New Research in the Treatment of Major Depressive Disorder

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No disclosures to report

Learning Objectives

1. Define depression, and describe the epidemiology, etiology, and pathophysiology of Major Depressive Disorder (MDD)
2. Outline DSM-5 criteria for diagnosing Major Depressive Disorder, and define treatment resistant depression
3. List first line and second line pharmacological treatment options for Major Depressive Disorder, as per CANMAT guidelines
4. Using the knowledge achieved from prior objectives, apply this learning to evaluate the potential roles of alternative therapies in treatment resistant depression

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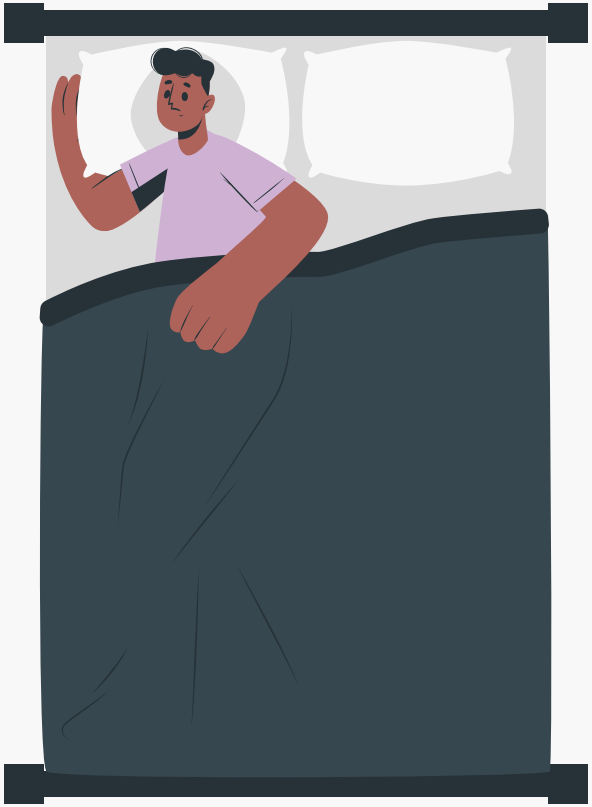


01

ABOUT DEPRESSION

Definitions, Epidemiology, Etiology, Signs & Symptoms

What is **depression**?

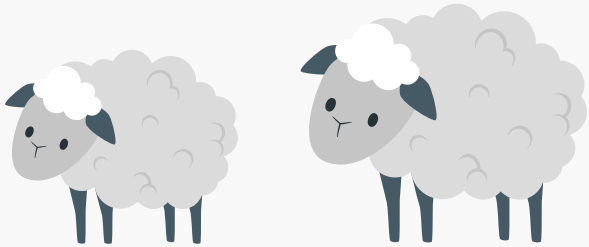
Depression is characterized by persistent sadness and a lack of interest or pleasure in previously rewarding or enjoyable activities. It can also effect:

- Sleep
- Appetite
- Concentration

Depression [Internet]. [cited 2023 Mar 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression

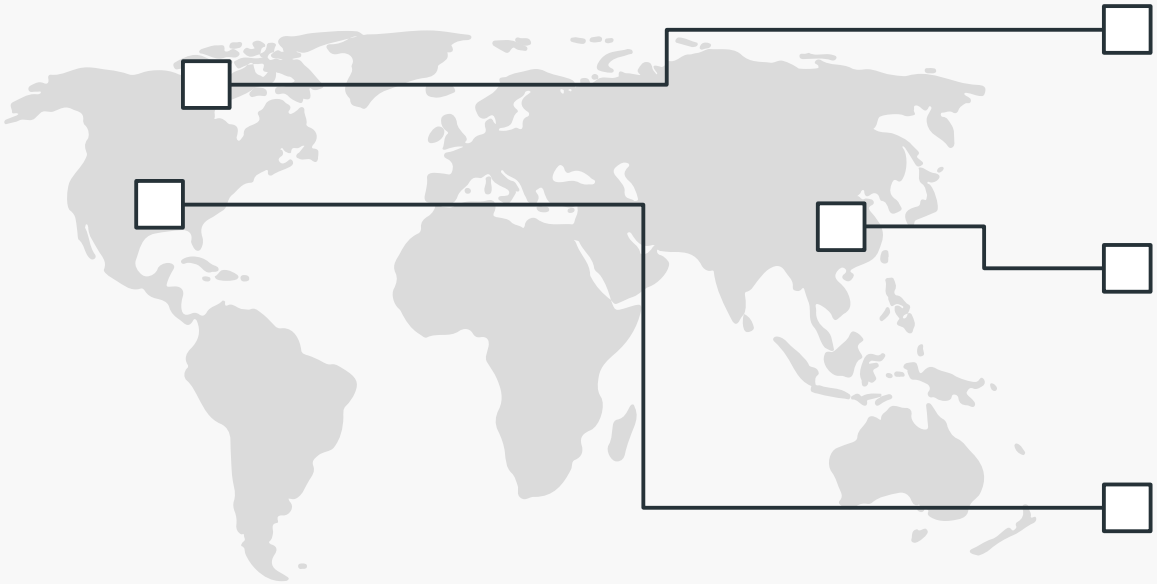
1,500,000+

Canadians aged 15+ years experienced a major depressive episode in 2016.



Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. Can J Psychiatry. 2016 Sep;61(9):510–23.

Lifetime Prevalence of MDD



Canada
11.3%

China
~4%

USA
~16%

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. Can J Psychiatry. 2016 Sep;61(9):510–23.

WHAT CAUSES **DEPRESSION**?

Biological

Genetic, neurological, hormonal factors

Psychological

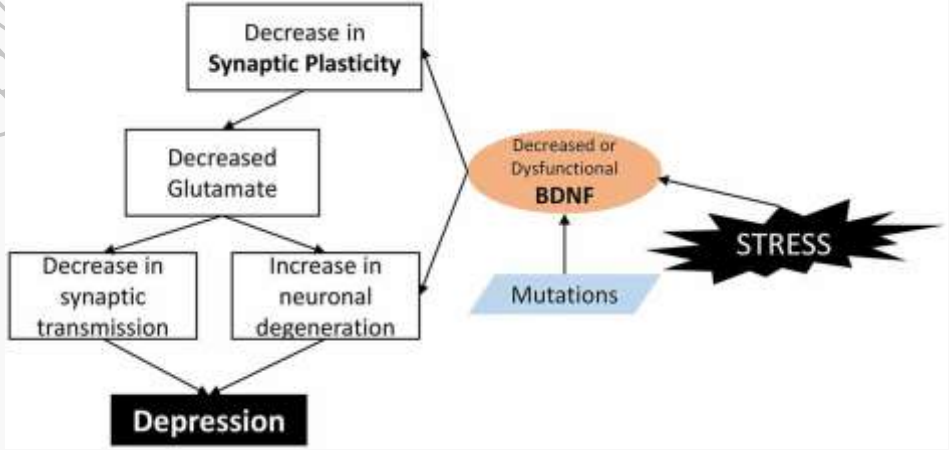
Personality factors

Environmental

Acute life events, childhood stressors

National Research Council (US) and Institute of Medicine (US) Committee on Depression PP, England MJ, Sim LJ. The Etiology of Depression [Internet]. Depression in Parents, Parenting, and Children: Opportunities to Improve Identification, Treatment, and Prevention. National Academies Press (US); 2009 [cited 2023 Mar 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK215119/

Neurotrophin Hypothesis of Depression

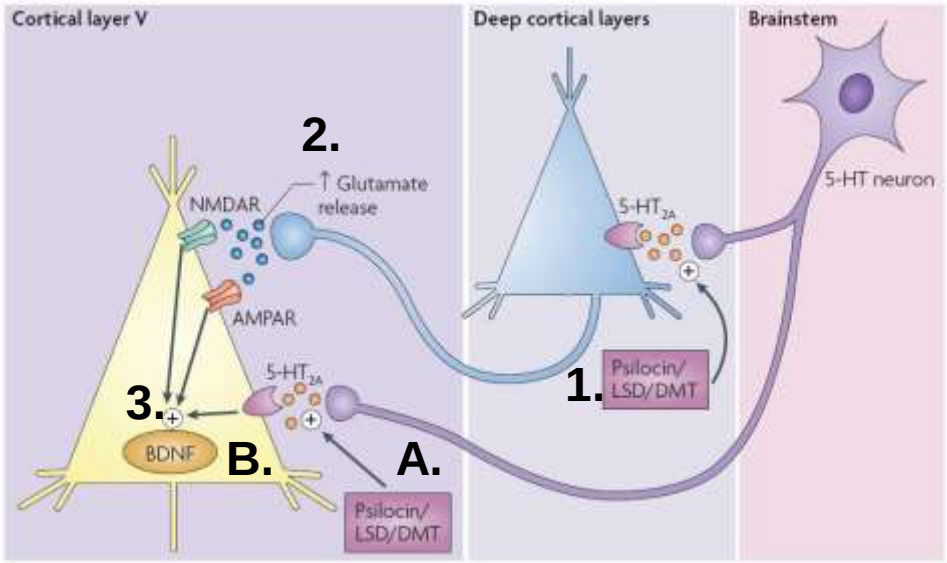


BDNF= Brain Derived Neurotrophic Factor

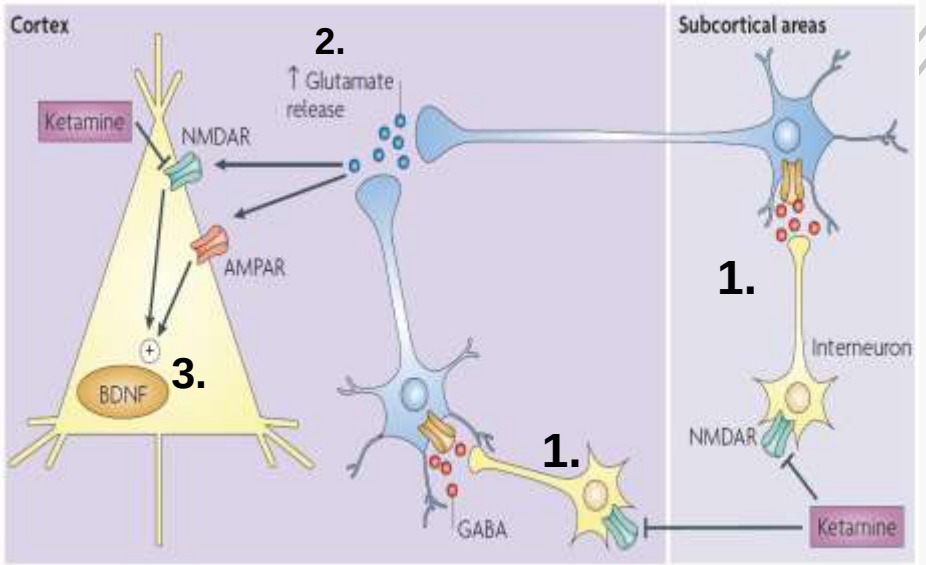
- Role:
  - Maintenance & survival of neurons: neurogenesis, proliferation, migration, maintenance of the CNS
  - Synaptic plasticity: modulate strength and number of synaptic connections and neurotransmission

Yang T, Nie Z, Shu H, Kuang Y, Chen X, Cheng J, et al. The Role of BDNF on Neural Plasticity in Depression. Front Cell Neurosci [Internet]. 2020 [cited 2023 Mar 21];14. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2020.00082
Dwivedi Y. Brain-derived neurotrophic factor: role in depression and suicide. Neuropsychiatr Dis Treat. 2009;5:433–49.

Psilocybin MOA



Ketamine MOA



Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat Rev Neurosci. 2010 Sep;11(9):642–51.

Signs & Symptoms

PHYSICAL SYMPTOMS

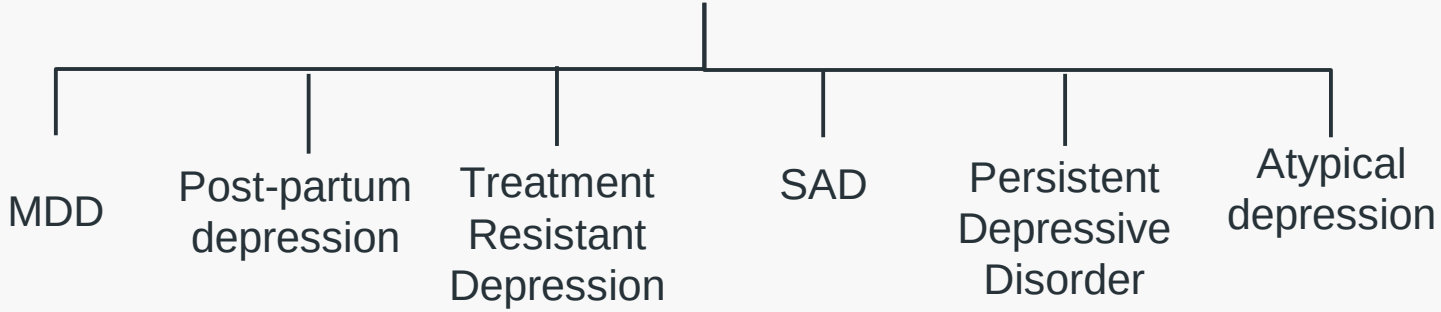
Fatigue, changes in appetite, lack of concentration, sleep disturbances

PSYCHOLOGICAL SYMPTOMS

Depressed mood, feelings of guilt, loss of interest & pleasure, suicidal ideation

Depressive Disorders. In: Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association Publishing; 2022 [cited 2023 Mar 17]. (DSM Library). Available from: https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425787.x04_Depressive_Disorders

Types of Depressive Disorders



Depressive Disorders. In: Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association Publishing; 2022 [cited 2023 Mar 17]. (DSM Library). Available from: https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425787.x04_Depressive_Disorders

02

DSM-5 Criteria: Diagnosis of **MDD**

DSM-5 CRITERIA

≥5 symptoms during the same two week period that are a change from previous functioning

- **Depressed mood**
- **Loss of interest/pleasure**
- Weight loss or gain
- Insomnia or hypersomnia
- Decreased concentration
- Psychomotor agitation or slowing
- Fatigue
- Feeling worthless
- Suicide/ideations

Depression Rating Scales

- **Montgomery-Asberg Depression Rating Scale (MADRS)**
  - Evaluates depression severity
  - 10 items
    - Overall score: 0-60
      - 0-6= symptoms absent
      - 7-19= mild depression
      - 20-34= moderate depression
      - 35-60= severe depression
  - Evidence that an improvement of two points or more on the MADRS is considered clinically relevant
    - 6-9 point change = clinically meaningful change

VALIDITY OF OUTCOME MEASURES Montgomery-Asberg Depression Rating Scale (MADRS) [Internet]. Canada's Drug and Health Technology Agency; 2016 [cited 2023 Mar 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409740/

03

Treatment of **MDD**

TREATMENT

Psychotherapy

CBT, mindfulness

Medications

SSRIs, SNRIs, TCAs, etc,

Exercise

Sleep Hygiene

Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016 Sep 1;61(9):540–60.

CANMAT Guidelines

- **First Line, Level I Evidence**
  - SSRIs: Citalopram, Fluoxetine, Sertraline, etc
  - SNRIs: Venlafaxine, Duloxetine, Desvenlafaxine
  - NDRIs: Buproprion
  - Others: Mirtazapine, Vortioxetine
- **Second line, Level I Evidence**
  - TCAs: Amitriptyline, Clomipramine, etc
  - Antipsychotics: Quetiapine
  - Trazodone
  - Reversible MAO-A inhibitor: Moclobamide

Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016 Sep 1;61(9):540–60.

Treatment Resistant Depression

- Inadequate response to 2 or more antidepressants

- Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial
  - Incidence of remission becomes progressively lower with each course of treatment
    - First course: 36.8%
    - Second course: 30.6%
    - Third course: 13.7%
    - Fourth course: 13%

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. Am J Psychiatry. 2006 Nov;163(11):1905–17.

04

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2022 VOL. 387 NO. 18

Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Bird, R.E. Blom, C. Brennan, D. Brusch, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, B.W. Dunlop, K. Eisen, D. Feifel, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, J. Kamphuis, J. Kawasaki, J.R. Kelly, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. Licht, J.L. Maples-Keller, J. Mars, L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirow, S. Mistry, T. Mletzko-Crowe, L.N. Modlin, R.E. Nielsen, E.M. Nielson, S.R. Offerhaus, V. O'Keane, T. Páleníček, D. Printz, M.C. Rademaker, A. van Reemst, F. Reinholdt, D. Repantis, J. Rucker, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. Somers, S.C. Stansfield, D. Sterling, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywema, S. Zisook, and E. Malievskaia

Methods

- Double-blind trial
- Setting: 22 sites, 10 countries
- Objective: identify an acceptable efficacious dose and assess the safety of a synthetic, proprietary formulation of psilocybin, administered together with psychological support in patients with a treatment resistant major depressive episode.
- Primary efficacy endpoint: change in baseline MADRS total score at 3 weeks
    - Secondary:
        - Response
        - Remission
        - Sustained response

Methods

- Recruitment
  - Through referrals, advertisements, word of mouth
- Inclusion
  - 18 years or older
  - Met criteria for treatment resistant depression
  - Current episode of depression, unresponsive to 2-4 adequate trials
- Exclusion
  - Psychotic features

Methods

- Trial Design
  - 3-6 week run in period to taper psychoactive medications
  - Randomized in 1:1:1 ratio to receive psilocybin at 25mg, 10mg, or 1mg (control)
  - Administration session day (Day 1)
    - Lasted 6-8h
    - Administration rooms: nonclinical, calming atmosphere
  - Follow up
    - Followed participants for 12 weeks post treatment
    - MADRS scale administered at baseline, day 2, weeks 1, 3, 6, 9, and 12
    - Safety assessments: vitals, urine drug screening, 12-lead ECG
    - Adverse events evaluated at every visit

Participants

- 428 screened
- 233 enrolled, underwent randomization, and received psilocybin treatment
  - 79 in 25mg group
  - 75 in 10mg group
  - 79 in 1mg group

Baseline Characteristics

Characteristic	Psilocybin 25mg	Psilocybin 10mg	Psilocybin 1mg
Female	56%	55%	46%
White race	89%	96%	92%
Failed 2 treatments for current depressive episode	84%	83%	80%
Failed 3-4 treatments for current depressive episode	15%	15%	18%
MADRS total score-Severe (>/= 31)	58%	72%	75%

Statistical Analysis

- 216 participants (72 per group) would provide 90% power
- Efficacy analysis: modified ITT
- Hierarchical test procedure for primary and three secondary efficacy endpoints
- Descriptive statistic used to analyze safety data

Results: Efficacy Endpoints

- **Primary efficacy endpoint: Change from baseline to week 3 in MADRS total score**

	Psilocybin 25mg	Psilocybin 10mg	Psilocybin 1mg
Least squares mean	-12.0 (CI -14.6 to -9.3)	-7.9 (CI -10.6 to -5.2)	-5.4 (CI -8.1 to -2.7)
Least squares mean difference vs 1mg	-6.6 (CI -10.2 tp -2.9) p<0.001	-2.5 (CI -6.2 to 1.2) P= 0.18	--

Change from baseline to week 3 in MADRS total score

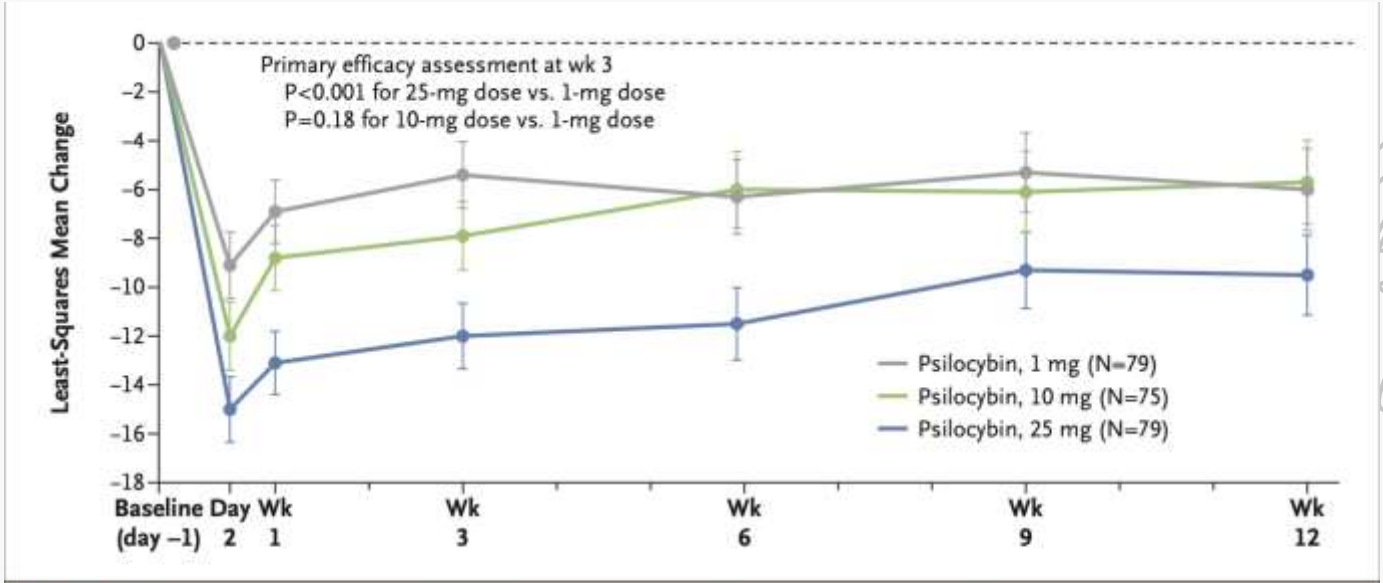


Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).

Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

Secondary Outcomes

- **Response at 3 weeks, defined as a decrease of at least 50% from baseline in the MADRS total score**
  - 25mg vs 1mg: OR 2.9 (CI 1.2-6.6)
  - 10mg vs 1mg: OR 1.2 (CI 0.5-3)
- **Remission at week 3 (MADRS total score ≤10)**
  - 25mg vs 1mg: OR 4.8 (CI 1.8-12.8)
  - 10mg vs 1mg: OR 1.2 (CI 0.4-3.9)
- **Sustained response at week 12 (meeting response criteria at week 3 and all subsequent visits)**
  - 25mg vs 1mg: OR 2.2 (CI 0.9-5.4)

Results: **Safety Endpoints**

- **Any adverse event, Day 1:**
  - 25mg group: 61%
  - 10mg group: 47%
  - 1mg group: 38%
- **Any serious adverse event, Day 2- Week 3**
  - Suicidal ideation: 3% in both treatment arms
- **Any serious adverse event, week 3-12**
  - Suicidal behavior: 4% in 25mg group

Strengths & Weaknesses

- **Strengths**
  - Minimized performance bias- Randomized, double blind
  - Validated scale (MADRS)
  - Clinically significant outcome achieved in 25mg arm
  - Least squares best fit- minimize outliers
- **Weaknesses**
  - Selection bias
  - MADRS scores significantly lower at baseline in 25mg group (58% vs 72%)
  - Generalizability- ~90% white
  - Allowed participants to restart antidepressants during trial
  - Applicability- synthetic, pharmaceutical grade psilocybin availability?

05

Intranasal Ketamine for Depression in Adults: A Systematic Review and Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials

*Dongjiao An, Changwei Wei, Jing Wang and Anshi Wu**

Department of Anesthesiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Methods

- **Study Design**: Systematic Review & Meta-Analysis of randomized, double blind, placebo controlled trials with allocation concealment evaluating intranasal ketamine in MDD
- **Search**: Medline, EMBASE, Cochrane
- **Study period**: Material up until April 1, 2022
- **Objective**: Assess efficacy and safety of intranasal ketamine in the treatment of MDD
- **Primary efficacy endpoint**: Depressive symptoms as assessed by MADRS
- **Secondary**: Clinical response, clinical remission

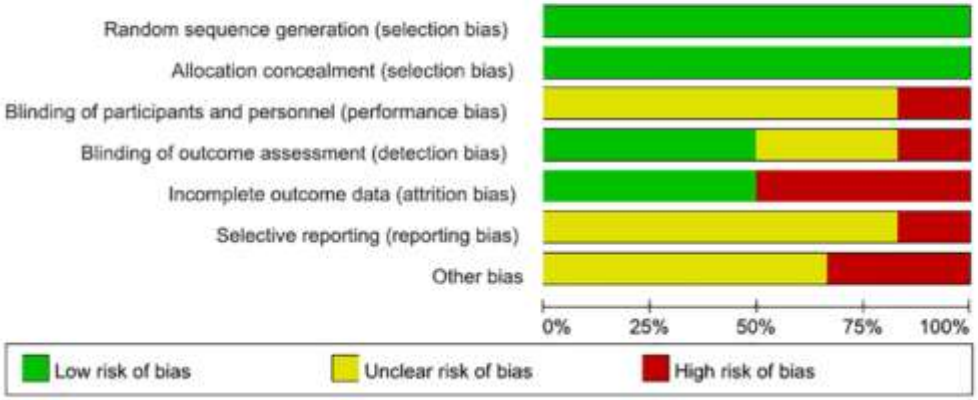
Methods

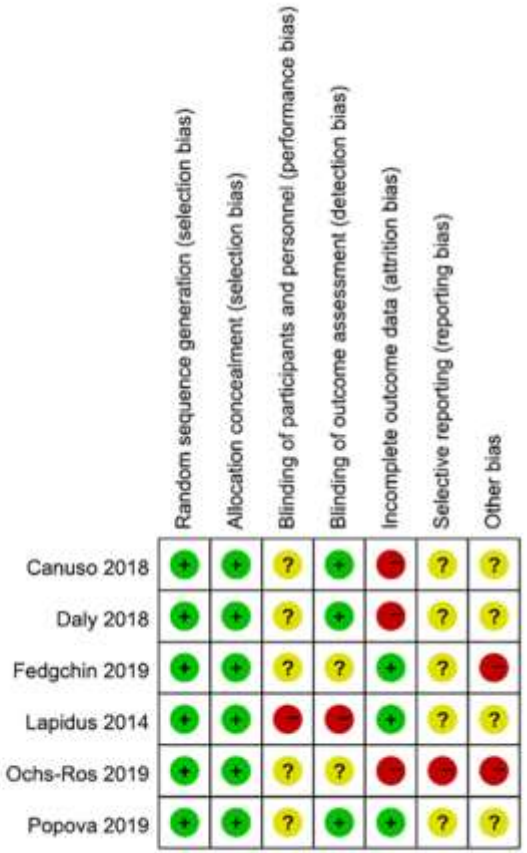
- Studies included
  - **Study validity**: random allocation; allocation concealment; double-blind; placebo-controlled; parallel or cross-over design; clinician-rated primary outcome measure; and ≥10 subjects total number.
  - **Sample characteristics**: subjects (age ≥ 18 years) with a clear diagnosis of a primary major depressive episode (only unipolar) according to DSM-IV criteria.
  - **Treatment characteristics**: intranasal administration of ketamine or esketamine (use in combination with other antidepressants was permitted).
  - Publication had to be written in English

- Studies excluded
  - “Narrow” diagnoses
  - ~~Ketamine as an electroconvulsive therapy adjunct.~~

Methods

- Data extraction
  - 2 independent observers
  - Collect data on:
    - Study characteristics
    - Ketamine dose/formulation
    - Control condition
    - Primary & secondary outcomes
    - Safety assessments
- Bias Risk assessment
  - 2 reviewers, with a third if needed to resolve any disagreements
  - Used Cochrane Handbook for Systematic Reviews of Interventions


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias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Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Canuso 2018
Daly 2018
Fedgchin 2019
Lapidus 2014
Ochs-Ros 2019
Popova 2019

Characteristics of Studies

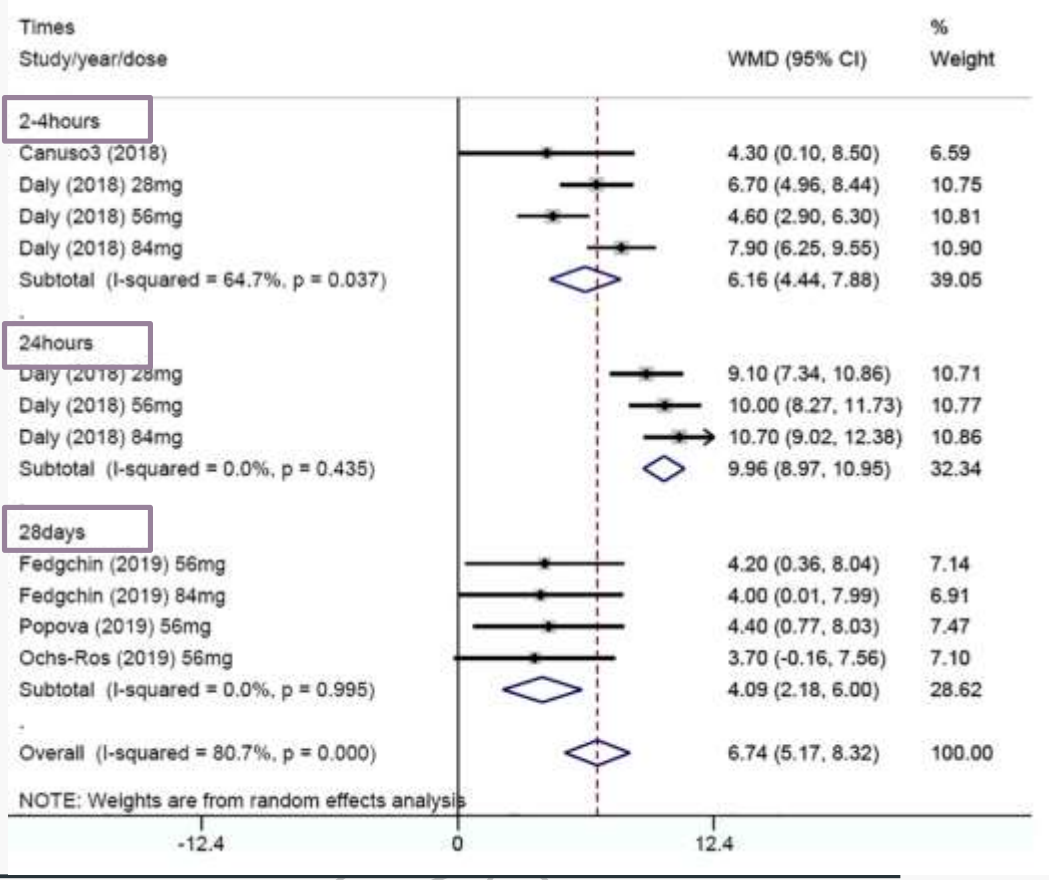
Study	Design	Patients	Sample	Intervention	Comparator	Primary outcome	Secondary outcomes
Lapidus et al., 2014	Crossover RCT, DB	21–65 years, MDD, TRD	18	50 mg of racemic ketamine (once per week)	0.9% saline solution	Change from baseline in MADRS total score to 24 h	Response rate at 24 h safety
Canuso et al., 2018	RCT, DB	19–64 years, MDD	66	84 mg of esketamine (56 mg if intolerance) twice weekly for 4 weeks	Placebo	Change from baseline in MADRS total score to 4 h, 24 h, and 25 day	Remission rate at 24 h, 25 day safety
Daly et al., 2018	RCT, DB, phase 2	20–64 years, TRD	67	28, 56, or 84 mg of esketamine (twice weekly)	Water for injection	Change from baseline in MADRS total score to 2, 24 h	Response rate at 24 h, remission rate at 24 h safety
Fedgchin et al., 2019	RCT, DB, phase 3	18–64 years, TRD	346	56 or 84 mg of esketamine (twice per week) plus OA	Placebo plus OA	Change from baseline in MADRS total score to day 28	Response rate at 24 h safety
Popova et al., 2019	RCT, DB, phase 3	18–64 years, TRD	223	56 or 84 mg of esketamine (twice per week) plus OA	Placebo plus OA	Change from baseline in MADRS total score to day 28	Response rate at 24 h, 28 day, remission rate at 28 day safety
Ochs-Ross et al., 2019	RCT, DB, phase 3	≥65 years, TRD	138	28, 56, or 84 mg of esketamine (twice per week, flexible dose) plus OA	Placebo plus OA	Change from baseline in MADRS total score to day 28	Response rate at 28 day, remission rate at 28 day safety

Statistical Analyses

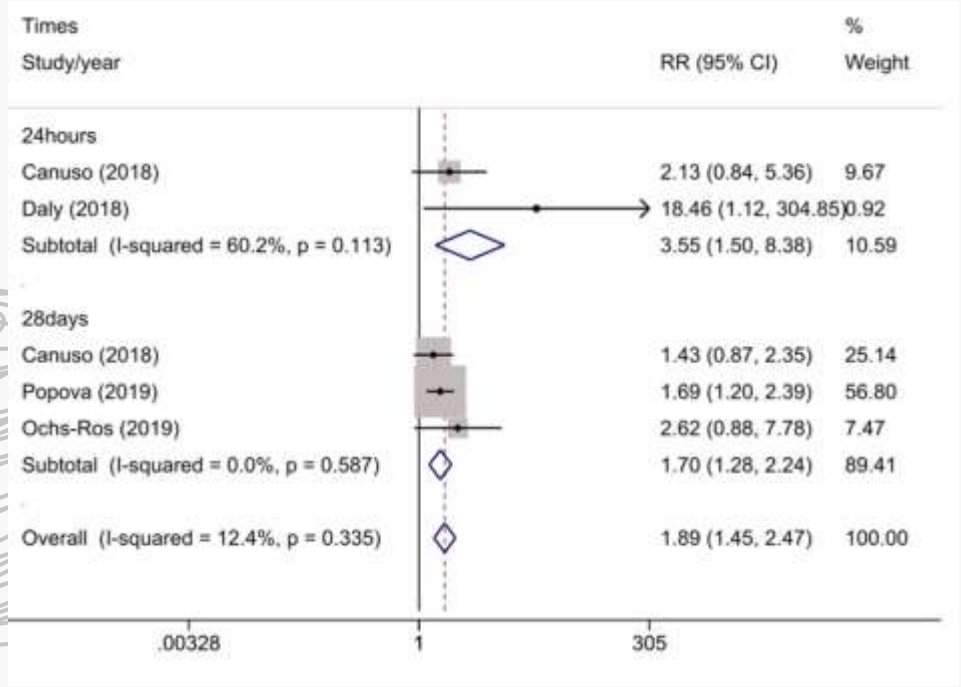
- Relative Risk (RR) + 95% CI for dichotomous outcomes (e.g. ADRs- headache, nausea)
- Weighted Mean Difference (WMD) + 95% CI for continuous outcomes

Results- **Efficacy**

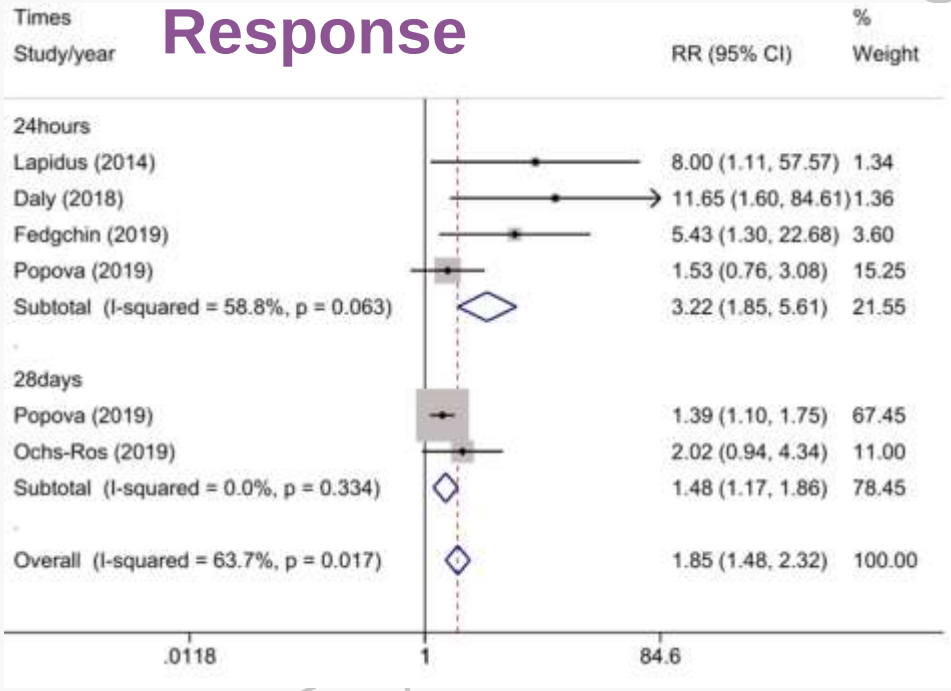
- Weighted mean difference in MADRS score decreased from baseline after 2–4 h, 24 h, and 28 days



Clinical Rates of



Clinical Rates of **Response**



Results- **Safety Analysis**

Adverse Event	Sample	RR (95% CI)
Dizziness	895	3.30 (2.20-4.95)
Dissociation	895	5.68 (3.34-9.65)
Dysgeusia	895	1.37 (0.99-1.89)
Vertigo	895	7.05 (3.56-13.93)
Nausea	895	3.25 (2.19-4.84)

Strengths & Weaknesses

Strengths

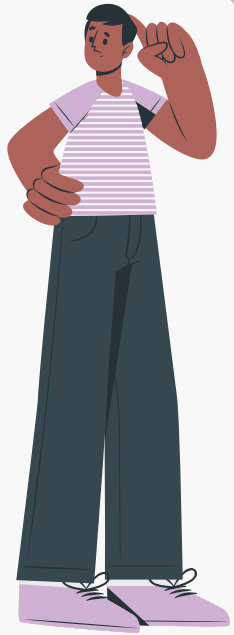
- Appropriate search strategy
- Appropriate inclusion/exclusion criteria for the research question
- Cochrane Risk of Bias Assessment
- Used 2 reviewers

Weaknesses

- Quality of studies- Risk of bias
- Heterogeneity?
- Placebo controlled…?→ performance bias
- “Real world” feasibility
- Short duration of time relative to duration of MDD
- Combined with oral antidepressant?

Conclusions

- Psilocybin and intranasal Ketamine show promising results in treatment resistant depression, at the cost of potentially bothersome adverse events
- Role in therapy: Treatment resistant depression, when 3-4 treatments have failed
- The feasibility and access to these treatments may cause issues
    - Eskatamine = $278/dose
    - Pharmaceutical grade psilocybin?



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THANKS!

Do you have any questions?

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