil (CP-101,606)	Dizocilpine (MK-801)		Rolicyclidine

¹AP5= amino-5-phosphonovaleric acid ²AP7=2-amino-7-phosphonoheptanoic acid ³Partial agonist at glycine receptor. ⁴One study (174) suggests ketamine may antagonize NMDA receptor activity by binding at an allosteric site in addition to blocking the receptor ion channel.

Online Supplemental Table 2 Characteristics of Included Randomized Clinical Trials of Other NMDA Antagonists

Source	Design	Active Regimen	Control Regimen	Concomitant Therapy	Diagnoses	Sample Size	Depression Scale
D-Cycloserine							
Heresco-Levy et al (111)	Cross Over	250 mg/day	Placebo	Various	MDD	22	HRSD ₂₁
Heresco-Levy et al (112)	Parallel	1000 mg/day	Placebo	Various	MDD	26	HRSD ₂₁
Rapastinel (GLYX-13)							
Preskorn et al (116) ¹	Parallel	1 mg/kg IV x 1	Placebo	None	MDD	58	HRSD ₁₇
Preskorn et al (116) ¹	Parallel	5 mg/kg IV x 1	Placebo	None	MDD	53	HRSD ₁₇
Preskorn et al (116) ¹	Parallel	10 mg/kg IV x 1	Placebo	None	MDD	50	HRSD ₁₇
Preskorn et al (116) ¹	Parallel	30 mg/kg IV x 1	Placebo	None	MDD	54	HRSD ₁₇
Lanicemine (AZD6765)							
Sanacora et al (102)	Parallel	100mg IV x 1	Placebo	Various	MDD	34	MADRS
Sanacora et al (102)	Parallel	100mg IV x 9 ²	Placebo	Various	MDD	101	MADRS
Sanacora et al (102)	Parallel	150mg IV x 9 ²	Placebo	Various	MDD	101	MADRS
Zarate et al (101)	Cross Over	150mg IV x 1	Placebo	None	MDD	22	MADRS
Memantine							
Anand et al (100)	Parallel	20 mg/day	Placebo	Lamotrigine	BD	29	HRSD ₁₇
Smith et al (99)	Parallel	20 mg/day	Placebo	Various	MDD	31	MADRS
Zarate et al (98)	Parallel	5-20 mg/day	Placebo	None	MDD	32	MADRS

MK-0657 (CERC-301)							
Ibrahim et al (105)	Cross Over	4-8 mg/day x 12 days	Placebo	None	MDD	5	MADRS
Nitrous Oxide							
Nagele et al (103)	Cross Over	50% Inhalation x 1 Hr.	Placebo	Various	MDD	20	HRSD ₂₁
Traxoprodil (CP-101,606)							
Preskorn et al (104)	Parallel	0.75 mg/kg	Placebo	Paroxetine	MDD	30	MADRS

Abbreviations: BD=Bipolar Disorder HRSD=Hamilton Rating Scale for Depression (Numerical subscript following HRSD indicates number of items used. If blank, the item count was not reported.) IV=Intravenous MDD=Major Depressive Disorder MADRS=Montgomery-Åsberg Depression Rating Scale

Notes: ¹Partial trial results were previously published by Moskal et al (117). ²Lanicemine was infused 3 times per week over a 3 week period.

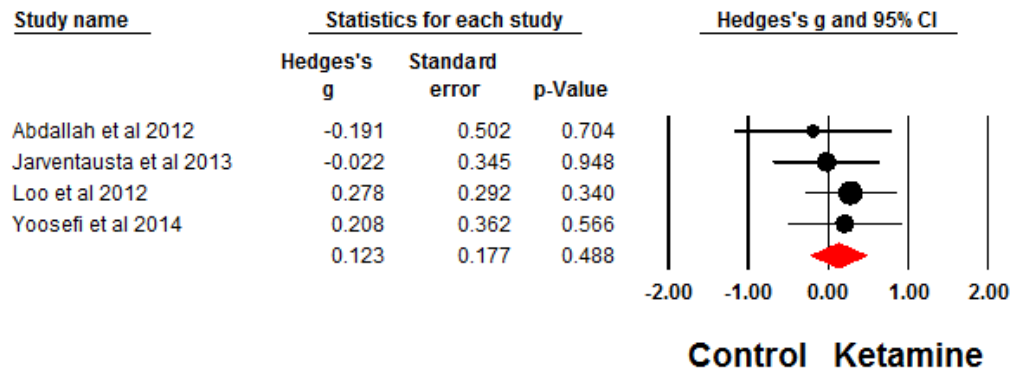
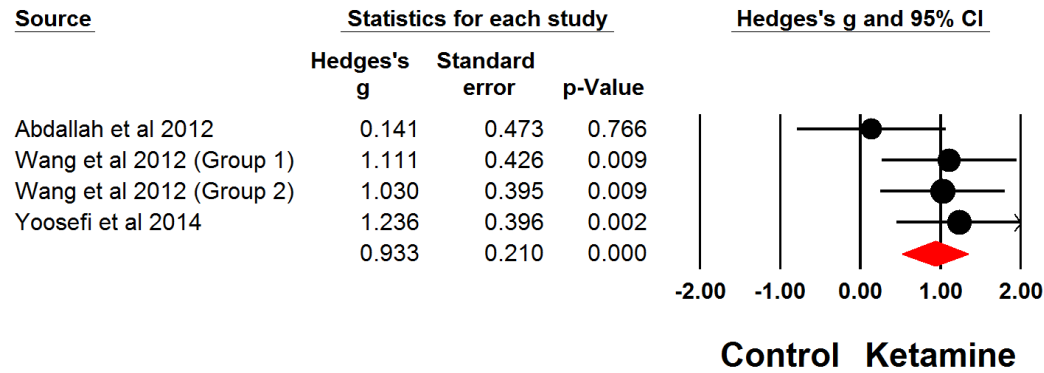
Online Supplemental Table 3 –Comparison of Ketamine and Memantine NMDA Receptor Activity

Test	Ketamine		Memantine	
	Finding	Sources	Finding	Sources
Antidepressant-Like Effects				
Animal Assay (Forced Swim Test)				
	↓ Immobility	Garcia et al (31), Autry et al (32), Nosyreva et al (33), Gideons et al (34), Zhou et al (35)	↓ Immobility No Effect	Moryl et al (36), Rogóz et al (37), Reus et al (38) Gideons et al (34), Skuza and Rogóz (175)
NMDA Blockade				
In Vitro Neuronal Culture				
No Magnesium	↓ PSC	Gideons et al (34), Emmett et al (176)	↓ PSC	Gideons et al (34), Emmett et al (176), Kotermanski et al (177)
Magnesium Added	↓ PSC	Gideons et al (34)	No Effect	Gideons et al (34), Kotermanski et al (177)
NMDA Trapping Block				
In Vitro Neuronal Culture				
	86-87%	Mealing et al (134)	71-76%	Mealing et al (134)
Second Messenger – eEF2				
In Vitro Culture of Hippocampal Neurons				
	↓ Phos	Autry et al (32), Nosyreva et al (33), Gideons et al (34)	No Effect	Gideons et al (34)
Second Messenger - BDNF				
In Vitro Culture of Hippocampal Neurons				
	↑ BDNF	Autry et al (32), Nosyreva et al (33), Gideons et al (34)	No Effect	Gideons et al (34)
Second Messenger - BDNF				
Animal Studies				
	↑ BDNF	Garcia et al (31), Zhou et al (35), Becker et al (178), Yang et al (179)	↑ BDNF	Reus et al (38) (acute); Reus et al (180)

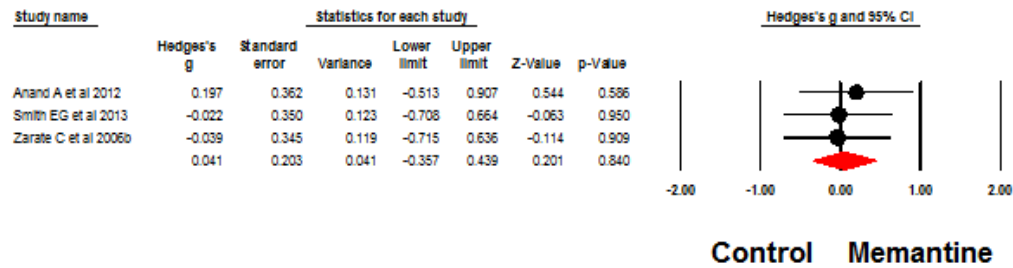
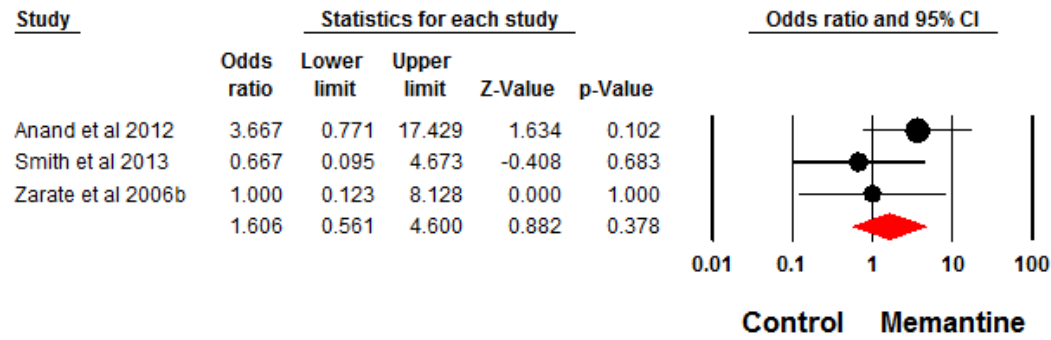
	↓ BDNF	Fraga et al (181) (chronic)	No Effect	Reus et al (38) (chronic)
Second Messenger – mTOR				
	↑ mTOR	Li et al (140); Yang et al (179); Yang et al (182); Zhou et al (35); Wesseling et al (183)		

BDNF=Brain-Derived Neurotrophic Factor eEF2=Eukaryotic Elongation Factor 2 mTOR=Mammalian Target of Rapamycin PSC=Postsynaptic Current Phos=Phosphorylation

Online Supplemental Figure 1A, 1B



Online Supplemental Figure 2A, 2B



Online Supplemental Figure 3A, 3B

