From Hallucinations to Healing: The Rise of Novel Mental Health Therapies

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Faculty/Presenter Disclosure

None

- **Salary:** College of Family Physicians of Canada, Locum
- **Relationships with financial sponsors:**
  - **Any direct financial relationships including receipt of honoraria:** Chapters of CFPC (ACFP, OCFP, PEICFP & NLCFP), HMO & Hospitals (Sharp Rees Stealy, Peterborough & Osler), Universities, CPD Departments (UBC & Queens), Conferences & Groups (Rx Files & BS Medicine).
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  - **Patents for drugs or devices:** N/A
  - **Other:** CIHR, PRIHS – Funding for clinical trials, Best Science Medicine Podcast

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We know what we're told: Media & Ketamine

- Newspaper/media sites, 10 each for US, UK, Canada, & Australia.
- Outcomes 119 articles
  - Research mentioned in 91%: 57% quoted results, 76% positive and efficacy 3x safety
  - Overall, 69% positive, 19% mixed, 10% negative, 2% neither.
  - 90% Key Opinion Leaders: 62% positive only, 24% mixed, 6% negative, 8% neither.
  - Wrong information (efficacy, safety, duration) in 37%: 25% of that was in quotes from Key Opinion Leaders
- Bottom-Line: Media (and Opinion Leaders) presents a pretty rosy picture.

BJPsych Open. 2023 Jun 7;9(4):e104.

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Canadian Network for Mood and Anxiety Treatments (CANMAT): Guideline Ketamine

- **Criteria for Level 1: meta-analysis with 'narrow' CI or RCT with n≥60.**
- **16 of 20 (80%) had Conflicts (including chair)**

- Mechanism of Action (quotes):
  - ketamine causes a burst in glutamate release and sustained synaptogenesis in depression-related neural circuits, dependent on an increase in brain-derived neurotrophic factor and protein synthesis.
  - Perhaps metabolites, particularly hydroxynorketamine, a metabolite of (R)-ketamine that affects a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.
  - Ketamine acts on other neurotransmitter systems, including dopaminergic, serotonergic, and cholinergic systems, in addition to acting on opioid receptors.

Swainson. Can J Psychiatry. 2021 Feb;66(2):113-125.

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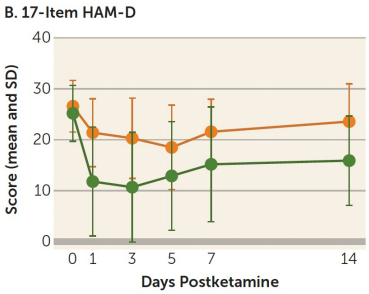
Mechanism of Action+



- NMDA (N-Methyl-D-Apsartate): Study 16 healthy people[1]
  - Lamotrigine attenuated (but didn't stop) dissociative/psychosis
  - No real effect on mood
  - Side Note: Other NMDA drugs don't seem to be effective[2]
- Opioid: study 12 (severe depression), ketamine +/- naltrexone.
  - Attenuation of score & "response" (5/7 vs 0/7 with naltrexone)
  - Dissociation score slightly attenuated (No diff in proportion or other AE)
  - Some say worrisome signal others say too early to tell
- Bottom-Line: Investigations into the possible mechanism raises more concerns than answers.

1) Anand. Arch Gen Psychiatry. 2000;57(3):270-6. 2) Williams. Curr Opin Neurobiol 2016; 36:112–17. 3) Williams. Am J Psychiatry. 2018 ;175(12):1205-15. 4) George MS. Am J Psychiatry. 2018;175(12):1157-8. 5) Sanacora G.. Am J Psychiatry. 2019;176(3):249.

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What Issues with the Evidence

1. Short treatments: IV ketamine - 89% studies single dose.[1]
2. Short Follow-up: Median follow-up 7 days (some 1 day).[1]
3. Study Size: 24hr response Ketamine 7 RCTs - mean 26/RCT (lowest =5 pts)[2]
4. Publication Bias[1,3] If looked for, consistently found for Ketamine
   - If corrected, benefit goes from 114% to 48%.[1]
5. Open-label RCTs[4] better than parallel RCTs – 7 days SMD 1.03 vs 0.49
6. Studies without control: SMD 2.19 vs 0.96 randomized.[5]
7. Cross-over (~28% of RCTs): response was RR 5.93 vs 2.19 parallel[1]

1) Bahji. Expert Opin Drug Saf. 2022;21(6):853-66. 2) *Cochrane 2021; 9: CD011612.* 3) eClinicalMedicine 2023;62: 102127 4) J Affect Disord. 2020 Dec 1:277:831-841. 5) Conley. Psychopharmacology (Berl). 2021 Jul;238(7):1737-52.

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Ketamine for Depression, Response + Scale

Outcomes (5 time points: 1 day, 3 days, 1 week, 2 weeks, 4 weeks)

- Ketamine vs Placebo: 4-7 RCTs, 83-185pts,
  - 2-9% on placebo & 18-24% more responded on ketamine (1 & 3 days)
- Ketamine vs Midazolam: 2-4 RCTs, 126-296 pts,
  - 26-29% on midazolam & 21-26% more responded on ketamine (1 & 7 days)
- Esketamine vs Placebo: 2-6 RCTs, 451-1117 pts, (4 of 5 stat sign)
  - 15%-44% on placebo responded & 9-15% more responded on Esketamine,
- SMD
  - Ketamine vs Placebo, 2-8 RCTs, 107-236 pts, SMD 0.43-0.87 (1 of 5 ns)
  - Ketamine vs Midazolam, 1-4 RCTs, 86- 297 pts, SMD 0.37-0.57 (1 of 5 ns)
  - Esketamine vs Placebo, 3-6 RCTs, 517 – 1182 pts, SMD 0.21-0.31 (all stat sign)

~35% more scale change than placebo

Cochrane 2021; 9: CD011612. BMJ Evid Based Med . 2022 Apr;27(2):69-73. Psychol Med. 2016 Feb;46(3):623-35.

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Esketamine intranasal spray x4 weeks

- Esketamine in Tx Res Depression (3 RCTs, 703 pts):[1] 28-84 mg 2x/wk x 4wks
  - MADRS (≥28) moved ~14 Placebo vs ~18 Esketamine (MCID ~3-6)
  - Response: 33% Esketamine vs 22% Placebo, NNT 9 (remission similar)
  - Serious Adverse Events: Not statistically Different
- Second Meta (7 RCTs, 1421 pts):[2] Similar (~MADRS 3-4 better vs placebo)[3]
  - Stat Sign Adverse Events: Blurred Vision, Dissociation, Dizziness, Bad taste in mouth, feeling drunk, hypesthesia, increased BP, nausea, oral paresthesia, any paresthesia, postural dizziness, sedation, somnolence, vertigo, vomiting, throat irritation.
- Bottom-Line: It works but less than hoped (~67% not responding)

Rev Assoc Med Bras (1992). 2023;69(6):e2023D696. (MCID = BMJ Evid Based Med . 2022 Apr;27(2):69-73. 2) Jawad. Expert Opin Drug Saf. 2022 Jun;21(6):841-852. 3) Ionescu Int J Neuropsychopharmacol. 2021 Jan 20;24(1):22-31.

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Time: Hear the Softly Spoken Magic Spells,…

- Meta- 48 RCTs, 3299 pts, ketamine/esketamine[2]
  - Responders/SMD: Ketamine effective ≤3 days. Esketamine effective to 28 d
- Meta – 8 RCTs, 1437 pts, esketamine 28-84 mg intranasal vs placebo, 1-4 wks
  - 24 hrs MADRS: esketamine ~3 better, Remission NNT 11
  - ~4 weeks MADRS: esketamine ~3 better, Remission NNT 20
- **Bottom-Line**: Esketamine appears to work over-time. Uncertain for Ketamine.

Roger Waters (PF); 1) Hock. J Clin Psychiatry. 2022;84(1):21r14086. 2) Nikolin. eClinicalMedicine 2023;62: 102127 3) Marcantoni. J Affect Disord. 2020;277:831-41. 4) Conley. Psychopharmacology (Berl). 2021 Jul;238(7):1737-52.

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What about stopping?

- RCT 297 pts with remission/response, on esketamine + antidepressant
  - Continued esketamine 56 or 84 mg, generally q2wks or placebo
  - After ~18 weeks, Relapse: 26% vs 50% (SS).
  - MADRS @ 18 weeks: 6-7 better if continue.
  - AE: Vertigo (25% vs 6%), Dizziness (20%vs 5%), somnolence (21% vs 2%), Bad taste (27% vs 7%), Blurred Vision (16% vs 1%), nausea (16% vs 1%), Dissociation (23% vs 0%) BP and Dissociation peaked at 40min and normal by 1.5 hours
- **Bottom-line**: If esketamine worked, stopping will see 50% have relapse in ~18 weeks, with half of those because esketamine was stopped. All the usual AE if continue.

Daly. JAMA Psychiatry. 2019 Sep 1;76(9):893-903.

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Ketamine vs ECT

- 1 Meta of RCTs: 5 (278 patients). 0.5mg/kg or ECT 2-3x/week 1-4 wks[1]
  - Generally, favors ECT: e.g. Response 75% ECT vs 59% ketamine
  - Ekstrand:[2] 186 European pts, all hosp, 40% past ECT, MADRS 34, Psychosis 17%
- RCT 403 pts: ECT 3x/wk or ketamine (0.5 mg/kg) 2x/wk, followed 3 wks[3]
  - 403 US pts, 11% hosp, 11% past ECT, MADRS 32, Psychosis 0 (excluded)
  - QIDS remission: Ketamine 55% vs ECT 41% (ss) & MADRS response similar (ns)
  - Change (MADRS): 15 better Ketamine vs 13 better ECT (ss)
- **Bottom-Line:** Mixed but seems Ketamine as good or better if moderate/severe and ECT as good or better if most severe?[4]

1) Menon. JAMA Psychiatry. 2023 June;80(6):639-42. 2) Ekstrand. Int J Neuropsychopharmacol. 2022;25:339-49. 3) Anand. NEJM. 2023 June;388:2315-25. 4) ACP Journal Club (Ann Int Med 2023; 176(9)

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Esketamine vs Antipsychotic Augmentation

- RCT 676 pts, Open-label, Esketamine (28-84 mg) vs Quetiapine 150-300mg
  - Age 45, MADRS 31. Esketamine at clinic
- Outcome: Remission - Esketamine vs Quetiapine
  - At 8 weeks: 27% vs 18% (NNT 11) & At 32 weeks: 22% vs 14% (NNT 14)
  - MADRS at 8 wks & 32 wks: Esketamine 3 & 2 better
  - stopping due to AE: 4% vs 11%; Tx related AE 85% vs 62%, 1 death each group.
    - Dissociation (28% vs 1%); Dizziness (47% vs 8%); Somnolence (15% vs 23%); Bad Taste (12% vs 0.3%), vertigo (19% vs 1%); Nausea (29% vs 4%); Headache (25% vs 13%), others.
- **Bottom-Line**: It works, maybe a little better than quetiapine, but need to visit clinic, lots of harms, costly, etc.

Reif. N Engl J Med 2023;389:1298-309.

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Adverse Events

- No difference in withdrawals

Ketamine vs Placebo		Keta	Control
	Agitation/anxiety	34%	17%
	Confusion	52%	21%
	Dissociative	13%	0%
	Cognitive Scores	Score worse	
Ketamine vs Midazolam			
infuse	Blurred Vision	43%	8%
	Dizziness	27%	8%
	Nausea/Vomiting	22%	6%
1 wk	Increase BP/HR	60%	14%

Esketamine vs Placebo		EsKeta	Control
	BP change	10%	4%
	Constipation	11%	3%
	Dissociative	28%	4%
	Dizziness	30%	11%
	Postural Dizzy	6%	1%
	Feeling Drunk	5%	0.4%
	Nausea/Vomiting	36%	15%
	Paresthesia/neuropathy	14%	4%
	Sensory Disturbance	19%	3%
	Sedation	8%	2%
	Sleepiness	20%	11%
	Vertigo	14%	1%
	Vision Blurred	10%	3%

Cochrane Database of Systematic Reviews 2021; 9: CD011612.

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Substance Use: Vitamin K, Special K, K, etc

- 0.5-2% teens/college students have used in North America
  - In Asia can be 2nd or 3rd most common abused substance.
  - Case reports of Iatrogenic Ketamine Misuse withdrawal and suicide.
  - FDA Black Box warning for abuse/misuse in USA
- Cognition – common in street use or high doses. (use in antidepressant less clear)
- Bladder: epithelial layer damage, then interstitial cystitis (even ulcerative cystitis)
  - In rec use ~30% have bladder Sx. In Esketamine trials ~1.8% vs ~0.3% placebo.
- CVD: Transient BP, Transient HR, Increased Qtc (1 of 1708 pts to ≥500ms)
- Pregnancy: Animal studies show dev harm (+ 1 case of rec use), advise against.
- Not with lamotrigine and maybe Benzo (maybe reduced effect of Ketamine).
- Death: 7 (4 were suicide) in 764 pt/years vs 0 in 175 patient/years for placebo

Nikayin. Expert Opin Drug Saf. 2022 Jun;21(6):777-787. Orsolini Expert Opin Drug Saf. 2022 Jun;21(6):803-812

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Costs

- Cost: Esketamine at 28 mg intranasal solution $273/dose.
  - Initial dose 56 mg, subsequent doses of 56-84 mg 2x weekly x 4 weeks,
  - Weekly for weeks 5-8.
  - Week ≥9 onwards, weekly or every 2weeks.
- Annual cost of esketamine (just meds) is $18,546- $45,591 in year 1
  - $14,196-$42,588 in subsequent years.

DRUG REIMBURSEMENT RECOMMENDATION Esketamine (Spravato) — CDEC Meeting — June 17, 2020; CDEC Reconsideration Meeting — December 9, 2020; Notice of Final Recommendation – December 16, 2020

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Last thoughts

- Suicide Prevention:
  - 2 meta, 9 & 15 RCTs, 341 & 572 pts
  - Change suicide ideation score ≤72 hrs
    - SMD 0.51-1.1
  - No diff in suicide attempts (0 both arms)
- PTSD: 5 RCTs, 248 pts meta.[3]
  - Right after Tx: SMD scores 1.71-3.36
  - >24 hours: SMD scores 1.23-1.57
- Anxiety[4]
  - 6 RCTS (1 OCD, 2 SAD, 3 PTSD): SAD yes, PTSD improved but NS.
  - 14 RCTs (10 RCTs, 357 pts, in meta): at 24hr SMD=0.44 (broad mix)
- Bipolar[5]
  - 2 RCTs, 33 pts: at 24 hours: Response 38% vs 0%, rest ns

1) Psychopharmacol Bull. 2020;50(4):137-163. 2) Xiong. J Psychiatr Res. 2021;134:57-68. Witt. Aust N Z J Psychiatry. 2020;54(1):29-45.

3) Albuquerque. J Cereb Blood Flow Metab. 2022;42(12):2175-87. 4) Whittaker. Ther Adv Psychopharmacol. 2021;11: 20451253211056743. Hartland. J Psychopharmacol. 2023 Aug;37(8):764-774. 5) Dean. Cochrane 2021; 10: CD011611.

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Psilocybin

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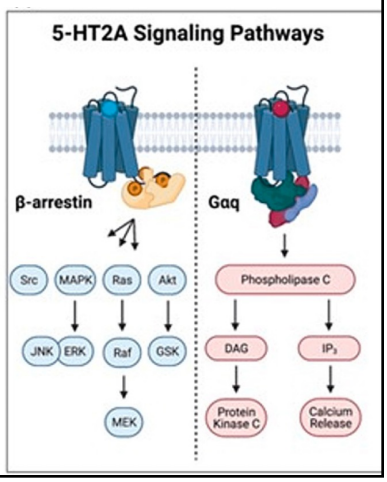
Over 10 Systematic Reviews: To ignore

- 3 Sys Rev+Meta, 6-14 studies (few parallel RCTs), mix conditions/treatments [1-3]
- 2 Sys Rev + Meta 8-9 RCTs (cross-over) include healthy people[4,5]
- 1 Depression 2022 Sys Rev with Meta – 2 RCTs (44 pts). Misses best RCTs.[6]
- 5 Systematic reviews are narrative (last terrible)[7-11]
- 1 Dose response 2023- 4 RCTS (366 pts) depression
  - 50% effect at ~10mg, 95% ~25mg. Curve for AE steeper.[12]



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Psilocybin as Therapy - Systematic Reviews

- Bias: Systematic Review – 10 RCTs (7 RCTs of Psilocybin)[13]
  - 6 of 7 Psilocybin RCTs disclose past psychedelic use: 6%, 45%, 55%, 67%, 92%, 100%
  - Blinding effectiveness reported in 4 of 7. 2 stated "unsuccessful" and 2 report 93-97% patients/study staff new treatment assignment.

1) Kisely. Aust N Z J Psychiatry. 2023;57(3):362-378. 2) Ko. J Affect Disord. 2023;322:194-204. 3) Romeo. J Psychopharmacol. 2020;34(10):1079-85. 4) Galvão-Coelho NL. Psychopharmacology (Berl). 2021;238(2):341-354.
5) Leger. J Psychopharmacol. 2022 Jan;36(1):20-30. 6) Li. J Affect Disord. 2022 Jan 1;296:26-34. 7) van Amsterdam. Expert Opin Drug Saf. 2022;21(6):833-840. 8) IsHak. Innov Clin Neurosci. 2023 Spring;20(4-6):39-48. 9) Hodge. J Psychoactive Drugs. 2023 Jan-Mar;55(1):40-50. 10) Rossi. Expert Opin Drug Saf. 2022 Jun;21(6):761-776. 11)Goel. Cureus. 2022;14(10):e30214. 12) Perez Eur Neuropsychopharmacol. 2023 Aug 7;76:61-76. 13) Hovmand. J Psychopharmacol. 2023 Jul;37(7):649-659.

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Magic Mushroom: Psilocybin for depression

- RCT 59 patients with long-term depression (66% male)
  - Psilocybin 25mg x2 doses q3 wks vs escitalopram 10mg x3wks, then 20mg x3 wks
  - Issues: 2 counsellors/pt x4-6 hours each treatment; >50 outcomes (15 scales)
- Outcomes: At 6 weeks,
  - Change in QIDS (baseline ~15): Psilocybin -8.0 vs escitalopram -6.0, NSS
  - QIDS remission: psilocybin 57% vs escitalopram 28%, NNT=4 (responder NSS)
  - Other depression scales (HAM-D, MADRS): favor psilocybin but NSS
- AE: day 1 psilocybin: headache (43% vs 17%);
  - Week 6 Escit: dry mouth/anxiety (14% vs 0, for either)
- **Bottom-Line**: Psilocybin may have a role in improving moderate to severe depression, but larger and longer trials are needed.

N Engl J Med 2021;384:1402-11.

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Psilocybin for treatment-resistant depression

- RCT: 233 patients, treatment-resistant depression (2-4 trials);
  - Psilocybin 25mg, 10mg, or 1mg x 1dose with psychological support,
- Outcome: MADRS (32 baseline): 25mg -12 better vs 1mg -5.4 better at 3 wks
  - 10mg vs 1mg: no diff (stopped significance testing)
- 25mg dose 'response' (37% vs 18%, NNT=5), remission rates (29% vs 8%, NNT 5)
  - response not sustained at 12wks, compared to 1mg
- Most common AE (day 1): HA, nausea, dizziness, fatigue; suicidal ideation/self-injurious behavior worsened in 25mg (14%) and 10mg (17%) v (9%)

Bottom line: Single-dose psilocybin 25mg (with ++ psychological support) improves depression symptoms at 3wks in patients with a refractory episode. Response not sustained at 12w.

Goodwin. N Engl J Med 2022;387:1637-48.

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Psilocybin monotherapy for Depression

- RCT 104 pts: 25-mg psilocybin vs 100-mg niacin
  - Age 41, 50% male, 22% were tapered off meds
- Outcome: MADRS (35 baseline) score improvement
  - Day 8: 18 better psilocybin and 6 niacin (12 pt diff). Similar at day 43
  - Response: 42% psilocybin vs 11% niacin (NNT=4),
  - AE (Psilocybin vs Niacin): ≥1 Tx related AE 82% vs 44%, most mild & early,
    - Headache 66% vs 24%,nausea 48% vs 6%, visual perceptual (day 1) 44% vs 6%
- **Bottom-Line**: It works, starting at 1 week, and last 6 weeks. Monotherapy but sicker patients (severity & duration).

Raison, JAMA. 2023;330(9):843-853.

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Last Issues: cost

- Cost effectiveness – over 4.5 months (?) – converted from pounds
  - Psilocybin ($10,269-$12,815) vs SSRI ($5,892) – missed days, Tx effect or not, etc
    - "Psilocybin was shown to be cost-effective"
  - Actual: Psilocybin ($6,206-$8,886) vs SSRI ($37)
    - "This analysis was shown to be a fairytale"

McCrone. Psychol Med. 2023 Jun 2:1-8.

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Important Populations: Life Threatening Illness

- 3 RCTs, 92 patients: Beck Depression 2.6 (1.0-4.2) better
  - Anxiety scores also improved.
- 5 RCTs, 132 patients: Anxiety in life threatening illness (2 measures)
  - 1 day: SMD 0.70 or 0.71 & 1 month: SMD 0.73 or 1.04
  - 3 months: SMD 0.60 or ns & 6 months: SMD 1.03 or ns
  - BP max increase 19/9
- No pooled data.
- Bottom-Line: Helps with mood and anxiety effects from Life Threatening Illness (e.g. Cancer), with the usual AE.

Vargas. Biomedicines. 2020 Sep 5;8(9):331. Yu Psychiatry Investig. 2021 Oct; 18(10): 958-967 Maia. J Pain Symptom Manage. 2022 Jun;63(6):e725-e738.

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What we've learned so far?

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Summing up what we know

- Esketamine: Helps ~10% more attain remission (3-4 better MADRS).
  - Short and medium term.
- Ketamine maybe better but as likely just biases in literature.
  - Short term only
- Psilocybin: helps ~20% more attain remission/response (6-12 better MADRS)
  - Short to medium term (3-6 weeks, stopping by 12 weeks)
- Adverse events are plentiful (dissociation, dizziness, etc).
- They cost a fortune and require more resources

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What we don't know

- We don't know much about any of these used longer term (3-6 months +)
  - Ketamine we know less.
  - We don't Esketamine outside clinic.
- Psilocybin we don't know against ECT or Ketamine
- We don't know long-term harms and safety
- We don't know the risks of dependence or how to manage.
- We absolutely need organized tracking of patients on these for monitoring harms.

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Supplemental Content

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Canadian Network for Mood and Anxiety Treatments (CANMAT): Recommendations

- *IV ketamine is efficacious in single infusion studies, but most relapse in 10 days. Limited evidence for course of 6-8 repeated infusions.*
- *Insufficient evidence for relapse prevention. Some protocols suggest tapering infusion for maintenance.*
- *Low evidence for efficacy of oral ketamine or intranasal and sublingual formulations of racemic ketamine. Non-IV formulations should only be used by specialists with ketamine expertise.*

Patient selection

- *IV ketamine is considered a 3rd-line recommendation for adults Treatment-Resistant Depression, includes failed trials of ≥2 first-line antidepressants (differing) classes and ≥1 adjunctive agents.*
- *Insufficient evidence for pediatric and geriatric populations.*
- *Patients informed of benefits and risks of ketamine and limited evidence for relapse prevention.*
- *Relative contraindications include psychotic Sx, poorly controlled hypertension, unstable medical conditions (e.g. CVD/Resp disease), substance use/dependence, and pregnancy/breastfeeding.*
- *Preinfusion assessment includes physical examination and selected lab as indicated.*

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Canadian Network for Mood and Anxiety Treatments (CANMAT): Setting & Monitoring

Treatment settings and personnel

- Provide where cardio/resp monitoring, with medications to manage behavioral or cardiovascular AE. Facility can provide resuscitation with ACLS.
- Clinicians (nurse/doc) have training/qualifications for behavioral/cardio AE & airway support. On-site anesthesiologist generally not needed for depression doses of IV ketamine in low-risk.

Safety monitoring

- Patients warned of potential dissociative effects.
- BP, HR, oximetry, and LOC monitored before/during and 1 hr post ketamine infusions.
- Don't proceed if baseline BP >140/90. Pause infusion if blood pressure >160/100 during treatment; resume if BP below this threshold (+/- BP Tx).
- Suitability for discharge if physiological and mental state baseline.
- Patients should be accompanied for drive home and no driving until next day after good sleep.
- If Maintenance therapy: Assessed for urinary symptoms, cognitive impairment, and substance misuse/dependence.

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Canadian Network for Mood and Anxiety Treatments (CANMAT): Administration

- *Typical protocol for IV ketamine is a dose of 0.5 mg/kg infused over 40 minutes,*
  - *A single infusion, or*
  - *A course of repeated infusions administered 2-3x/wk for 4-8 infusions total.*
- *Common AE include dissociative symptoms, increase HR and BP, drowsiness, blurred vision, headache, restlessness, and nausea.*
- *Concurrent use of benzodiazepines and other anticonvulsant/sedative meds should be avoided (may interfere with response or worsen sedation).*
- *Concurrent antidepressants appear safe and well tolerated (caution with monoamine oxidase inhibitors). An untried antidepressant or adjunctive medicine should be started concurrently or shortly after.*
- *Maintenance ketamine is case-by-case basis and only for individuals who've exhausted other options.*

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Canadian Psilocybin guideline

Mechanism of Action:

- Direct 5HT2A agonist effects
- Bio-psychosocial-spiritual effects of acute mind revealing experience
- Increased brain-derived neurotrophic factor; and neuroplasticity
- Changes in the default mode network
- Potential anti-inflammatory and anti-oxidant effects
- Neurobiological effect of placebo

Rosenblat Can J Psychiatry. 2023 Jan;68(1):5-21.

Acute Effects:

- initial effects ~30 min, peak ~90 min, resolution ~6 h

Common components of **psychotherapy** in trials:

- Prep: build rapport, set intentions, expectations, psychoed
- Monitor dosing: 2 monitors/therapists for support & safety
- Integration: reflecting on psychedelic exp, revisit intentions

Recommendations

- Psychedelics cannot be prescribed outside of a Health Canada approved clinical trial or the special access program (SAP) as of 2022
- A Subsection 56(1) Exemption from the Minister of Health is required pursuant to the Controlled Drugs and Substances Act (CDSA)

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Veterans 2022 Depression Guideline: Ketamine and Psilocybin Recommendations

1. *When choosing an initial pharmacotherapy, we suggest against using: Esketamine, Ketamine, MAOIs, Nefazodone, &TCAs*
2. *For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine for augmentation.*
   - *"Ketamine lacks long-term and most trials were ≤7 days follow-up. Esketamine has risk evaluation and mitigation strategy requirements, which include requirements for pharmacy, health care setting certification, and mandatory monitoring for 2 hours after treatment"*
3. *Given the limited Information on the safety and efficacy of psilocybin, we recommend against using this agent for depression outside a research setting.*

McQuaid. Ann Intern Med. 2022;175(10):1440-51.

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