TREATMENT OPTIONS FOR MAJOR DEPRESSIVE DISORDER

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WHAT KEEPS ME BUSY?

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Disclosures

Relationships with commercial interests:

- **Grants/Research Support:** *None*
- **Speakers Bureau/Advisory Boards Honoraria:** *Lilly, AA Pharma, HLS, Lundbeck, Allergan, Astra Zeneca, Mylan, BMO-Otsuka, Shire/Takeda, Janssen, Sunovion, Pfizer, and Purdue.*
- **Consulting Fees:** *None*

Potential Conflict(s) of Interest

- *This program has not received financial support from any pharmaceutical organizations.*

OBJECTIVES

1. *Overview of Major Depressive Disorder and factors affecting risk of suicide.*
2. *Current algorithm in selection of treatment options.*
3. *Discussion of the most recent Meta-Analysis in the Lancet.*
4. *Options when treating concurrent addiction and depression.*

IS DEPRESSION A NEW ILLNESS OF THE PAST CENTURY?

- *Old Testament Story of King Saul describes a depressive syndrome.*
- *The Suicide of Ajax in Homer's Iliad.*
- *Hippocrates described melancholia as a medical condition as the condition was thought to be caused by melan 'black' and chole 'bile' in Greek.*

WHAT'S THE BIG DEAL ABOUT DEPRESSION?

Social burden

11.3% of Canadians will experience a major depressive episode in their lifetime[1]

All Canadians are indirectly affected through family, friends, or colleagues[2]

Economic burden

$51 billion: estimated annual burden of mental illness on the Canadian economy[3]

Patient burden

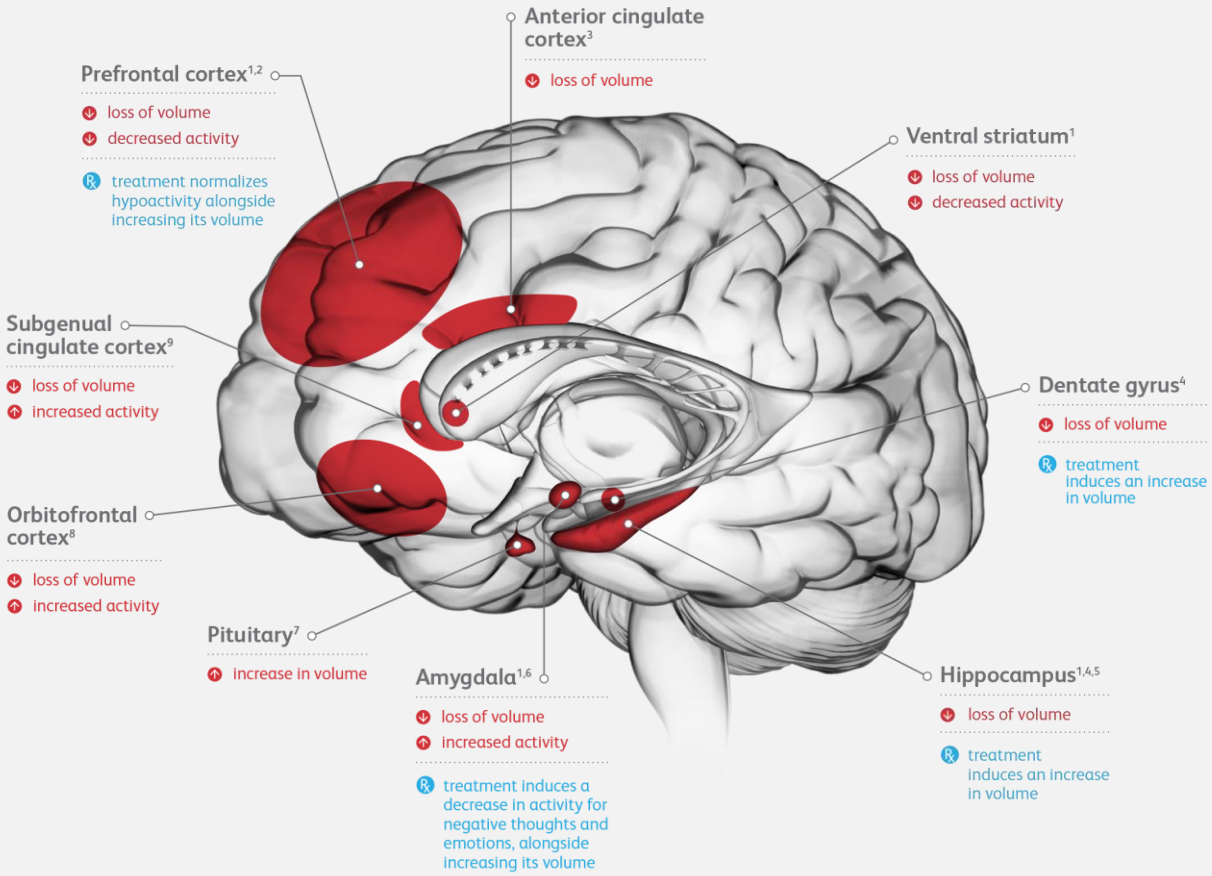
Up to 50% of patients with Major Depressive Disorders (MDD) are untreated[4.5]

Problems linked to MDD such as social dysfunction can result in decreased income due to workplace absenteeism, underperformance or unemployment[6]

1. Lam RW et al. Can J Psychiatry 2016;61(9):510-23; 2. Health Canada (2002). www.phac-aspc.gc.ca/publicat/miic-mmac/index-eng.php; 3. Canadian Mental Health Association (2011). www.cmha.ca/public-policy/research-reports; 4. Patten. Can J Psychiatry. 2006;51:84-90; 5. Lecrubier. J Clin Psychiatry. 2007; 68 Suppl 2: 36-41; 6. Lepin JP et al. Neuropsychiatr Dis Treat. 2011; 7(Suppl 1): 3–7.

STRUCTURAL AND FUNCTIONAL EFFECTS OF MDD AND ANTIDEPRESSANT TREATMENT ON DIFFERENT BRAIN REGIONS

A comprehensive visual comparison



1. Russo SJ et al. Nat Rev Neurosci. 2013;14(9):doi:10.1038/nrn3381; 2. Si X et al. Neuropsychopharmacology. 2004;29(11):2088-2096; 3. Yucal K et al. Neuropsychopharmacology. 2008;33:3157-3163; 4. Malykhin NV et al. J Psychiatry Neurosci. 2010;35(5):337-343; 5. Sheline YI et al. Am J Psychiatry. 2003;160(8):1516-1518; 6. Hamilton JP et al. Mol Psychiatry. 2008;13(11):993-1000; 7. Rubin RT et al. Arch Gen Psychiatry. 1995;52(3):213-218; 8. Scheuerecker J et al. J Psychiatry Neurosci. 2010;35(5):311-320; 9. Drevets WC et al. CNS Spectr. 2008;13(8):663–681.

GRAND CHALLENGES IN GLOBAL MENTAL HEALTH: THE BURDEN OF DEPRESSION

Rank	Cause – Worldwide	DALYs (millions)	Cause – High-income Countries	DALYs (millions)	Cause – Low- and Middle-income Countries	DALYs (millions)
1	Unipolar depressive disorders	65.5	Unipolar depressive disorders	10.0	Unipolar depressive disorders	55.5
2	Alcohol-use disorders	23.7	Alzheimer's and other dementias	4.4	Alcohol-use disorders	19.5
3	Schizophrenia	16.8	Alcohol-use disorders	4.2	Schizophrenia	15.2
4	Bipolar affective disorder	14.4	Drug-use disorders	1.9	Bipolar affective disorder	12.9
5	Alzheimer's and other dementias	11.2	Schizophrenia	1.6	Epilepsy	7.3
6	Drug-use disorders	8.4	Bipolar affective disorder	1.5	Alzheimer's and other dementias	6.8
7	Epilepsy	7.9	Migraine	1.4	Drug-use disorders	6.5
8	Migraine	7.8	Panic disorder	0.8	Migraine	6.3
9	Panic disorder	7.0	Insomnia (primary)	0.8	Panic disorder	6.2
10	Obsessive-compulsive disorder	5.1	Parkinson's disease	0.7	Obsessive-compulsive disorder	4.5
11	Insomnia (primary)	3.6	Obsessive-compulsive disorder	0.6	Post-traumatic stress disorder	3.0
12	Post-traumatic stress disorder	3.5	Epilepsy	0.5	Insomnia (primary)	2.9
13	Parkinson's disease	1.7	Post-traumatic stress disorder	0.5	Multiple sclerosis	1.2
14	Multiple sclerosis	1.5	Multiple sclerosis	0.3	Parkinson's disease	1.0

DALY: Disability-Adjusted Life-Year

Collins et al. Grand Challenges in Global Mental Health. Nature. 2011;475:27-30.

PRESENCE OF RESIDUAL SYMPTOMS ASSOCIATED WITH MORE SEVERE AND LONG-TERM DISEASE BURDEN

- *Subjects that recovered* **asymptomatically** *remained relapse/recurrence-free* **4.2 times longer** *than those with residual subsyndromal symptoms of depression (SSD)*

- *SSD was associated with significantly:*
  - *longer and more severe episodes*
  - *more symptoms of illness*
  - *increased long-term psychosocial dysfunction*
  - *greater depressive illness burden during the following 10–20 years*

- **Asymptomatic resolution was the strongest predictor of remaining relapse/recurrence-free**
  (e.g., vs. age of onset, number of prior episodes, etc.)

Judd LL *et al. J Clin Psychiatry* 2016; 77(8):1065-73.

SUICIDE RISK FACTORS

- Previous suicide attempt
- Mental illness, such as depression
- Social isolation
- Criminal problems
- Financial problems
- Impulsive or aggressive tendencies
- Job problems or loss
- Legal problems
- Serious illness
- Substance use disorder

Centres for Disease Control and Prevention. https://www.cdc.gov/suicide/factors/index.html

SUICIDE RISK FACTORS

- **Relationship:**
- Adverse Childhood Events as child abuse and neglect
- Bullying
- Family history of suicide
- Relationship problems such as a break-up, violence, or loss
- Sexual violence
- **Community:**
- Barriers to health care
- Cultural and religious beliefs such as a belief that suicide is noble resolution of a personal problem
- Suicide cluster in the community
- **Societal:**
- Stigma associated with mental illness or help-seeking
- Easy access to lethal means among people at risk (e.g. firearms, medications)
- Unsafe media portrayals of suicide

Centres for Disease Control and Prevention. https://www.cdc.gov/suicide/factors/index.html

SUICIDE PROTECTIVE FACTORS

- Coping and problem-solving skills
- Cultural and religious beliefs that discourage suicide
- Connections to friends, family, and community support
- Supportive relationships with care providers
- Availability of physical and mental health care
- Limited access to lethal means among people at risk

Centres for Disease Control and Prevention. https://www.cdc.gov/suicide/factors/index.html

CANMAT CLINICAL GUIDELINES: RECOMMENDED NON-PHARMACOLOGIC FIRST-LINE TREATMENTS

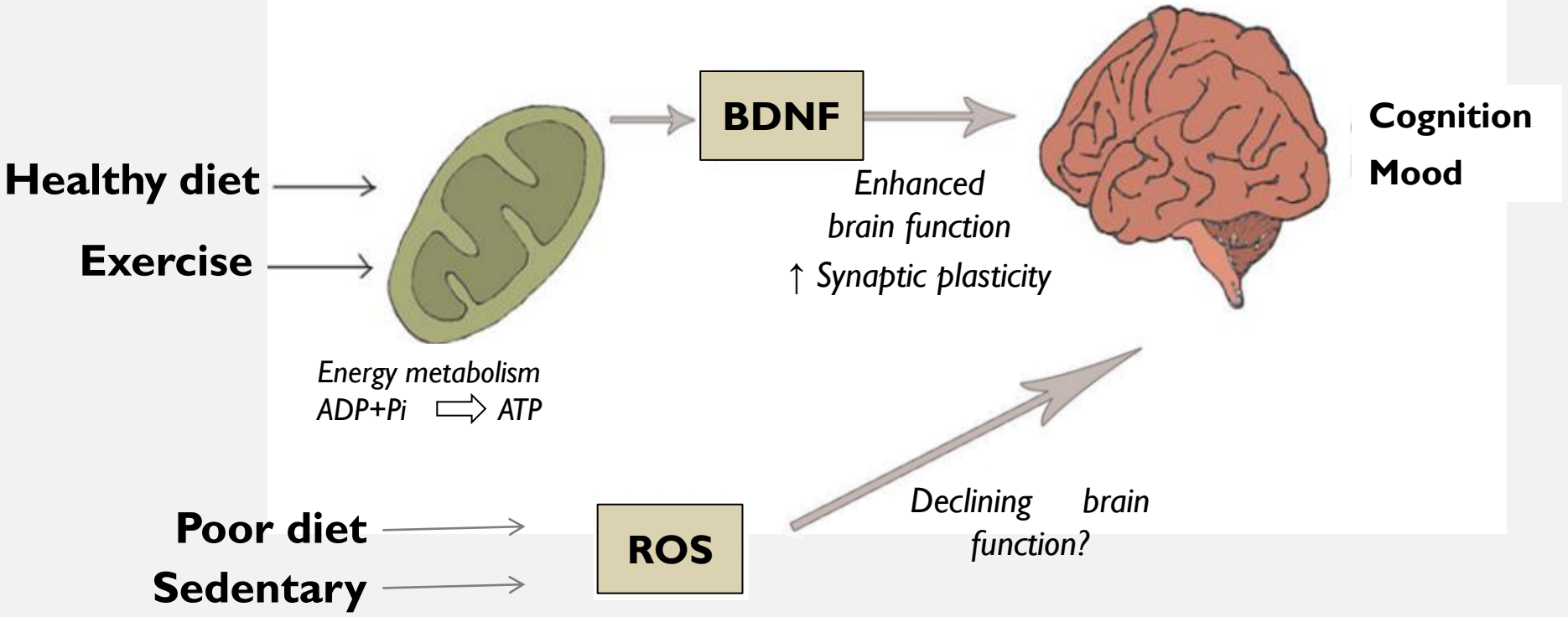
Modality	Recommendation
Complementary and alternative medicine treatments[1]	
Exercise	*Monotherapy for mild to moderate MDD*
Light therapy	*Monotherapy for seasonal (winter) MDD*
St. John's wort	*Monotherapy for mild to moderate MDD*
Psychological treatments[2]	
Cognitive-behavioural therapy (CBT)	*Acute and maintenance (relapse prevention) phases of treatment*
Interpersonal therapy (IPT)	*Acute phase of treatment*
Behavioural activation (BA)	*Acute phase of treatment*
Mindfulness-based cognitive therapy (MBCT)	*Maintenance (relapse prevention) phases of treatment*

CANMAT, Canadian Network for Mood and Anxiety Treatments; MDD, major depressive disorder.

1. Ravindran AV, et al; CANMAT Depression Work Group. Can J Psychiatry 2016;61(9):576-87.
2. Parikh SV, et al; CANMAT Depression Work Group. Can J Psychiatry 2016;61(9):524-39.

LIFESTYLE MODIFICATIONS

Healthy diet and regular physical activity can regulate energy metabolism, reduce inflammation and ROS, and increase BDNF



ADP, adenosine diphosphate; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; P_i, orthophosphate; ROS, reactive oxygen species.

Adapted from: Gomez-Pinilla F, Nguyen TT. Nutr Neurosci. 2012;15(3):127-33.

WHAT ARE CANMAT RECOMMENDATIONS FOR FIRST-LINE ANTIDEPRESSANTS?

Agent	Mechanism	Dose
Agomelatine	MT_1 and MT_2 agonist; $5HT_2$ antagonist	25–50 mg
Bupropion	NDRI	150–300 mg
Citalopram	SSRI	20–40 mg
Desvenlafaxine	SNRI	50–100 mg
Duloxetine	SNRI	60 mg
Escitalopram	SSRI	10–20 mg
Fluoxetine	SSRI	20–60 mg
Fluvoxamine	SSRI	100–300 mg
Mianserin	α_2 antagonist; $5HT_2$ antagonist	60–120 mg
Milnacipran	SSRI	100 mg
Mirtazapine	α_2 antagonist; $5HT_2$ antagonist	15–45 mg
Paroxetine	SSRI	20–50 mg*
Sertraline	SSRI	50–200 mg
Venlafaxine	SNRI	75–225 mg
Vortioxetine	SSRI; $5HT_{1A}$ agonist; $5HT_{1B}$ partial agonist; $5HT_{1D}$, $5HT_{3A}$, and $5HT_7$ antagonist	10–20 mg

* 25–62.5 mg for CR version

CANMAT. Can J Psychiatry. 2016;61(9):540–560.

CANMAT-RECOMMENDED ADJUNCTIVE MEDICATIONS

First-line Recommendations

Agent	Level of Evidence	Dose
Aripiprazole	*Level 1*	*2–15 mg*
Quetiapine	*Level 1*	*150–300 mg*
Risperidone	*Level 1*	*1–3 mg*

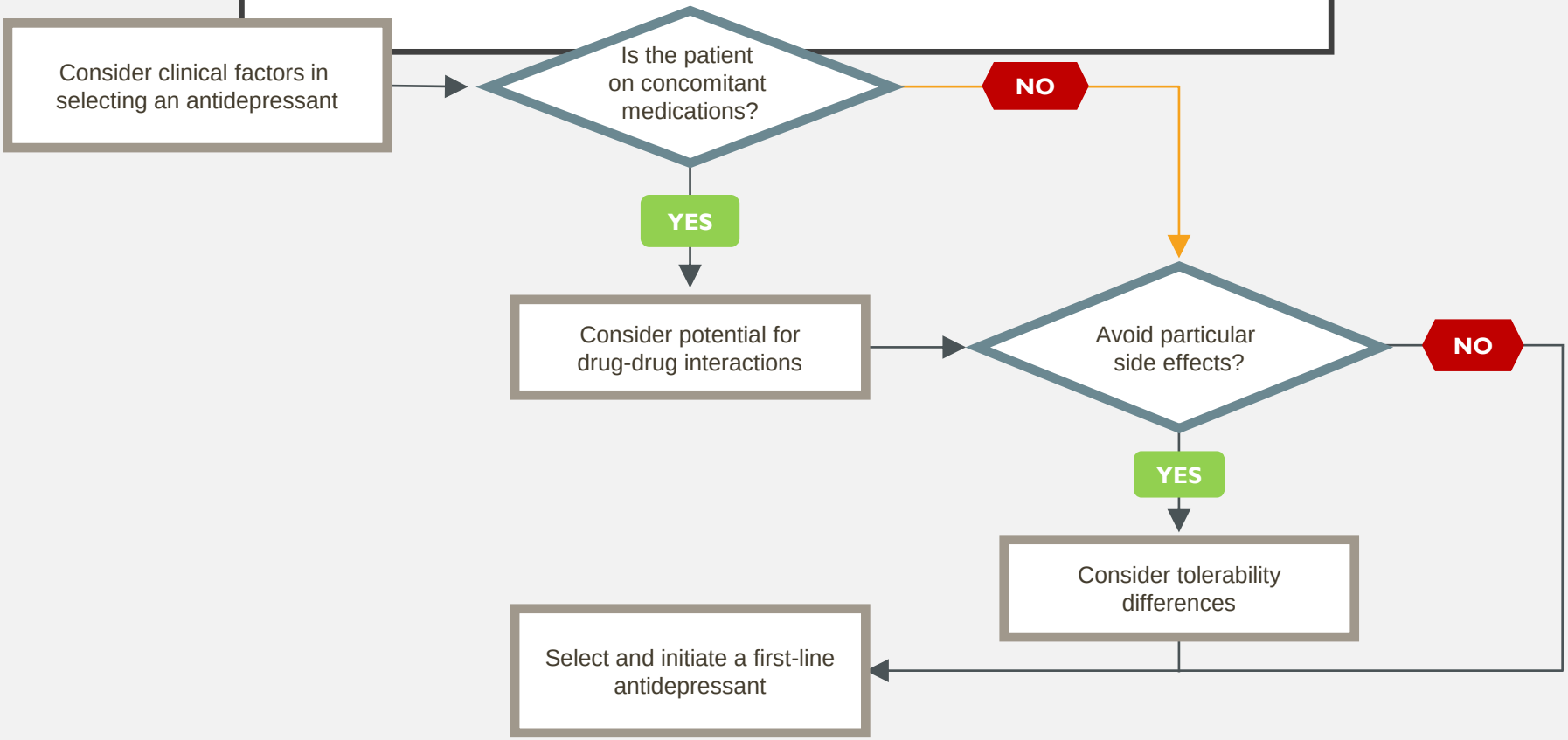
Second-line Recommendations

Agent	Level of Evidence	Dose
Brexpiprazole	*Level 1*	*1–3 mg*
Bupropion	*Level 2*	*150–300 mg*
Lithium	*Level 2*	*600–1200 mg**
Mirtazapine/ mianserin	*Level 2*	*30–60 mg*
Modafinil	*Level 2*	*100–400 mg*
Olanzapine	*Level 1*	*2.5–10 mg*
Triiodothyronine	*Level 2*	*20–50 mcg*

**Therapeutic serum levels*

CANMAT. Can J Psychiatry. 2016;61(9):540–560.

HOW DO WE CURRENTLY DECIDE ON WHICH ANTIDEPRESSANT TO USE?



CANMAT. Can J Psychiatry. 2016;61(9):540–560.

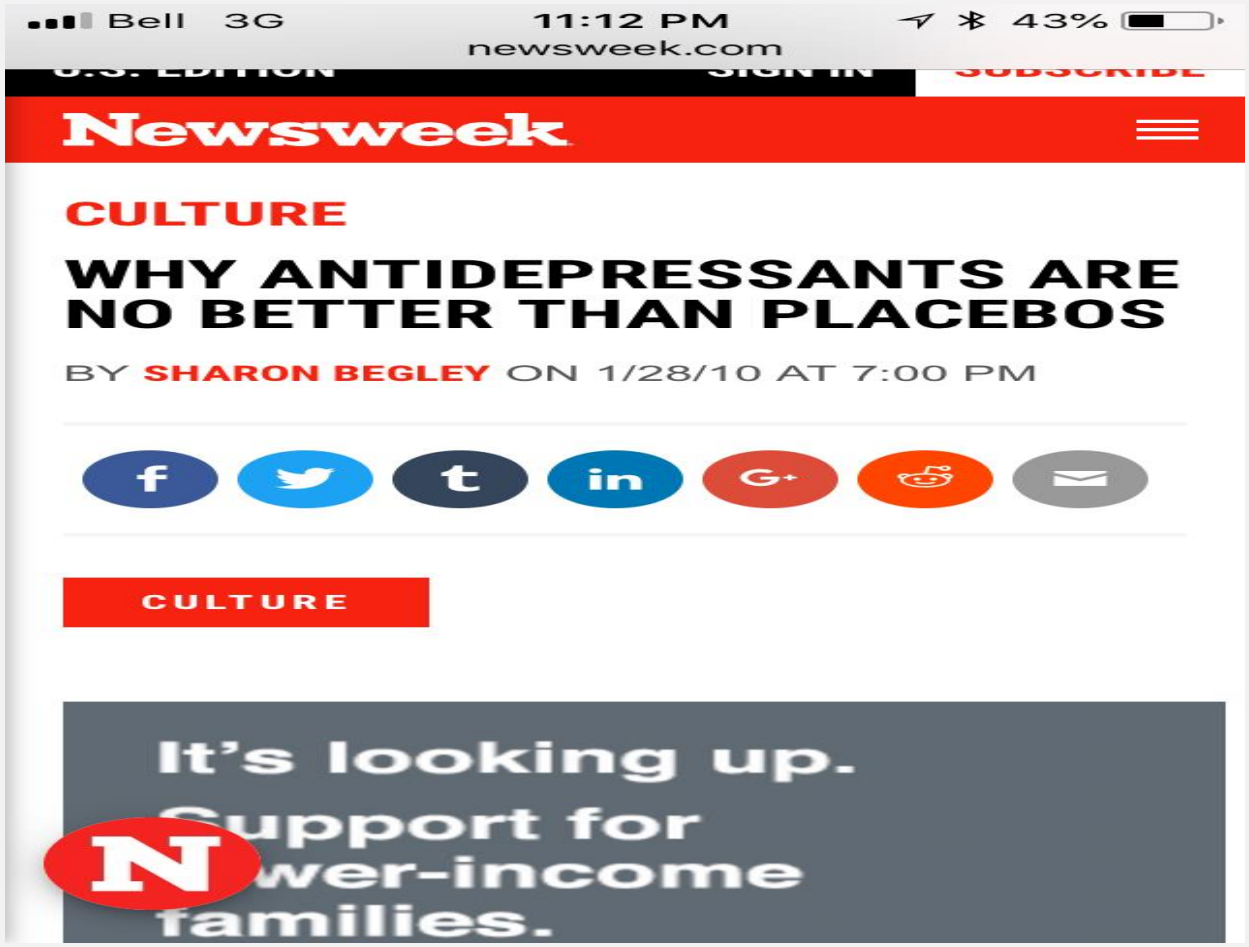
CANMAT
ANTIDEPRESSANT RECOMMENDATION: SPECIFIERS AND DIMENSIONS[1]

Specifiers/Dimensions[1]	Recommendations and level of evidence	
With psychotic features	*Use antipsychotic and antidepressant cotreatment*	**Level 1**
With melancholic features	*No specific antidepressants have demonstrated superiority*	**Level 2**
With atypical features	*No specific antidepressants have demonstrated superiority*	**Level 2**
With cognitive dysfunction	• *Vortioxetine*	**Level 1**
	• *Buproprion, Duloxetine, SSRIs, Moclobemide*	**Level 2**
With catatonic features	*Benzodiazepines*	**Level 3**
With seasonal pattern	*No specific antidepressants have demonstrated superiority*	**Level 2 and 3**
With anxious distress	*Use an antidepressant with efficacy in generalized anxiety disorder*	**Level 4**

[1] From DSM-5 (e.g, MDD with anxious distress, etc.); *Comparisons only with placebo

Kennedy *SH et al. Can J Psychiatry.* 2016;61(9):540-560.

SHOULD WE EVEN BE CONSIDERING ANTIDEPRESSANTS?



THE LANCET

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

ARTICLE SELECTION PROCESS

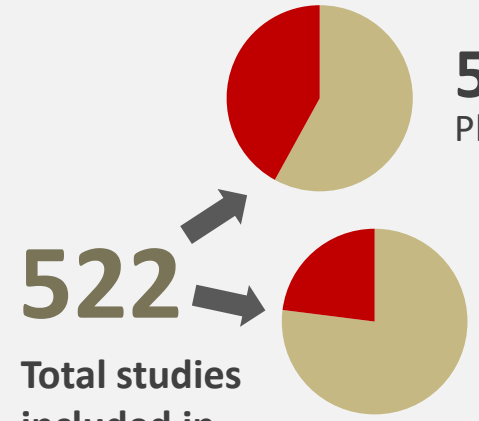
24,200 *Records identified through database searching*

421 *Eligible full-text articles*

\+ **86** *Unpublished records*

\+ **15** *Records identified from hand-searched reviews*

116,447 Patients



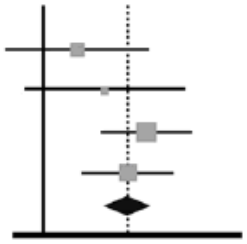
Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

Multiple treatments (network) meta-analysis

A newer technique that allows multiple treatments (placebo-controlled and head-to-head) to be compared within a single meta-analysis

Technique is used in other areas of medicine (e.g., statins to prevent cardiovascular mortality; smoking cessation therapies in COPD)

Allows for both direct and indirect comparisons



Pairwise meta-analysis
Direct comparison

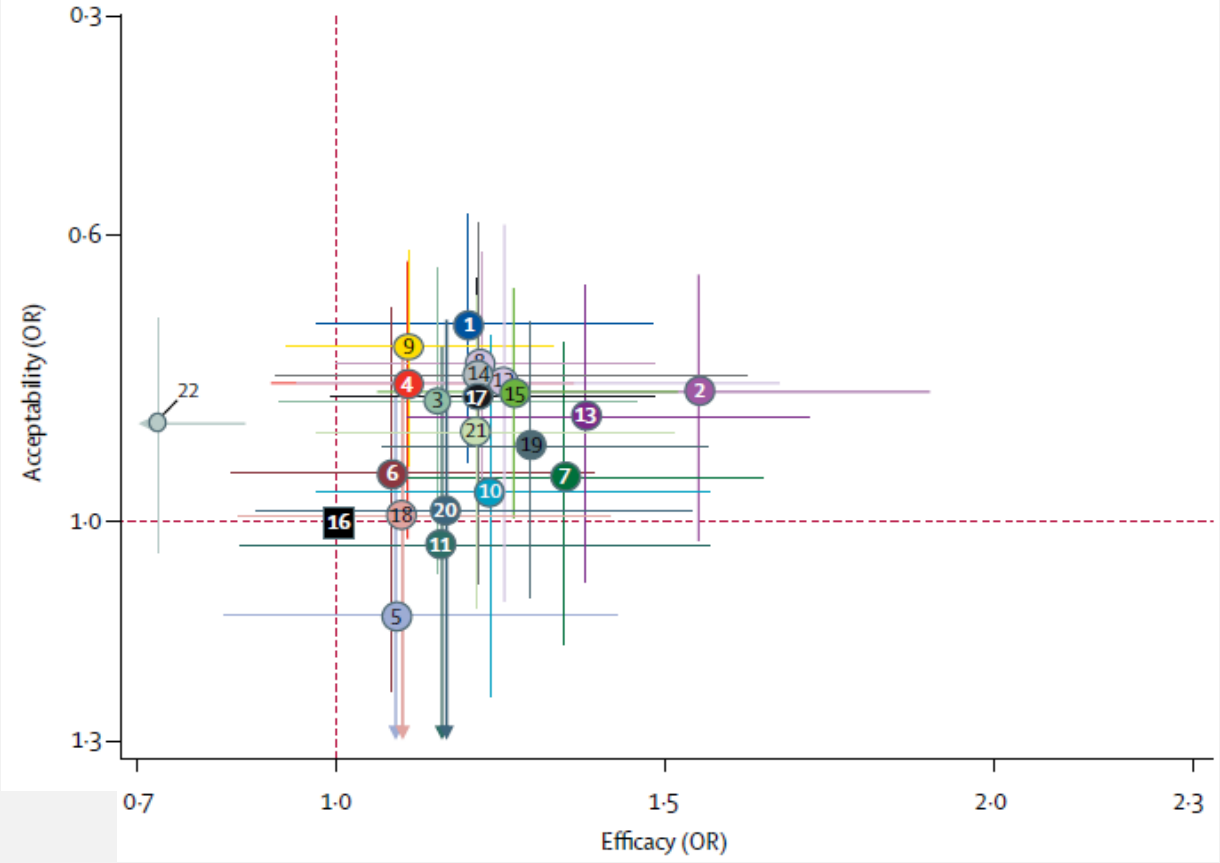
Network meta-analysis
Direct comparison &
Indirect comparison

Example of indirect comparison:
2 treatments can be compared if both have been compared to a 3rd treatment, and all 3 have been compared to placebo

e.g. **If A > B and B > C, then A > C**

Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

COMBINED EFFICACY AND ACCEPTABILITY: ALL TRIALS



- *Antidepressants are closely clustered*
- *All are better than placebo (22)*

Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% CrIs. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials. ORs=odds ratios. 1=agomelatine. 2=amitriptyline. 3=buproprion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran. 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine. 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine. 22=placebo.

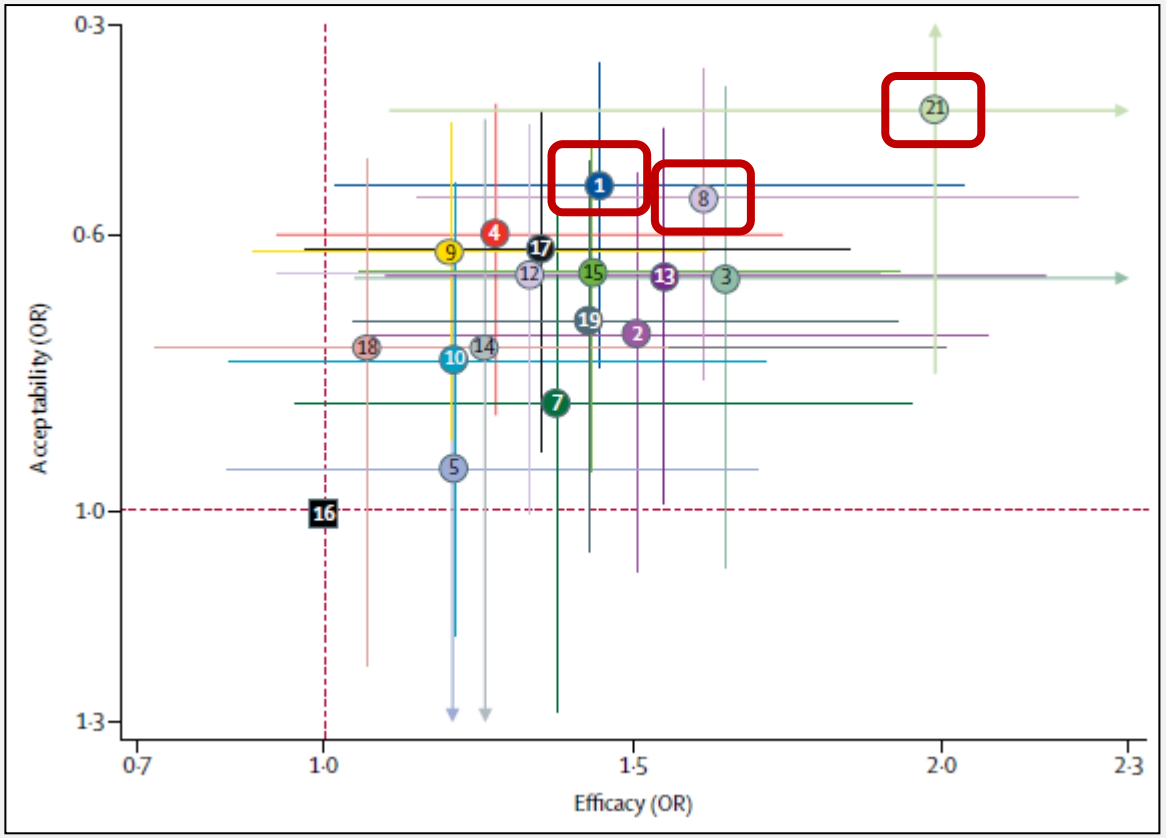
Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

ALL ANTIDEPRESSANTS ARE EFFECTIVE IN MDD

- *Summary effect sizes were mostly modest*
- *Differences between antidepressants were small when all studies were included*
- *When only head-to-head studies were considered, there was more variability between antidepressants*
- *Novel antidepressants tended to show a better efficacy profile than older agents*
- *Industry sponsorship did not influence results*

Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

COMBINED EFFICACY + ACCEPTABILITY BASED ON HEAD-TO-HEAD TRIALS



- *3 antidepressants had the most favourable profile for efficacy and acceptability:*

1. *Vortioxetine (21) had the greatest net clinical benefit*
   - *Highest OR for efficacy*
   - *Lowest OR for all-cause discontinuation*
2. *Escitalopram (8)*
3. *Agomelatine (1)*

Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% CrIs. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials. ORs=odds ratios. 1=agomelatine (not available in Canada). 2=amitriptyline. 3=buproprion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran. 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine. 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine. 22=placebo.

Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

MORE DATA, MORE ANSWERS: PICKING THE OPTIMAL ANTIDEPRESSANT

- *This work represents a major contribution to the field*
  - *Addresses key clinical questions:*
    - *Do some antidepressants work better than others for depression?*
    - *Are some more tolerable than others?*
  - *Reassures patients and clinicians of the efficacy of antidepressants despite high placebo response rates*
  - *Identifies significant differences between antidepressants that are relevant to all stakeholders, notably: agomelatine, escitalopram, and vortioxetine offered the best net clinical benefit*

"In everyday clinical practice, medications with the highest net efficacy and acceptability ratings merit discussion with patients for use as the first treatment."

Parikh & Kennedy. Lancet 2018 Feb 21. dx.doi.org/10.1016/S0140-6736(18)30421-5.

HOW LONG DO YOU LEAVE PATIENTS ON ANTIDEPRESSANTS?

CANMAT 2016 Guidelines for the Management of Adults with MDD[2]

"…maintain treatment with antidepressants for 6 to 9 months after achieving symptomatic remission, while those with risk factors for recurrence extend antidepressant treatment to 2 years or more."

Risk factors for recurrence include:

- *Frequent, recurrent episodes*
- *Severe episodes (psychosis, severe impairment, suicidality)*
- *Chronic episodes*
- *Presence of comorbid psychiatric or other medical conditions*
- *Presence of residual symptoms*
- *Difficult-to-treat episodes*

CANMAT: Canadian Network for Mood and Anxiety Treatments

Olfson et al. Am J Psychiatry. 2006;163:101-108;

CANMAT. Can J Psychiatry. 2016;61(9):540-560.

HOW DO I TAPER PATIENTS OFF ANTIDEPRESSANTS?

- Discontinuation symptoms include flu-like experiences such as nausea, headache, light-headedness, chills, and myalgias.
- Neurological symptoms include parasthesias, insomnia, and 'electric-shock' phenomena (similar to L'Hermittes sign in MS).
- These symptoms spontaneously resolve in about 1-2 weeks for most patients.
- Paroxetine causes the most protracted discontinuation.
- There are some patients that may present with a persistent post-withdrawl disorder for months or years. This however generally is regarded as potential somatic symptoms secondary to an untreated mental illness.

- Slow taper is the first recommendation but is primarily based on case report data.
- Switch from medications with a short half life (such as Paroxetine and Venlafaxine) and switch to Fluoxetine.
- Clonazepam
- CBT
- Review interactions with other medications. For instance Fluvoxamine is a potent Cytochrome p450 1A2, 2D6 and 3A4 inhibitor. Removing an inhibitor would then decrease plasma levels of other medications including other antidepressants, PPIs, and anti-epileptics.

Fava G, et al. Understanding and Managing Withdrawl Syndromes. J Clin Psych. 2019; 80 (6).

MAJOR DEPRESSIVE DISORDER WITH CONCURRENT ALCOHOL USE DISORDER

Integrated Treatment recommended.

Cognitive Behavioral Therapy.

Close monitoring in consultation (at least weekly)

The electrocardiogram before treatment administration,

PHARMACOLOGIC OPTIONS FOR CONCURRENT MDD AND AUD

The prescription of antidepressant treatment after reassessment of mood, once appropriate care for physical withdrawal syndrome is over.

Mirtazapine monotherapy

Naltrexone monotherapy

Add-on naltrexone to sertraline

Add-on acamprosate to escitalopram

Escitalopram and Aripiprazole

Majority of SSRIs and SNRIs can be considered.

Imipramine may differentiate for impact on mood, but not on SRE.

Orexin Antagonist therapy

Bealieu et al. The CANMAT task force recommendations for the mgmt. of patients with mood disorders and comorbid SUDs. Annals of Clinical Psych. 2012;24(1):38-55

Bennabi et. al. Clinical guidelines for the mgmt. of MDD with specific psych. Conditions. BMC Psych. 2019. 19. 50

McHugh, K. et. Al. Alcohol Use Disorder and Depressive Disorders. Alcohol Research. 2019. 40(1)

OREXIN RECEPTOR ANTAGONISM

- *Orexin receptor antagonists reduce wakefulness and hence assist in prolonging sleep.*
- *Sleep disruption is common with acute and prolonged alcohol use due to changes in sleep architecture and continuity, increasing proportion of NREM sleep.*
- *Sleep deprivation is a potent factor predicting relapse to alcohol use.*
- *Treating insomnia improves sleep quality and ameliorates depressive symptoms in AUD patients with comorbid insomnia.*

- *Orexin-1 antagonism prevents alcohol seeking behavior in lab studies, while Orexin-2 antagonism has reduced motivation for cocaine.*
- *Orexin receptor antagonism ameliorates alcohol withdrawl-induced negative affective state.*
- *May benefit for abstinence if combined with Baclofen or Gabapentin.*

Campbell E. et. al. Suvorexant for the treatment of AUD. Brain Research. 2020. Vol 1731

CONCLUSIONS

- *There a number of risk factors and protective factors involved in suicide assessment.*
- *There are non-pharmacologic options with good evidence for treatment of mild to moderate depression.*
- *All 21 antidepressants were more efficacious than placebo with a modest effect size. Some have better evidence in different clinical scenarios.*
- *In head-to-head comparisons, agomelatine, escitalopram, and vortioxetine offered the best net clinical benefit*
- *There are some specific options for treatment of concurrent Alcohol Use Disorder.*

Cipriani, A. et al., Lancet. 2018 Feb 20. doi: 10.1016/S0140-6736(17)32802-7. [Epub ahead of print]

QUESTIONS, COMMENTS?
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