UHN Centre for Mental Health

The Poul Hansen Family Centre for Depression presents:

Clinical Advances in Depression Care

Friday September 30, 2022 | Virtual Event

Ketamine for Mood Disorders

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FACULTY/PRESENTER DISCLOSURE

- Faculty: Joshua Rosenblat
- Relationships with financial sponsors:
  - Dr. Joshua D Rosenblat has received research grant support from the Canadian Institute of Health Research (CIHR), Physician Services Inc (PSI) Foundation, Labatt Brain Health Network, Brain and Cognition Discovery Foundation (BCDF), Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from iGan, Janssen, Allergan, Lundbeck, Sunovion and COMPASS. He is the Chief Medical and Scientific Officer of Braxia Scientific and the medical director of the Canadian Rapid Treatment Centre of Excellence (Braxia Health).

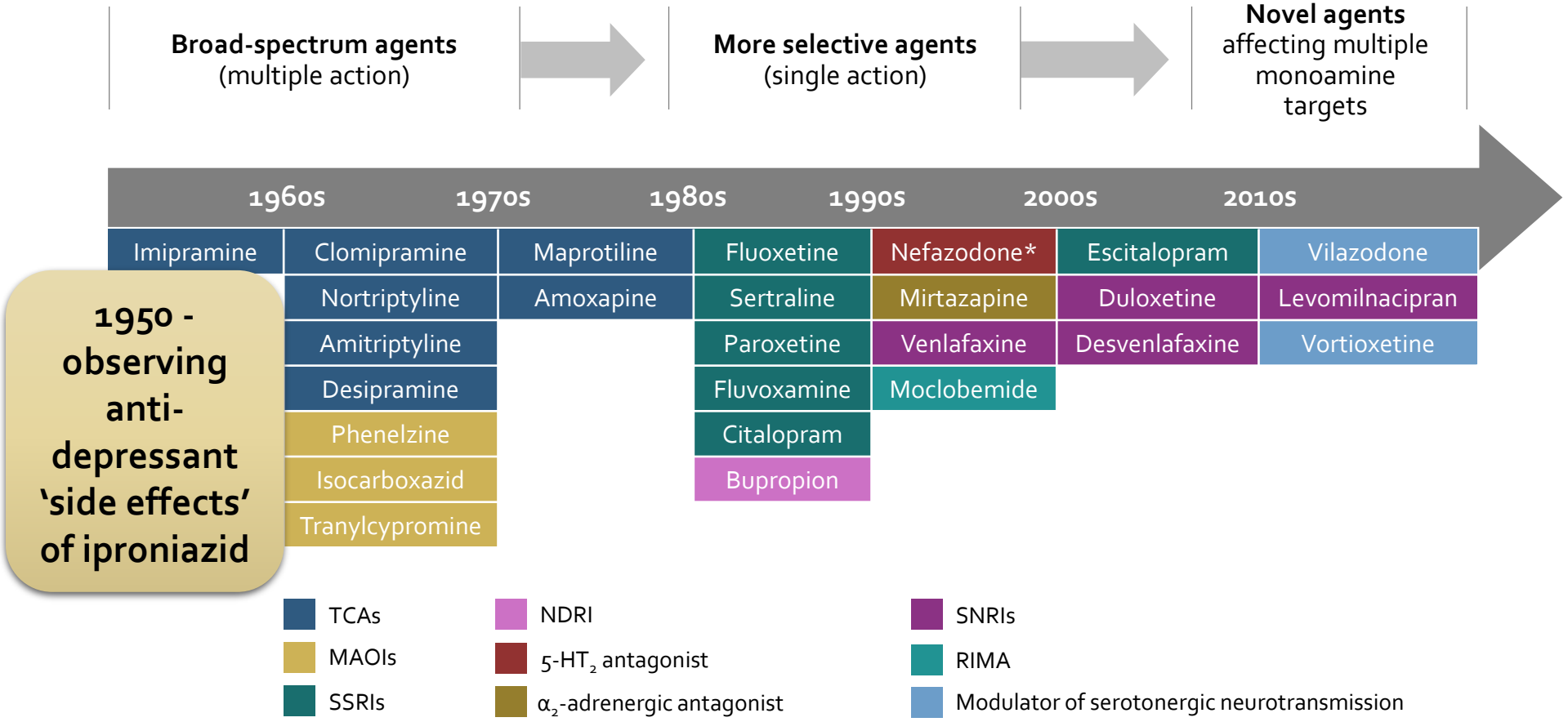
MITIGATING POTENTIAL BIAS

- Dr. Rosenblat has a detailed Risk Mitigation Plan (RMP) developed and approved by an independent group at University Health Network to mitigate potential risk of bias from aforementioned conflicts of interest. The RMP includes detailed disclosures and limitation on his role in research projects involving ketamine and any form of collaboration with organizations he is involved with.

LEARNING OBJECTIVE

- Understand the mechanism of action of ketamine
- Describe the evidence for ketamine's antidepressant effects
- Appreciate key limitations of our knowledge for this emerging treatment

EVOLUTION OF ANTIDEPRESSANTS[1,2]



*Withdrawn from the Canadian market

5-HT: 5-hydroxytryptamine; MAOI: monoamine oxidase inhibitor; NDRI: norepinephrine–dopamine reuptake inhibitor; RIMA: reversible monoamine oxidase inhibitor; SNRI: selective norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

1. Lam RW et al. *J Affect Disord.* 2009; 117(Suppl 1):S26-43;
2. Health Canada. *Health Product Information*. Available at: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=91734.

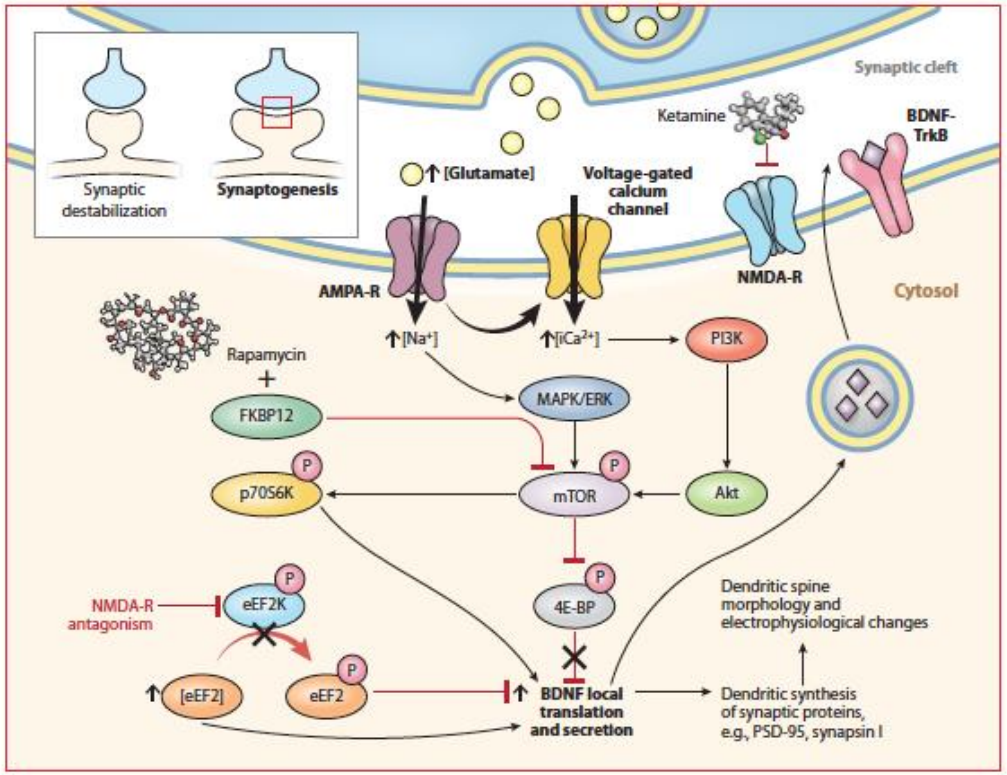
Beyond Monoamines: FDA Approval for Three Non-Monoaminergic Antidepressants

- Esketamine Nasal Spray (glutamate)
- Combination of Dextromethorphan and Bupropion (glutamate)
- Brexanolone (neuro-steroid and GABA-A)

An exciting time for psychiatry!

Ketamine for TRD: Mechanism of Action

- Ketamine is an NMDA antagonist used clinically as an anesthetic agent
- Mechanism of action for antidepressant effects remains controversial, but broadly exerts its effects through modulation of the glutamate system



Niciu et al. *Annual Review of Pharmacology and Toxicology.* 2014.

TABLE 1. Key pharmacodynamic targets of ketamine and esketamine

Target	Pharmacodynamic Effect	Potential Clinical Effect[a]
Glutamate system		
N-methyl-D-aspartate (NMDA) receptor	Strong antagonist	Antidepressant and procognitive effects; acute dissociative effects
α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor	Indirect agonist (through increase glutamate release)	Antidepressant effects
D-Serine site	Antagonist	Antidepressant effects
Glutamate	Increased release	Antidepressant effects
Opioid system		
μ Opioid receptor	Weak agonist	Antidepressant and analgesic effect and potentially acute euphoric effect
μ Opioid 2 receptor	Antagonist	
κ Opioid receptor	Agonist	
δ Opioid receptor	Agonist	
Monoamine system		
Serotonin transporter	Weak inhibitor	Antidepressant effect
Norepinephrine transporter	Weak inhibitor	Antidepressant effect
Dopamine transporter	Weak inhibitor	Antidepressant effect
Dopamine 2 receptor	Agonist	Acute psychotomimetic effects
Serotonin (5-HT_3) receptor	Weak antagonist	Antidepressant effect
Cholinergic system		
Cholinesterase	Inhibitor	Procognitive effects
α7 Nicotinic receptor	Antagonist	Antidepressant effects
α4 β2 Nicotinic receptor	Antagonist	
Muscarinic receptors (M1–3)	Antagonist	Increased blood pressure and heart rate
Other		
σ_1 Receptor	Agonist	Antidepressant and cardiac effects
σ_2 Receptor	Agonist	Antidepressant and cardiac effects
Mammalian target of rapamycin (mTOR)	Downstream activation via glutamate system	Antidepressant effects
Brain-derived neurotrophic factor (BDNF)	Downstream from mTOR increasing BDNF levels	Antidepressant and procognitive effects
$GABA_A$ receptor	Agonist	Acute anxiolytic effects
mTORC1	Activation	Neuroplastic effects

[a] The clinical significance of specific targets remains unclear, and results have been mixed. Potential proposed clinical effects are synthesized and summarized here.

Table created by Joshua Rosenblat for McIntyre, Rosenblat, et al. Ketamine Guidelines. AJP. 2021.

Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetal Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., Carlos Lopez Jaramillo, M.D., Ph.D., Siegfried Kasper, M.D., Kevin Kratiuk, B.Pharm., Jung Goo Lee, M.D., Ph.D., Yena Lee, H.B.Sc., Leanna M.W. Lui, Rodrigo B. Mansur, M.D., Ph.D., George I. Papakostas, M.D., Mehala Subramaniapillai, M.Sc., Michael Thase, M.D., Eduard Vieta, M.D., Ph.D., Allan H. Young, M.Phil., M.B.Ch.B., Carlos A. Zarate, Jr., M.D., Stephen Stahl, M.D., Ph.D.

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for its competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of ketamine and esketamine in adults with treatment-resistant depression. The authors also provide guidance for the implementation of these agents in clinical practice, with particular attention to practice parameters at point of care. Areas of consensus and future research vistas are discussed.

Am J Psychiatry 2021; 00:1–17; doi: 10.1176/appi.ajp.2020.20081251

International Ketamine Guidelines *(McIntyre, Rosenblat, et al., AJP, 2021)*

- Intravenous (IV) ketamine and intranasal (IN) esketamine now have Level 1 evidence for acute efficacy in adults with TRD.
- Clinically relevant adverse effects of ketamine infusions include psychological (e.g., dissociative symptoms) and physical (e.g., hypertension, nausea) changes.
- There is insufficient evidence to routinely recommend other formulations of ketamine (oral, intramuscular, subcutaneous). Oral ketamine has some positive preliminary results.
- Consensus recommendations are given for clinical administration of IV ketamine including patient selection, facility and personnel issues, monitoring requirements, and maintenance of response.

Does Route of Administration Matter?

TABLE 2. Comparison of routes of administration of ketamine and esketamine

Route	Bioavailability	Dose Range (Acute)
Intravenous	100%	0.5–1.0 mg/kg infused over 40–60 minutes twice weekly for 2 weeks
Intramuscular	90%–95%	Not established, likely similar to intravenous
Subcutaneous	90%–95%	Not established, likely similar to intravenous
Intranasal	30%–50% (significant differences between devices and solution)	Esketamine: 56–84 mg intranasally twice weekly for 4 weeks Racemic ketamine: 50–150 mg intranasally twice weekly
Oral	10%–20% (potential variability between capsules and liquid forms)	Highly variable (0.5–7.0 mg/kg daily to once weekly), with 100–250 mg 2–3 times per week most accepted
Sublingual	20%–30%	Not established, likely similar to oral
Transdermal	10%–50% (highly variable by vehicle used)	Not established

Table created by Joshua Rosenblat for McIntyre, Rosenblat, et al. Ketamine Guidelines. AJP. 2021.

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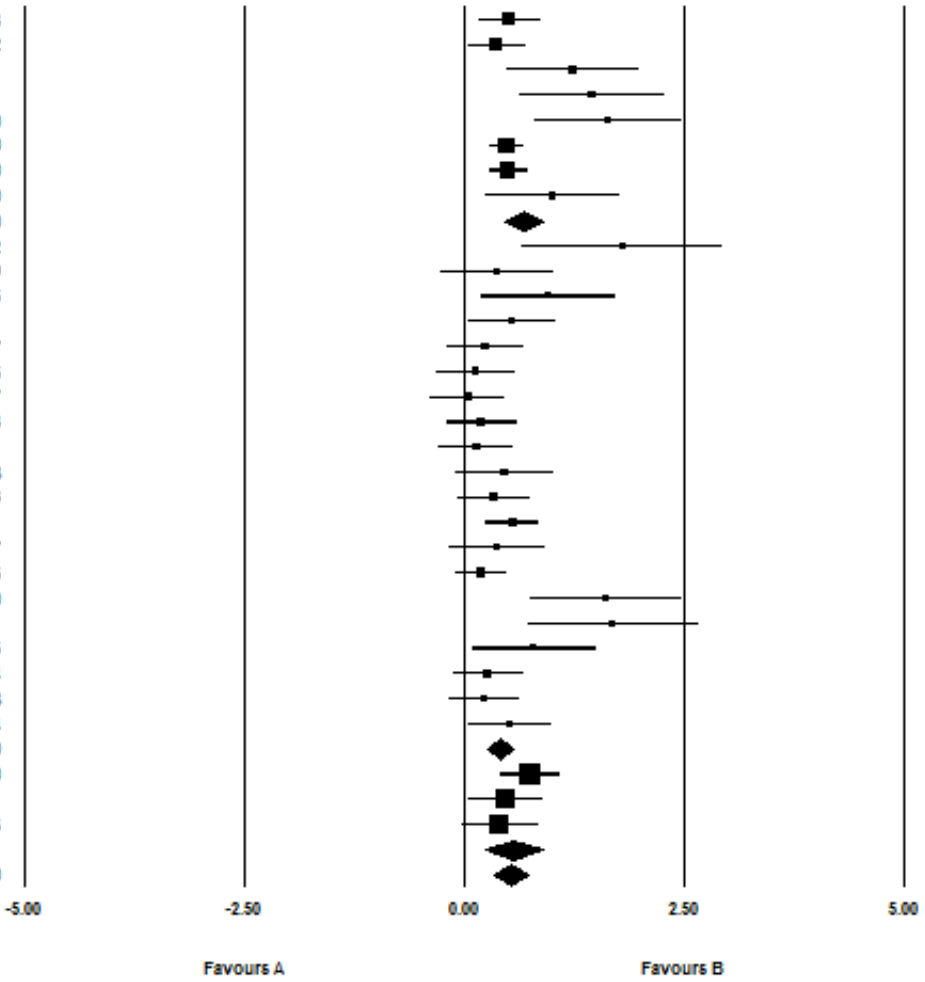
Sublingual	20%–30%	
Transdermal	10%–50% (highly variable by vehicle used)	Not established

- Only IV ketamine and IN esketamine are considered evidence based options
- Level 1 data supports moderate to large antidepressant effects with IV ketamine and IN esketamine.
- Oral ketamine RCTs yielded mixed results and had critical sources of bias identified.

Table created by Joshua Rosenblat for McIntyre, Rosenblat, et al. Ketamine Guidelines. AJP. 2021.

Meta-Analysis Results Pooling Together 21 RCTs of Ketamine for Depression

Hedges's g	Standard error	Group by Administration	Study name	Variance	Lower limit	Upper limit	Z-Value	p-Value
0.516	0.176	Intranasal	Canuso, Signh, Fedgchin, et al 2018	0.031	0.170	0.861	2.924	0.003
0.368	0.172	Intranasal	Canuso, Singh, Fedgchin, et al 2018	0.030	0.031	0.706	2.142	0.032
1.237	0.387	Intranasal	Daly, Singh, et al 2017 (28mg)	0.149	0.479	1.995	3.199	0.001
1.446	0.417	Intranasal	Daly, Singh, et al 2017 (56mg)	0.174	0.630	2.263	3.472	0.001
1.637	0.429	Intranasal	Daly, Singh, et al 2017 (84mg)	0.184	0.796	2.477	3.818	0.000
0.481	0.100	Intranasal	Fedgchin, Trivedi, Daly, et al 2019 (56mg)	0.010	0.286	0.676	4.828	0.000
0.501	0.106	Intranasal	Fedgchin, Trivedi, Daly, et al 2019 (84mg)	0.011	0.293	0.710	4.711	0.000
1.001	0.389	Intranasal	Lapidus, Levitch, et al 2015	0.152	0.237	1.764	2.570	0.010
0.667	0.110	Intranasal		0.012	0.451	0.882	6.064	0.000
1.793	0.583	Intravenous	Berman, Cappiello, Anand, et al 2000	0.340	0.651	2.936	3.077	0.002
0.361	0.327	Intravenous	Chen, Li, Lin, et al 2018 (0.2mg)	0.107	-0.280	1.002	1.104	0.269
0.952	0.394	Intravenous	Chen, Li, Lin, et al 2018 (0.5mg)	0.155	0.180	1.725	2.416	0.016
0.542	0.252	Intravenous	Diazgranados, Ibrahim, Brutsche, et al 2010	0.063	0.049	1.035	2.154	0.031
0.237	0.218	Intravenous	Fan, Yang, Sun, et al 2017	0.048	-0.190	0.665	1.087	0.277
0.130	0.226	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.1mg)	0.051	-0.314	0.573	0.573	0.566
0.036	0.215	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.2mg)	0.046	-0.385	0.457	0.167	0.867
0.197	0.208	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.5mg)	0.043	-0.210	0.604	0.948	0.343
0.132	0.216	Intravenous	Fava, Freeman, Flynn, et al 2018 (1mg)	0.047	-0.291	0.555	0.611	0.541
0.455	0.283	Intravenous	Hu, Xiang, Fang, et al 2016	0.080	-0.100	1.011	1.608	0.108
0.333	0.216	Intravenous	Ibrahim, Diazgranados, et al 2012	0.047	-0.091	0.757	1.541	0.123
0.544	0.158	Intravenous	Murrough, Iosifescu, Chang, et al 2013	0.025	0.235	0.853	3.448	0.001
0.377	0.279	Intravenous	Murrough, Soleimani, DeWilde, et al 2015	0.078	-0.170	0.925	1.350	0.177
0.183	0.151	Intravenous	Phillips, Norris, Talbot, et al 2019	0.023	-0.113	0.479	1.214	0.225
1.598	0.440	Intravenous	Singh, Fedgchin, Daly, 2016 (0.4mg)	0.194	0.736	2.461	3.633	0.000
1.686	0.499	Intravenous	Singh, Fedgchin, Daly, et al 2016 (0.2mg)	0.249	0.709	2.663	3.382	0.001
0.794	0.354	Intravenous	Sos, Klirova, Novak, et al 2013	0.126	0.099	1.488	2.239	0.025
0.267	0.201	Intravenous	Su, Chen, Li et al 2017 0.5mg	0.040	-0.127	0.662	1.328	0.184
0.226	0.204	Intravenous	Su, Chen, Li, et al 2017 0.2mg	0.042	-0.174	0.626	1.108	0.268
0.514	0.242	Intravenous	Zarate, 2006	0.059	0.039	0.989	2.120	0.034
0.406	0.074	Intravenous		0.005	0.261	0.552	5.482	0.000
0.749	0.174	Oral	Arabzadeh et al 2018	0.030	0.407	1.091	4.294	0.000
0.471	0.218	Oral	Domany, Bleich-Cohen, et al 2019	0.047	0.044	0.898	2.162	0.031
0.398	0.224	Oral	Jafarinia et al 2016	0.050	-0.040	0.837	1.781	0.075
0.556	0.169	Oral		0.029	0.224	0.887	3.285	0.001
0.529	0.102	Overall		0.010	0.328	0.729	5.169	0.000



McIntyre,…,Rosenblat. JAD. 2020.

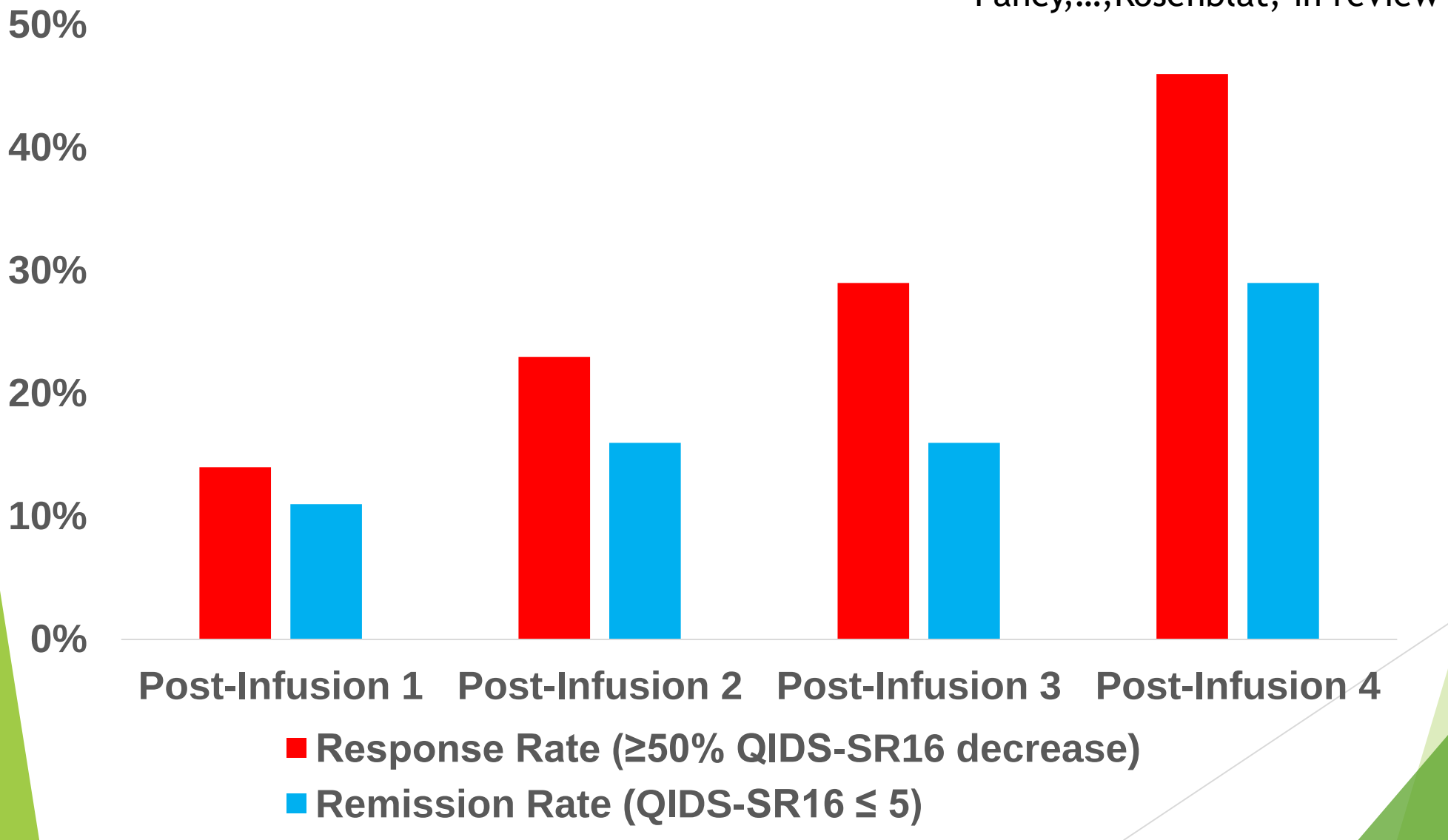
Meta-Analysis Results Pooling Together 21 RCTs of Ketamine for Depression

- 21 RCTs demonstrated robust & rapid antidepressant effects in TRD ($p<0.0001$)
- Level 1 data supports moderate to large antidepressant effects with IV ketamine and IN esketamine.
- Evidence supports anti-suicidality effects

McIntyre,…,Rosenblat. JAD. 2020.

Ketamine for Bipolar TRD:
Preliminary data from open label sample (n=55)

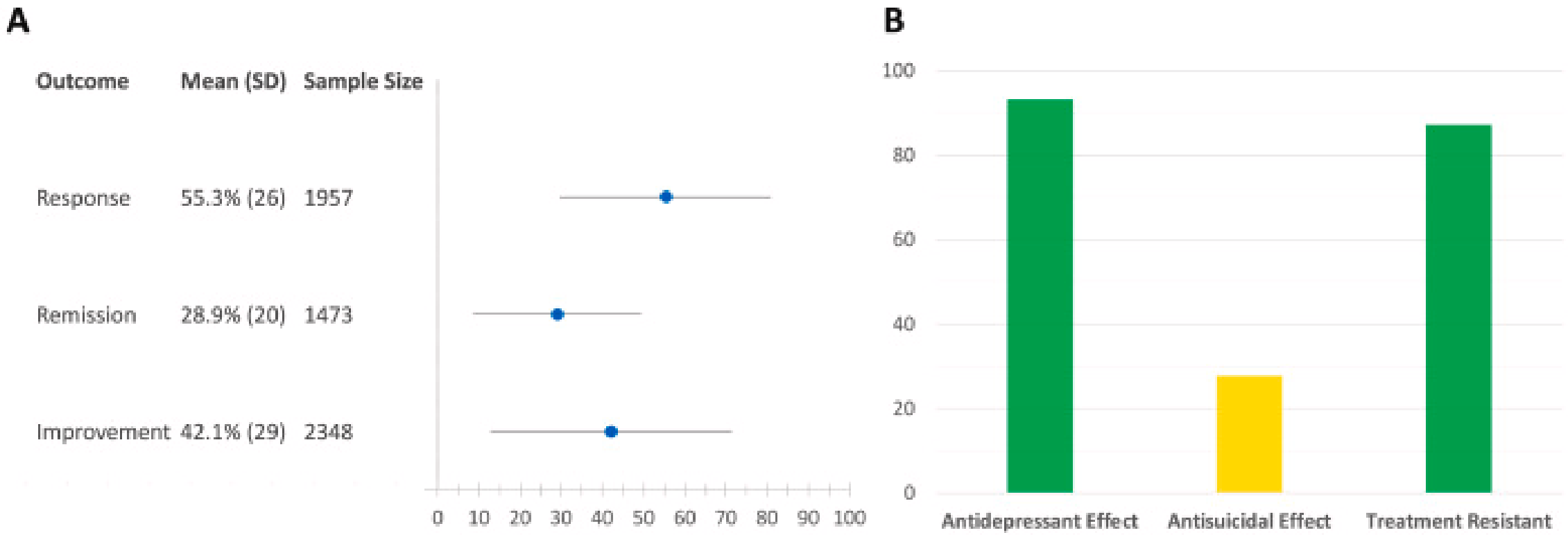
Fancy,…,Rosenblat, in review



Ketamine for Bipolar Depression

- Appears to be especially promising and effective with low risk for treatment emergent mania or psychosis based on preliminary results
- Pilot findings used to obtain two grants:
  - Repeated Ketamine Infusions for Treatment-Resistant Bipolar Depression: A Randomized, Midazolam-Controlled Clinical Trial (Funded by CIHR; 2021-2024)
  - Maintenance Ketamine Infusions for Treatment-Resistant Bipolar Depression (Funded by PSI; 2021-2024)

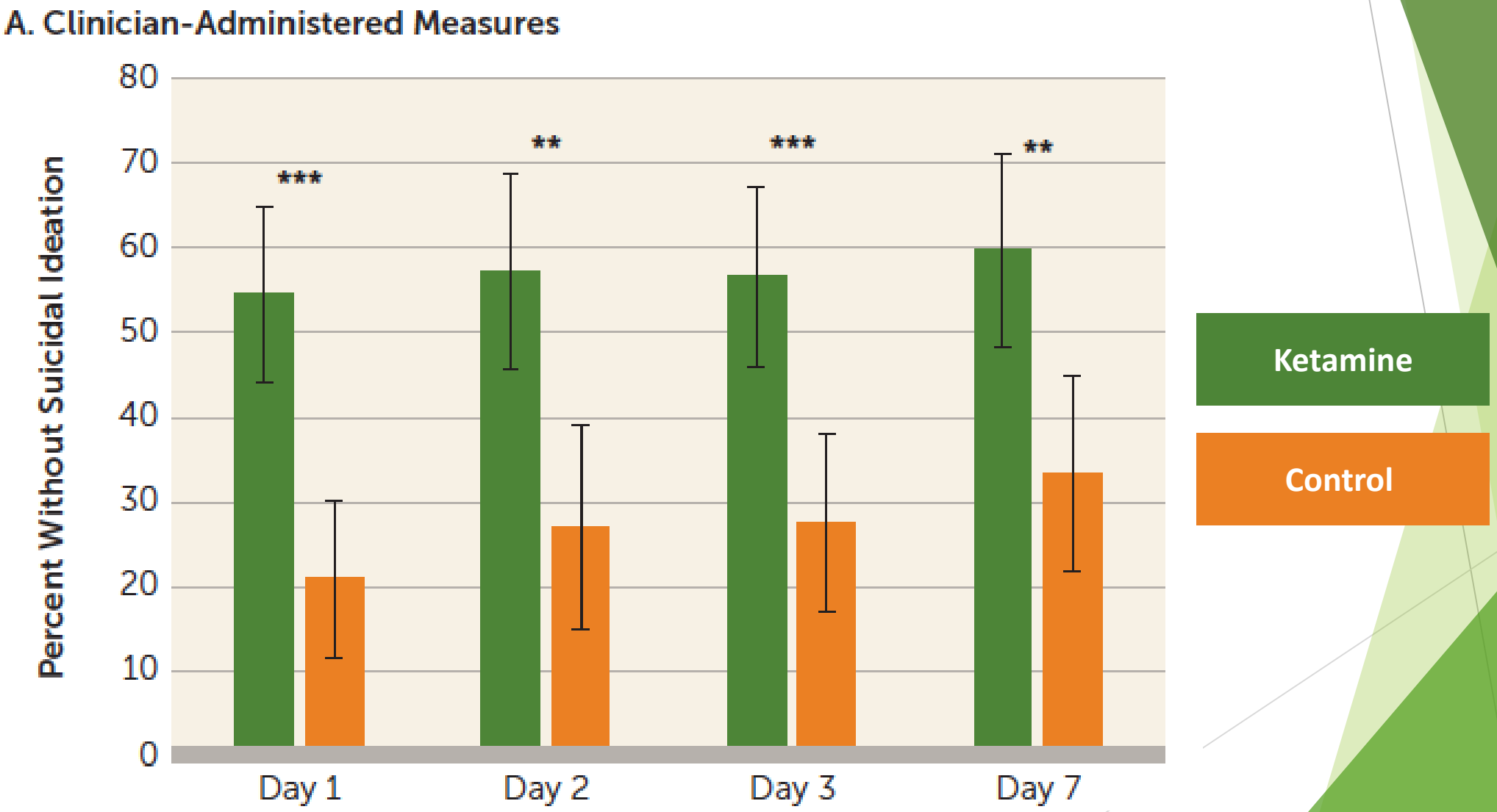
Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis (k=79)



Real world effectiveness of IV ketamine was comparable to observed efficacy in RCTs, suggesting that previous RCT findings are likely generalizable to clinical practice in a difficult to treat population, including more resistant and complex subgroups

Alnefeesi,…, Rosenblat, 2022.

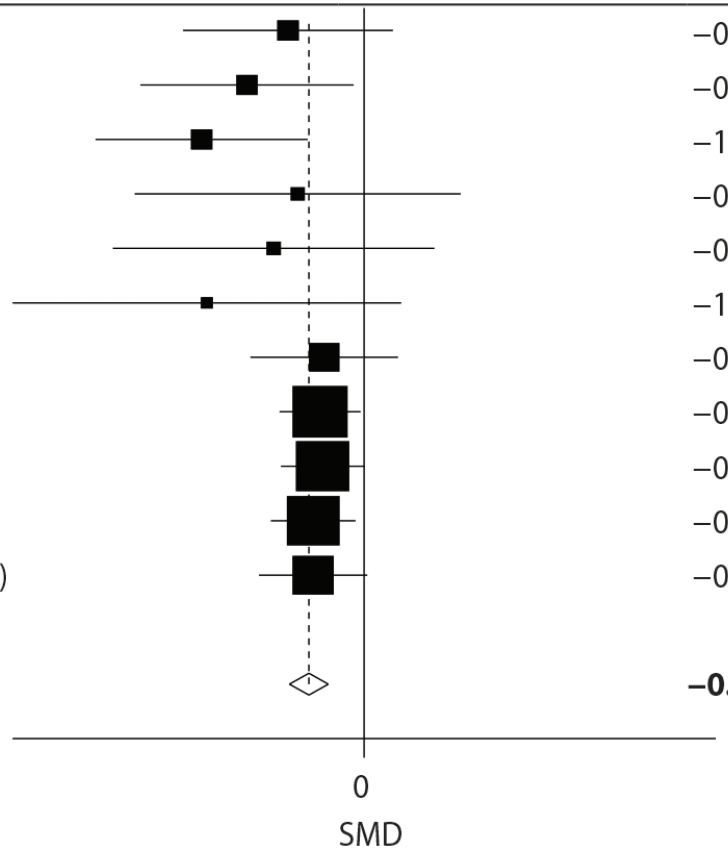
Ketamine Decreases Suicidal Thoughts *(mood-independent effect)*



Wilkinson et al. *Am J Psych.* 2018 Feb 1;175(2):150-158.

Evidence for IN Esketamine

Figure 1. Forest Plot of Standardized Mean Difference (SMD) in Change in Primary Outcome Scores Between Adjunctive Esketamine (EK) and Placebo



Study	SMD (95% CI)	% Weight
Daly et al, 2018[15] Stage I 28 mg EK (N = 44)	−0.50 (−1.19 to 0.19)	3.4
Daly et al, 2018[15] Stage I 56 mg EK (N = 44)	−0.77 (−1.47 to −0.07)	3.3
Daly et al, 2018[15] Stage I 84 mg EK (N = 45)	−1.07 (−1.77 to −0.37)	3.4
Daly et al, 2018[15] Stage II 28 mg EK (N = 14)	−0.44 (−1.51 to 0.64)	1.4
Daly et al, 2018[15] 56 mg EK (N = 15)	−0.60 (−1.65 to 0.46)	1.5
Daly et al, 2018[15] 84 mg EK (N = 11)	−1.04 (−2.32 to 0.24)	1.0
Canuso et al, 2018[25] 84 mg EK (N = 66)	−0.26 (−0.75 to 0.22)	7.0
Fedgchin et al, 2019[30] 56 mg EK (N = 219)	−0.29 (−0.56 to −0.02)	23.1
Fedgchin et al, 2019[30] 84 mg EK (N = 206)	−0.27 (−0.55 to 0.00)	21.7
Popova et al, 2019[27] 56–84 mg EK (N = 201)	−0.34 (−0.61 to −0.06)	21.2
Ochs-Ross et al, 2019[28] 28–84 mg EK (N = 123)	−0.34 (−0.69 to 0.02)	12.9
Overall (95% CI)	**−0.36 (−0.49 to −0.24)**	

Papakostas et al., 2020

Evidence for IN Esketamine

Table 2. Primary and Exploratory Meta-Analyses

	Intranasal Esketamine Augmentation	Intranasal Placebo Augmentation	Estimate (SMD or RR)	*P* Value
Total pooled sample				
Sample size	442	332		
SMD			0.36	<.0001
Response (%)	53.2	36.4	1.4	<.0001
Remission (%)	38.5	24.7	1.45	<.0001
TRD subjects only (without Canuso et al[25])				
Sample size	407	301		
SMD			0.37	<.0001
Response (%)	50.2	31.3	1.41	<.0001
Remission (%)	35.8	22.2	1.45	<.0001
New/optimized antidepressant sample (without Daly et al[15])				
Sample size	408	299		
SMD, day 28			0.30	<.0001
Response (%), day 28	55.1	39.8	1.38	<.0001
Remission (%), day 28	40	27	1.42	<.0001

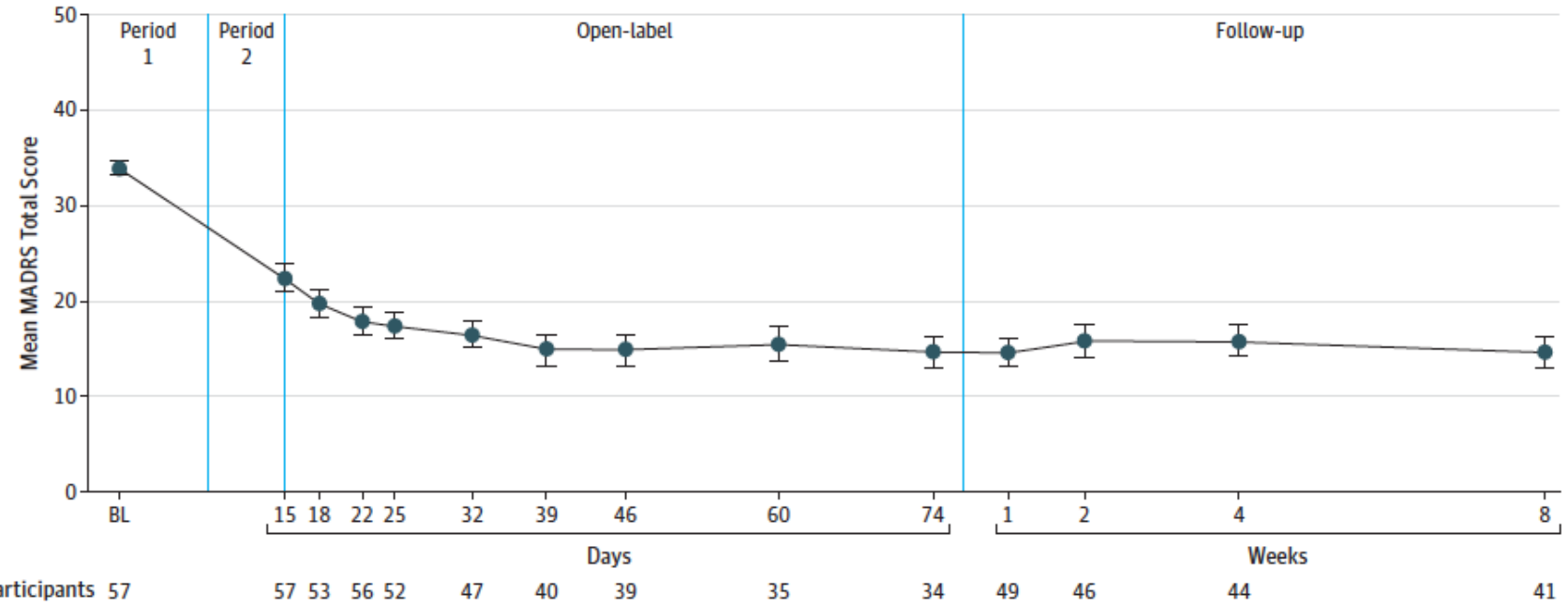
Abbreviations: RR = risk ratio, SMD = standardized mean difference, TRD = treatment-resistant depression.

Papakostas et al., 2020

53% Response and 39% Remission Rate for TRD

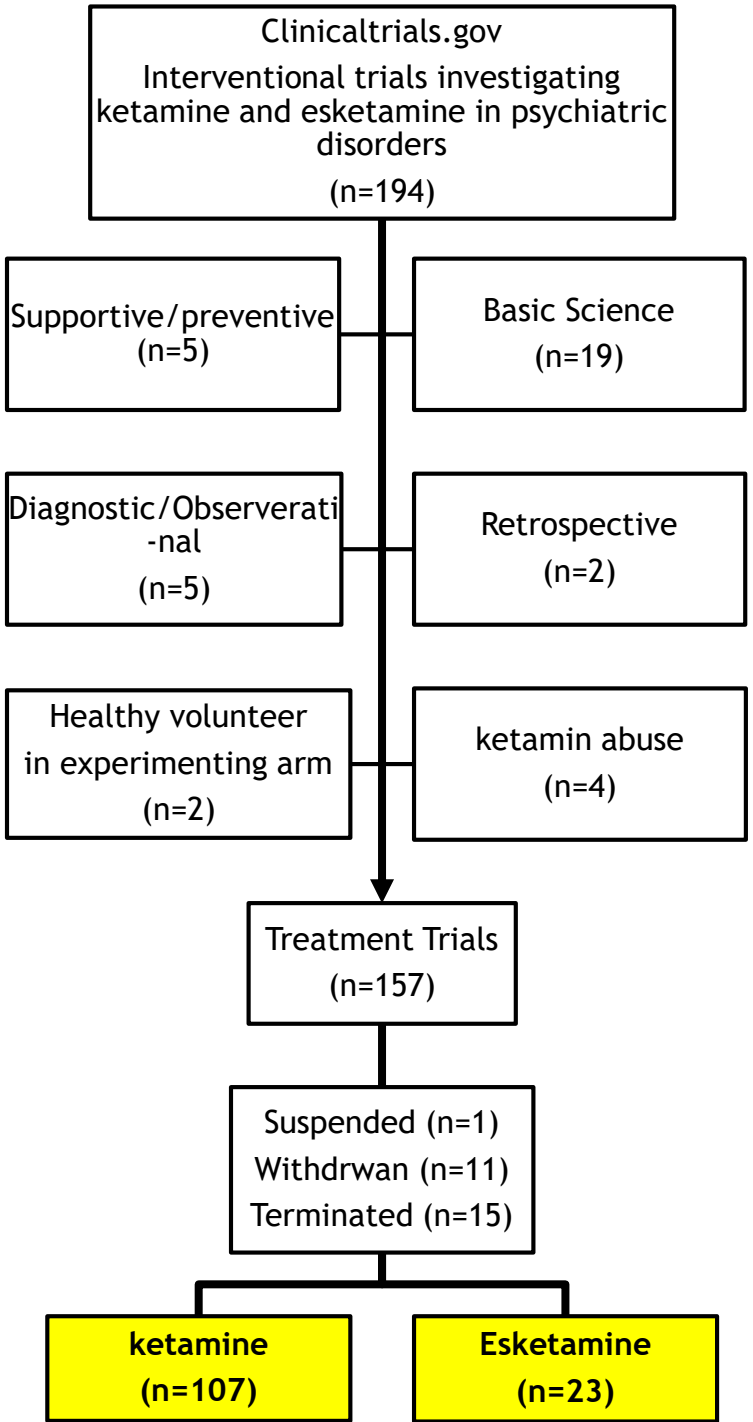
Sustained Antidepressant Effects With Repeated Doses of Intranasal Esketamine

Figure 3. MADRS Total Score: Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score From Baseline to Follow-up End Point for Participants Who Entered the Open-Label Phase



Period 1 (days 1-8), period 2 (days 8-15), open-label period (days 15-74), and the follow-up period (days 74-130) are discussed in the Design section of the Methods and shown in the vertical axis of Figure 1. BL indicates baseline; error bars, SE.

Daly et al. *JAMA Psychiatry*. 2018;75(2):139-148.



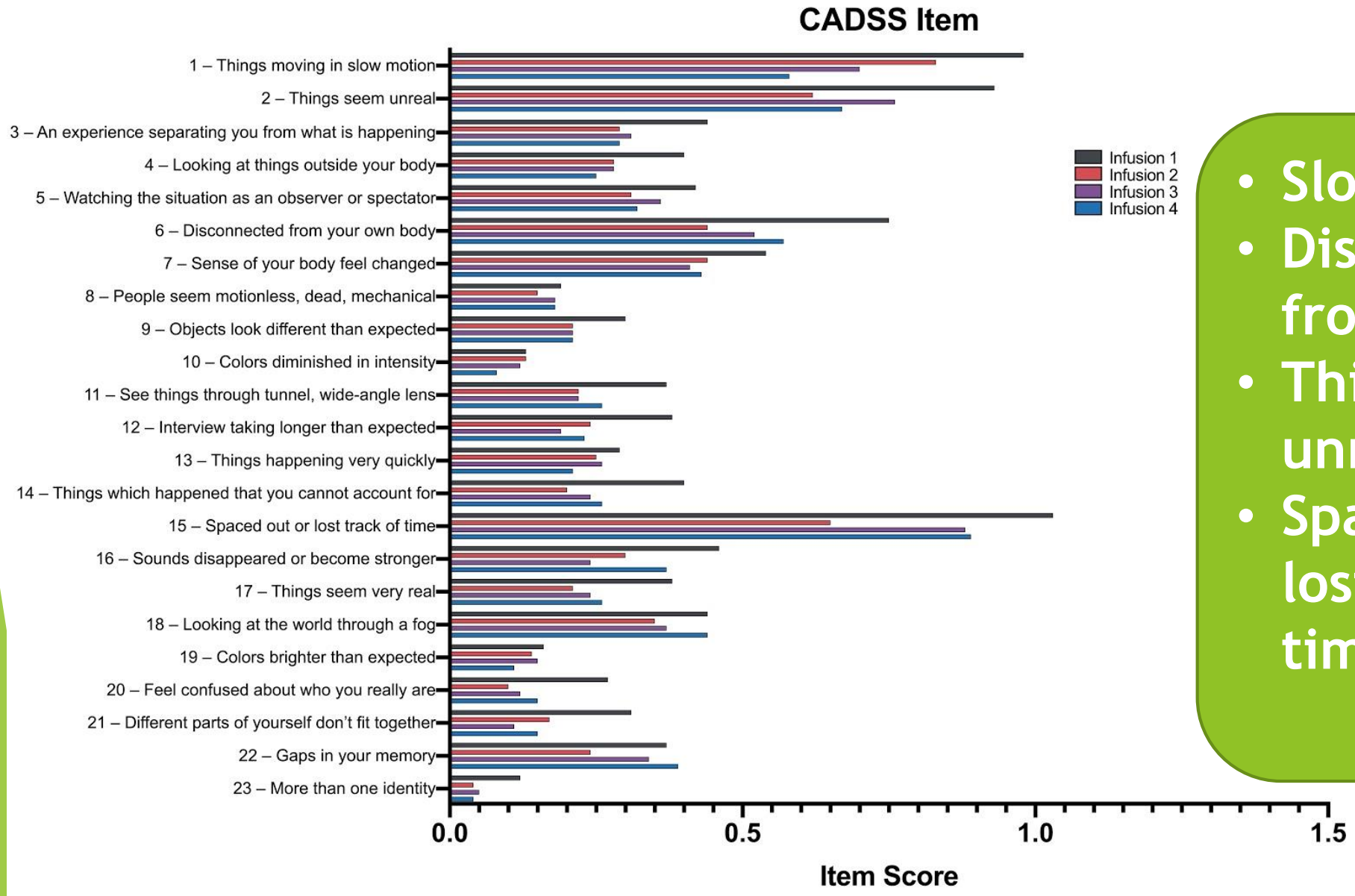
>100 ongoing clinical trials assessing the use of ketamine and esketamine in psychiatry

Pevoreh,…, Rosenblat. J Psyc Research. *2020*

What is the safety and tolerability profile of ketamine for depression?

Side Effect	During Infusion n(%)	After Infusion n(%)
Nausea	47 (13.9)	38 (11.1)
Vomiting	1 (0.29)	8 (2.50)
Dizziness	153 (48.2)	152 (49.2)
Headache	42 (13.2)	59 (19.3)
Double Vision	69 (20.8)	58 (18.8)
Blurred Vision	105 (31.9)	92 (29.8)
Drowsiness	184 (57.1)	164 (53.1)
Confusion	141 (43.5)	78 (25.1)
Jerky muscle movements	18 (5.42)	7 (2.3)
Depersonalization	113 (38.2)	54 (17.6)
Derealization	119 (40.8)	51 (16.7)

Rodrigues…Rosenblat, *2021*



- Slow motion
- Disconnected from body
- Things seem unreal
- Spaced out or lost track of time

McIntyre, Rodrigues…Rosenblat, *2021*

Dissociation Poorly Predicts Response

Key point:

You do NOT need to dissociate to have antidepressant effects.

Antidepressant effects do NOT rely on a dissociative epiphany or insight to gain benefits. This is a very common misconception.

Luckenbaugh et al. *J Affect Disord.* 2014.

How About Ketamine Assisted Psychotherapy (KAP)?

- 24 RCTs support the use of ketamine for TRD
- **ZERO published RCTs support the use of KAP for any indication**
- **Lack of research does not mean it is ineffective**
- A couple case series on KAP, however, unable to say if the therapy added any benefit
- Off label KAP is problematic as it is not evidence-based and inappropriately draws focus to the dissociative episode
- Dissociative symptoms are NOT predictive of antidepressant effects. Focusing on producing a dissociative experience can lead to inappropriate doses of ketamine when targeting dissociation rather than antidepressant effects

Current Ketamine Projects Underway

- Acute treatment of TRBD RCT (n=100)
- Maintenance IV ketamine for BD (n=50)
- Ketamine+CBT for suicidality (n=140)
- PGx predictors or response and adverse effects (n=100)
- Evaluation of switch protocols from different routes of administration (n=200)
- Ketamine versus ECT for TRD (n=240)
- Comparative efficacy of different routes of administration (observational)
- Three psilocybin trials

Summary

- IV ketamine and IN esketamine have strong evidence for rapid and robust antidepressant and anti-SI effects in TRD with many more ongoing trials
- Numerous difficult to treat subgroups have real world evidence to support effectiveness
- Careful patient selection and infrastructure are essential with evolving considerations
- Depression Centre has several active and upcoming ketamine trials (refer to Depression Centre attention Joshua Rosenblat)

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  - Nelson Rodrigues
  - Orly Lipsitz
  - Flora Nasri
  - Saja Jaberi
  - Shakila Meshkat
- Students
  - Farhan Fancy
  - Sipan Haikazian
  - Danica Johnson
  - David Chen-Li
  - Josh Di Vencenzo
  - Hana Nazel
  - Bahareh Peyvori
  - Leanna Lui
  - Ashley Segal

UHN Centre for Mental Health

The Poul Hansen Family Centre for Depression presents:

Clinical Advances in Depression Care

Friday September 30, 2022 | Virtual Event

Ketamine for Mood Disorders

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