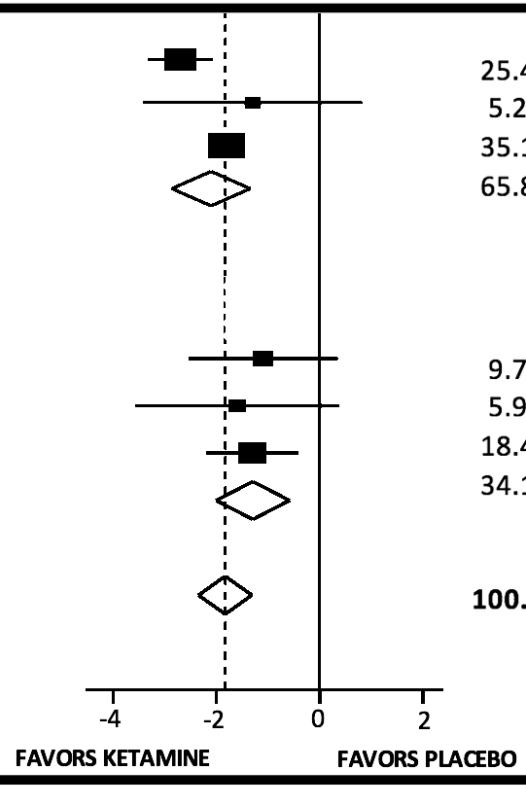
Supplemental Figure 1: Subgroup analysis broken down by ketamine dose

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
High-Dose Group									
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Subtotal (95% CI)			59			60	-2.11 (-2.87, -1.35)		65.82
Heterogeneity: Tau^2=0.27, Chi^2 =6.49, df=2 (P=0.039): I^2=69.2%									
Test of Overall effect: Z = 5.43, P<0.0001									
Low-Dose Group									
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Noppers,[28] 2011	0.8	0.3	12	2.0	0.3	12	-1.60 (-3.57, 0.37)		5.93
Mitchell,[29] 2002	5.1	2.3	16	6.3	2.5	12	-1.31 (-2.21, -0.42)		18.47
Subtotal (95% CI)			38			34	-1.30 (-2.01, -0.59)		34.18
Heterogeneity: Tau^2=0.00, Chi^2 =0.16, df=2 (P=0.922): I^2=0.0%									
Test of Overall effect: Z = 3.58, P<0.0001									
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**
Heterogeneity: Tau^2=0.17, Chi^2 =9.71, df=5 (P=0.084): I^2=48.5%									
Test of Overall effect: Z =6.93, P<0.0001									
Subgroup comparison with meta-regression:									
Coefficient: -0.81 (95% CI, -2.32, 0.71), P=0.213, Tau^2=0.15, I^2=39.83%									

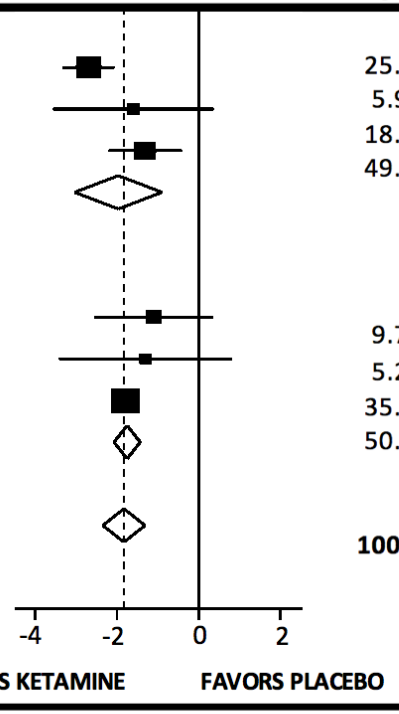


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 2. Subgroup analysis broken down by Nociceptive or Nociplastic pain and Neuropathic or Mixed pain group

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
Nociceptive or Nociplastic Pain Group									
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Noppers,[28] 2011	0.8	0.3	12	2.0	0.3	12	-1.60 (-3.57, 0.37)		5.93
Mitchell,[29] 2002	5.1	2.3	16	6.3	2.5	12	-1.31 (-2.21, -0.42)		18.47
Subtotal (95% CI)			58			54	-1.97 (-3.04, -0.90)		49.88
Heterogeneity: Tau^2=0.58, Chi^2 =6.55, df=2 (P=0.038): I^2=69.5%									
Test of Overall effect: Z = 3.61, P<0.00001									
Neuropathic or Mixed Pain Group									
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Subtotal (95% CI)			39			40	-1.75 (-2.08, -1.43)		50.12
Heterogeneity: Tau^2=0.00, Chi^2 =1.03, df=2 (P=0.596): I^2=0.0%									
Test of Overall effect: Z = 10.71, P<0.00001									
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**
Heterogeneity: Tau^2=0.17, Chi^2 =9.71, df=5 (P=0.084): I^2=48.5%									
Test of Overall effect: Z =6.38, P<0.0001									
Subgroup comparison with meta-regression:									
Coefficient: 0.45 (95% CI, -1.29, 2.19), P=0.720, Tau^2=0.296, I^2=47.7%									

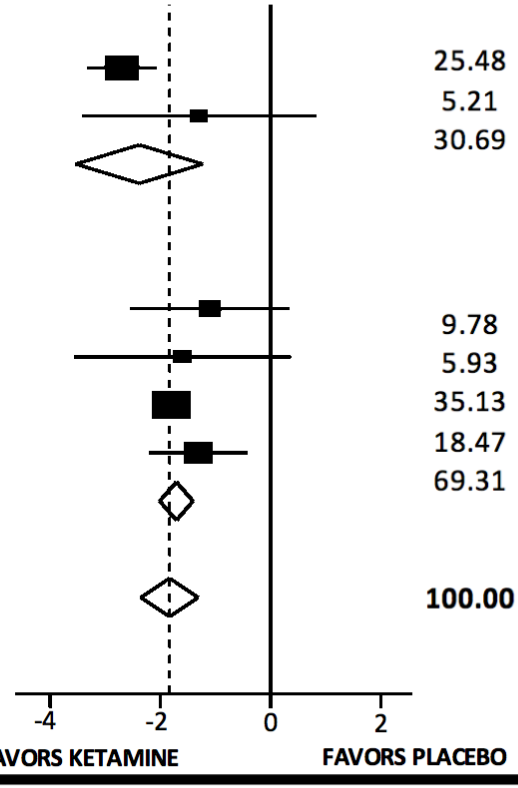


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 3. Subgroup analysis broken down by CRPS vs non-CRPS diagnosis

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
CRPS Group									
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Subtotal (95% CI)			39			40	-2.38 (-3.53, -1.23)		30.69
Heterogeneity: Tau^2=0.34, Chi^2 =1.54, df=1 (P=0.215): I^2=34.9%									
Test of Overall effect: Z=4.05, P<0.0001									
Non-CRPS Group									
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Noppers,[28] 2011	5.7	3.3	12	7.3	1.1	12	-1.60 (-3.57, 0.37)		5.93
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Mitchell,[29] 2002	5.1	2.3	16	6.3	2.5	12	-1.31 (-2.21, -0.42)		18.47
Subtotal (95% CI)			58			54	-1.71 (-2.01, -1.41)		69.31
Heterogeneity: Tau^2=0.00, Chi^2 =1.74, df=3 (P=063): I^2=0.0%									
Test of Overall effect: Z = 3.37, P=0.001									
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**
Heterogeneity: Tau^2=0.17, Chi^2 =9.71, df=5 (P=0.084): I^2=48.5%									
Test of Overall effect: Z =6.38, P<0.0001									
Subgroup comparison with meta-regression:									
Coefficient: -0.89 (95% CI, -1.95, 0.16), P=0.079, Tau^2=0.017, I^2=0.0%									

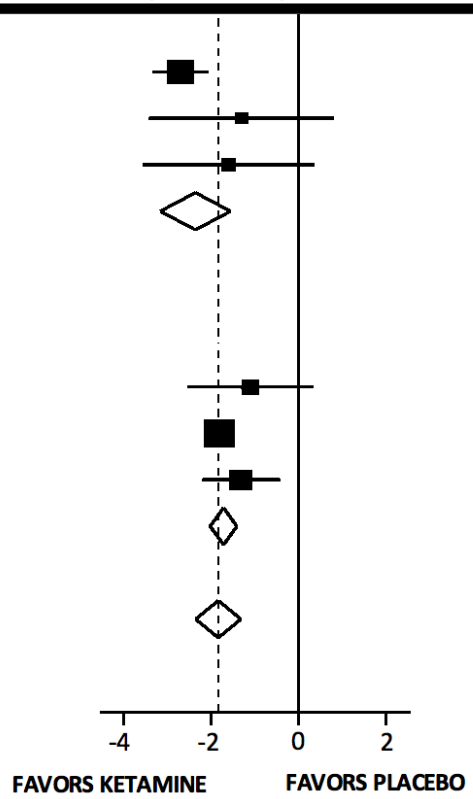


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 4. Subgroup analysis broken down by add-on vs stand-alone therapy

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
Ketamine only									
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Noppers,[28] 2011	5.7	3.3	12	7.3	1.1	12	-1.60 (-3.57, 0.37)		5.93
Subtotal (95% CI)			51			52	-1.80 (-3.04, -0.56)		36.62
Heterogeneity: Tau^2=0.13, Chi^2 =2.42, df=2 (P=0.299): I^2=17.2%									
Test of Overall effect: Z = 5.75, P<0.00001									
Ketamine with Adjunct									
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Mitchell,[29] 2002	5.1	2.3	16	6.3	2.5	12	-1.31 (-2.21, -0.42)		18.47
Subtotal (95% CI)			46			42	-1.90 (-3.26, -0.53)		63.38
Heterogeneity: Tau^2=0.00, Chi^2 =1.73, df=2 (P=0.421): I^2=0.0%									
Test of Overall effect: Z = 10.99, P<0.00001									
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**
Heterogeneity: Tau^2=0.17, Chi^2 =9.71, df=5 (P=0.084): I^2=48.5%									
Test of Overall effect: Z =6.93, P<0.00001									
Subgroup comparison with meta-regression:									
Coefficient: -0.80 (95% CI, -1.97, 0.36), P=0.127, Tau^2=0.05, I^2=3.54%									



[1] Lowest mean pain score ≥ 48-hours post-infusion

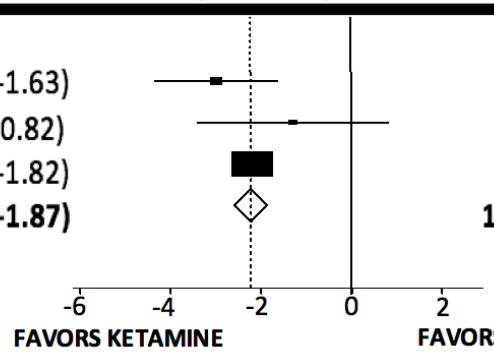
D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 5. Forest plot of the effects of ketamine Infusion on mean pain score two weeks after ketamine infusion

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight
Pain Score at Week 2									
Sigtermans,[23] 2009	4.2	2.7	30	7.2	2.7	30	-3.00 (-4.37, -1.63)		6.87
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		2.85
Amr,[27] 2010	2.2	0.7	20	4.4	0.5	20	-2.20 (-2.58, -1.82)		90.27
Total (95% CI)			**59**			**60**	**-2.23 (-2.59, -1.87)**		**100.00**

Heterogeneity: $Chi^2 = 1.98$, df=2 ($P<0.0001$): $I^2 = 0.0\%$

Test of Overall effect: Z = 12.20, P<0.001

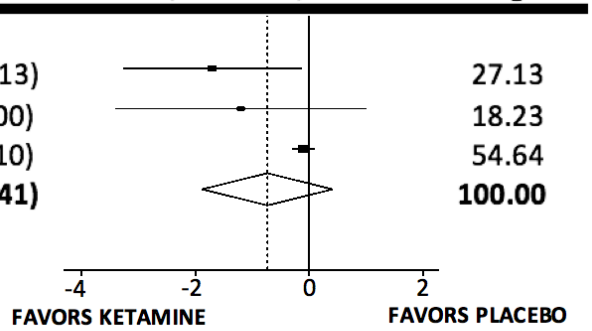


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 6. Forest plot of the effects of ketamine Infusion on mean pain score four weeks after ketamine infusion

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight
Pain Score at Week 4									
Sigtermans,[23] 2009	5.5	3.8	30	7.2	2.2	30	-1.70 (-3.27, -0.13)		27.13
Schwartzman,[24] 2009	6.4	3.0	9	7.6	1.6	10	-1.20 (-3.40, 1.00)		18.23
Amr,[27] 2010	4.2	0.4	20	4.3	0.2	20	-0.10 (-0.30, 0.10)		54.64
Total (95% CI)			**59**			**60**	**-0.74 (-1.88, 0.41)**		**100.00**
Heterogeneity: $Chi^2 = 4.84$, df=2 (P=0.089): $I^2 = 58.6\%$									
Test of Overall effect: Z = 1.26, P=0.208									

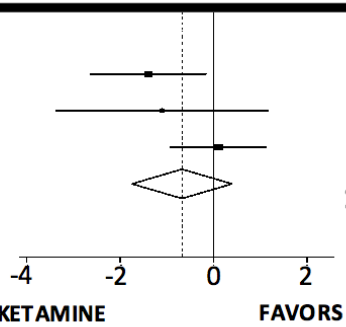


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 7. Forest plot of the effects of ketamine Infusion on mean pain score eight weeks after ketamine infusion

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight
Pain Score at Week 8									
Sigtermans,[23] 2009	6.2	2.2	30	7.6	2.7	30	-1.40 (-2.65, -0.15)		37.98
Schwartzman,[24] 2009	6.6	3.0	9	7.7	1.9	10	-1.10 (-3.39, 1.19)		17.14
Noppers,[28] 2011	6.2	1.4	12	6.1	1.2	12	0.10 (-0.94, 1.14)		44.88
Total (95% CI)			**51**			**52**	**-0.68 (-1.75, 0.40)**		**100.00**
Heterogeneity: $Chi^2 = 3.49$, df=2 (P=0.174): $I^2 = 48.2\%$									
Test of Overall effect: Z = 1.24, P=0.217									

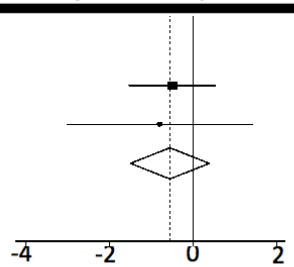


[1] Lowest mean pain score ≥ 48-hours post-infusion

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 8. Forest plot of the effects of ketamine Infusion on mean pain score twelve weeks after ketamine infusion

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight
Pain Score at Week 12									
Sigtermans,[23] 2009	6.5	2.7	30	7.0	1.1	30	-0.50 (-1.54, 0.54)		82.04
Schwartzman,[24] 2009	6.8	2.7	9	7.6	2.2	10	-0.80 (-3.03, 1.43)		17.96
Total (95% CI)			**39**			**40**	**-0.55 (-1.50, 0.39)**		**100.00**
Heterogeneity: $Chi^2 = 0.06$, df=1 (P=0.811): $I^2 = 0.0\%$									
Test of Overall effect: Z = 1.15, P=0.251									



[1] Lowest mean pain score ≥ 48-hours post-infusion

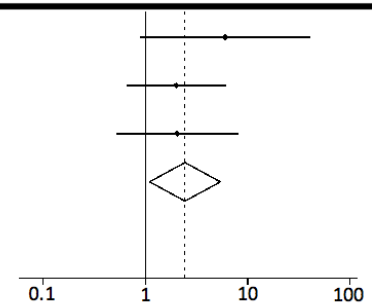
D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 9. Forest plot of the effects of ketamine Infusion for positive categorical outcome

Author, Year	Ketamine Events[1]	Total	Placebo Events[1]	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Eichenberger,[26] 2008	6	10	1	10	6.00 (0.87, 41.21)		17.12
Noppers,[28] 2011	6	12	3	12	2.00 (0.65, 6.20)		49.65
Salas,[25] 2012	5	11	2	9	2.05 (0.51, 8.16)		33.23
Total (95% CI)		**33**		**31**	**2.43 (1.10, 5.40)**		**100.00**

Heterogeneity: $Chi^2 = 1.07$, df=2 (P=0.586): $I^2 = 0.00\%$

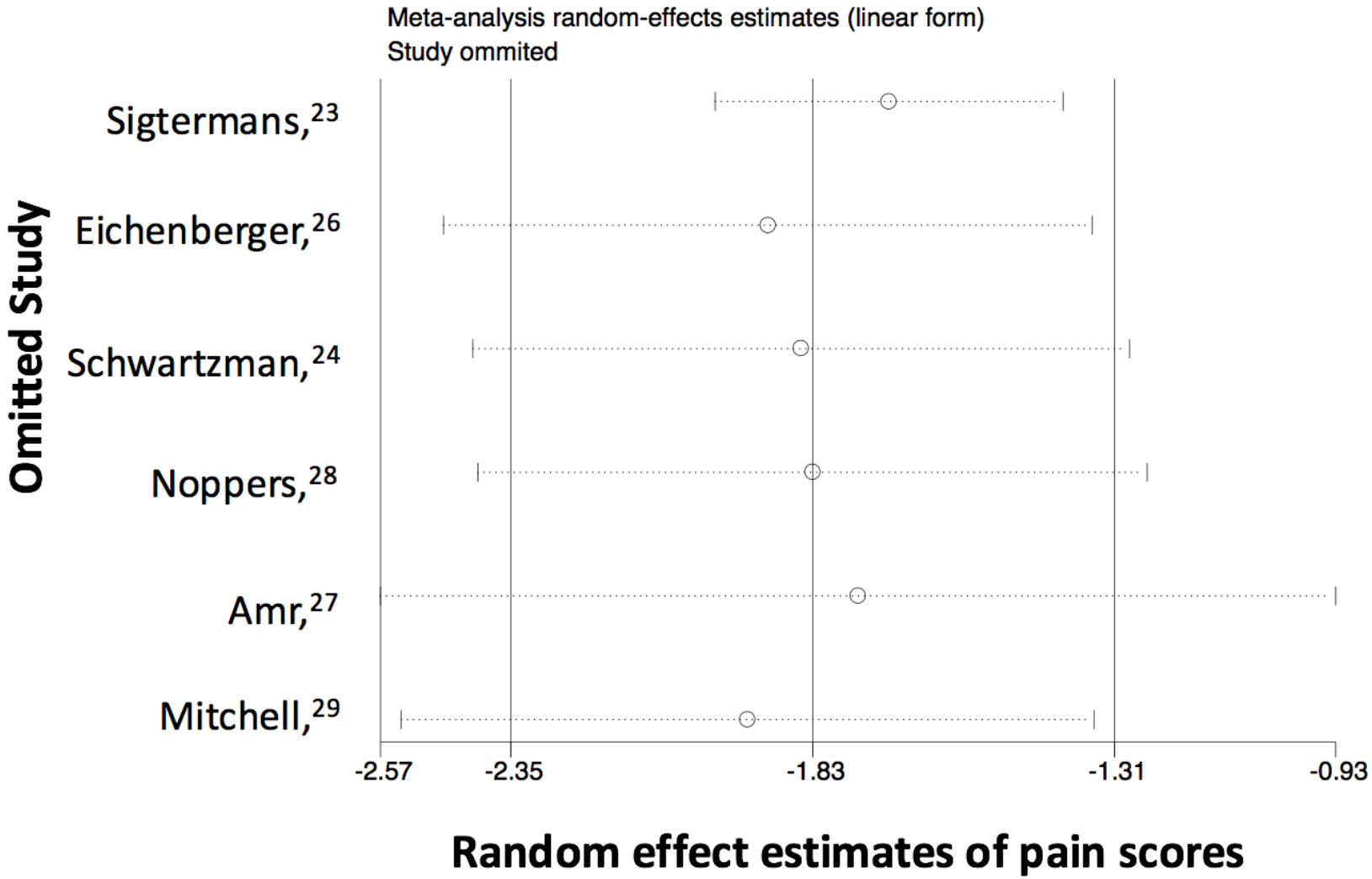
Test of Overall effect: Z = 2.18, P=0.029



[1] Defined as ≥ 30% pain [25] or ≥ 50% [26,28] pain relief

D + L represents DerSimonian and Laird random effects meta-analysis model

Supplemental Figure 10: Sensitivity analysis of the primary outcomes from six studies



Review/Search Topic: Ketamine + Neuropathic Pain + limited to human, adults (where possible)	Searcher: Dr. Vwaire Orhurhu
Investigator(s): Dr. Vwaire Orhurhu, Dr. Mariam Salisu, Dr. Anuj Bhatia, Dr. Steven Cohen, Anesthesia, Critical Care and Pain Medicine	Date: Tuesday, 16 October, 2017

Databases	**Database Dates covered**	**Date Database was searched**	**# Citations**	**# Duplicate Citations**	**Total Citations remaining**	**Notes/Comments**
Embase and MEDLINE	< 1966 to December 19th 2017	Tuesday, December 19th, 2017	277			Limited to articles, abstracts, adults, reviews, meta-analysis, RCT, and controlled trials
Web of Science	1900 to December 19th 2017	Tuesday, December 19th 2017	313			Conference Proceedings Citation Index-Science (CPCI-S)
PubMed-NOT-Medline (NLM)	Inception to December 19th, 2016	Tuesday, December 16th 2017	102			Clinical trial, full text, human study
			692	**0**	**0**	**Final Results**

Embase and MEDLINE Search Term

((((ketamine OR 'n methylketamine' OR 's ketamine' OR nmda) AND antagonist AND crps OR complex) AND regional AND pain AND syndrome OR fibromyalgia OR chronic) AND pain OR analgesia OR pain OR neuropathic) AND pain AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [article in press]/lim AND [adult]/lim AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND [embase]/lim

Web of Science Search Term

(ketamine or N-methylketamine or S-ketamine or NMDA antagonist) and (CRPS or complex regional pain syndrome or fibromyalgia or chronic pain or analgesia or pain or neuropathic pain)

Pubmed-NOT-Medline (NML)

(("ketamine"[MeSH Terms] OR "ketamine"[All Fields]) OR ("N-methylketamine"[Supplementary Concept] OR "N-methylketamine"[All Fields] OR "n methylketamine"[All Fields]) OR S-ketamine[All Fields] OR (("n-methylaspartate"[MeSH Terms] OR "n-methylaspartate"[All Fields] OR "nmda"[All Fields]) AND antagonist[All Fields])) AND (CRPS[All Fields] OR ("complex regional pain syndromes"[MeSH Terms] OR ("complex"[All Fields] AND "regional"[All Fields] AND "pain"[All Fields] AND "syndromes"[All Fields]) OR "complex regional pain syndromes"[All Fields] OR

("complex"[All Fields] AND "regional"[All Fields] AND "pain"[All Fields] AND "syndrome"[All Fields]) OR "complex regional pain syndrome"[All Fields]) OR ("fibromyalgia"[MeSH Terms] OR "fibromyalgia"[All Fields]) OR ("chronic pain"[MeSH Terms] OR ("chronic"[All Fields] AND "pain"[All Fields]) OR "chronic pain"[All Fields]) OR ("analgesia"[MeSH Terms] OR "analgesia"[All Fields]) OR ("pain"[MeSH Terms] OR "pain"[All Fields]) OR ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields] OR "cancer"[All Fields])) AND (Clinical Trial[ptyp] AND "loattrfull text"[sb] AND "humans"[MeSH Terms])

**** The authors have made every effort to provide accurate and complete database search results. However, we assume no liability for information retrieved, its interpretation, applications or omissions.***

Supplemental Table 1: Details of search strategy

	Ketamine				Placebo			
Adverse Outcomes	**Studies, n**	**Patients, n**	**Rate (95%CI), %**	**I^2, %**	**Studies, n**	**Patients, n**	**Rate (95%CI), %**	**I^2, %**
Nausea	3	49	55.3 (40.4 – 69.9)*	96.5	3	50	11.0 (1.2 – 26.4)	34.6
Vomiting	1	30	46.6 (30.2 – 63.9)*	--	1	30	10.0 (3.5 – 25.6)	--
Psychotomimetic effects	4	76	52.5 (9.8 – 93.2)	93.7	4	72	4.69 (0.0 – 16.2)	51.0
Headache	2	39	38.2 (22.8 – 54.6)	--	2	40	29.6 (15.8 – 45.4)	--
Tiredness	2	29	18.5 (5.40 – 35.7)	--	2	30	8.70 (0.41 – 22.9)	--
Sedation	1	10	50.0 (23.7 – 73.6)	--	1	10	20.0 (5.7 – 51.0)	--

Supplemental Table 2: Incidence of adverse outcomes amongst chronic pain patients receiving ketamine infusion.

* indicates significantly higher incidence in ketamine group as compared to placebo.