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Depression: Where Are We At in2021?

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Disclosures: last 5 years

Advisory Boards

- Lundbeck
- Janssen-Ortho
- Sunovion
- Otsuka

Speaker Honoraria

- Lundbeck
- Janssen-Ortho
- Sunovion
- Otsuka
- Allergan

LEARNING OBJECTIVES

- At the conclusion of this presentation, participants will be able to:
  - adopt an overall management approach to Major Depressive Disorder (MDD)
  - identify the importance of persistent symptoms in MDD
  - recognize recommended treatments for patients with MDD
  - screen for symptoms in the bipolar spectrum

More than one in ten Canadian adults will develop MDD in their lifetime … [1]

…more than 50% will not be treated

…30-50% will have an inadequate response to treatment

- CCHS. *Can J Psychiatry* 2006;51:84-90;
- Hirschfeld et al. *Can J Psychiatry* 2006;51:84-90;
- Lecubrier. *J Clin Psychiatry* 2007; 68 Suppl 2: 36-41;
- Kennedy & Lam. *Bipolar Disord* 2003; 5 Suppl 2: 36-47.

Prevalence and Burden of MDD

Epidemiology

- Canadian Prevalence Estimates
  - Lifetime: 10.8%
  - Past Year: 4.0%
  - Past 30 days: 1.3%
  - 50% of FLEDs are SLEDs!

Canadian Community Health Survey, Mental Health and Wellbeing. *Can J Psychiatry* 2006;51:84-90

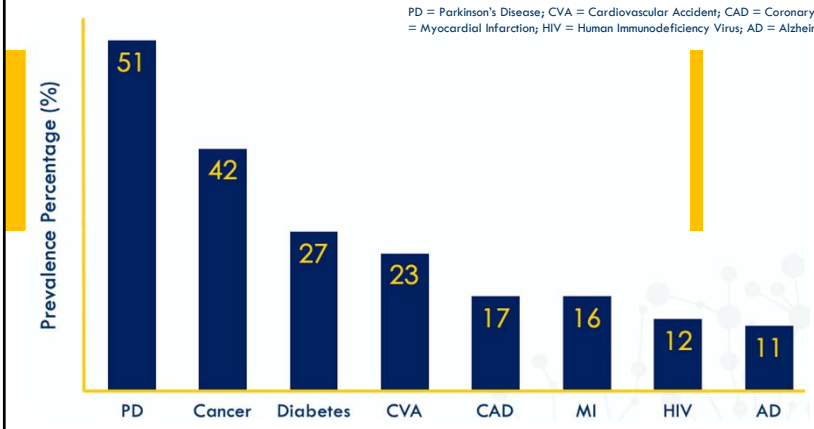
Medical Conditions Strongly Associated with MDD in the Canadian Population

Medical Condition	Odds Ratio	Medical Condition	Odds Ratio
Emphysema / COPD	2.7	Asthma	1.9
Migraine	2.6	Stroke	1.7
Multiple sclerosis	2.3	Thyroid disease	1.4
Back problems	2.3	Diabetes	1.4
Cancer	2.3	Heart disease	1.4
Epilepsy	2.0		

Estimates derive from the Canadian Community Health Survey 1.1, Patten et al., 2005

Depression Is Common In Patients With Many Chronic Diseases

PD = Parkinson's Disease; CVA = Cardiovascular Accident; CAD = Coronary Artery Disease; MI = Myocardial Infarction; HIV = Human Immunodeficiency Virus; AD = Alzheimer's Disease.



Preskorn. *Primary Psychiatry*. 2009;16(12):45-74.

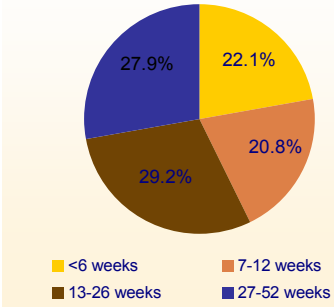
MDD is a Chronic Disease

- The evidence supports the need for a **chronic disease management strategy** including:
  - Active screening & detection
  - Deliver evidence-based care
  - Collaborative "stepped care"
  - Patient education & self-management
  - Monitoring of outcomes

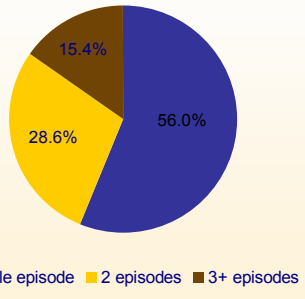
CANMAT Clinical Guidelines for the Management of Major Depressive Disorder in Adults, *J Affect Disord*. 2009; Andrews, 2001; Kates & Mach, 2007; Neumeyer-Gromen et al., 2004.

Long-term Course of MDD

weeks depressed in past year



Recurrence MDD: # of lifetime episodes



CANMAT Clinical Guidelines for the Management of Major Depressive Disorder in Adults, *J Affect Disord.* 2009;
CCHS 1.2, Public Use Microdata File.

Treatment Goals

Treat to remission

Avoid chronicity

Restore functionality

Unmet Clinical Needs

- As many as **half** of all patients enrolled in two depression specialty clinics did not achieve remission despite receiving numerous adequate antidepressant trials[1]
- **Residual symptoms** among remitters are common
  - associated with poorer psychosocial functioning[2]
  - increased relapse rates[3]

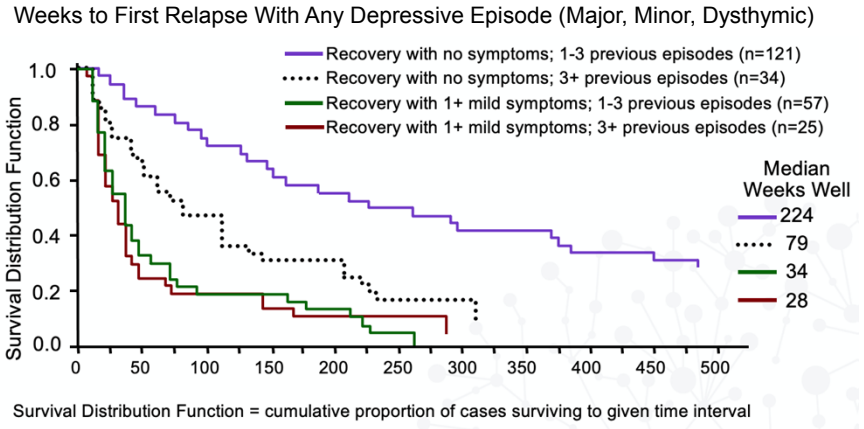
1. Petersen T et al. 2005. J Clin Psychopharmacol 25:336341
2. Papakostas GI et al. 2004. J Clin Psychopharmacol 24:507511
3. Paykel ES et al. 1995. Psychol Med 25:11711180

Consequences of Failing to Achieve Remission and Settling for Response

- Greater risk of **relapse**
- Increased risk of **treatment resistance**
- Continued **psychosocial limitations and work impairment**
- Worsened prognosis for medical conditions
- Increased use of medical services
- **Increased risk of suicide and substance abuse**

1. Nierenberg A. J Clin Psychiatry1999;60 Suppl 22:7
2. Thase M. J Clin Psychiatry 1999;60 Suppl 22:3
3. Stahl SM. *J Clin Psychiatry.* 1999;60(4):213-214.

Residual Symptoms Associated with Worse Outcomes

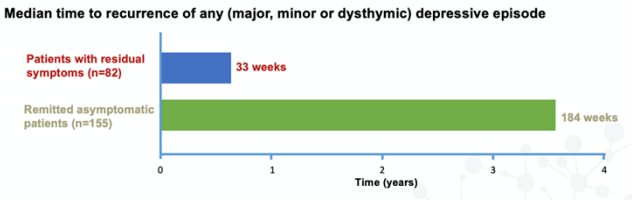


Judd LL, et al. *J Affect Disord.* 1998;50:97-108.

Patients with residual symptoms relapsed to next depressive episode 5.5 times faster than patients treated to remission (*p*<.0001)[1]

Residual symptoms can lead to faster relapse

- Patients with residual symptoms relapsed to next major depressive episode **more than 3 times faster** than patients treated to remission (68 vs 231 weeks, respectively; *P*<.0001)
- Overall, patients with residual symptoms were **368% more likely to relapse** during recovery than patients treated to remission (OR, 3.68; 95% CI, 2.64–5.12)
- *Remission was defined as asymptomatic recovery with ≥80% of well interval weeks rated asymptomatic*



1. Judd LL et al. J Affect Disord 1998; 50 (2-3): 97-108

First Line Treatment

- Pharmacotherapy or focused psychotherapy (CBT)?
- Pharmacotherapy preferred if:
  - No motivation
  - No access to psychotherapy
  - Severe symptoms
  - Urgency in treatment response
- Pharmacotherapy + psychotherapy may be best approach in more complex and/or chronic cases

Antidepressants 2021

CANMAT Canadian Network for Mood and Anxiety Treatments

TCA

Amitriptyline
Imipramine
Clomipramine
Trimipramine
Maprotiline
Amoxapine
Nortriptyline
Desipramine

MAOI

Phenelzine
Tranylcypromine

SSRI

Citalopram [Celexa]
Escitalopram [Cipralex]
Fluoxetine [Prozac]
Fluvoxamine [Luvox]
Sertraline [Zoloft]
Paroxetine [Paxil]

SARI

Trazodone

Multimodals

Vortioxetine [Trintellix]
Vilazodone [Viibryd]

NDRI

Bupropion-SR/XL [Wellbutrin]

SNRI

Duloxetine [Cymbalta]
Venlafaxine-XR [Effexor]
Desvenlafaxine [Pristiq]
Levo-milnacipran [Fetzima]

NaSSA

Mirtazapine [Remeron]

RIMA

Moclobemide [Manerix]

WHAT ARE THE FIRST LINE ANTIDEPRESSANTS?

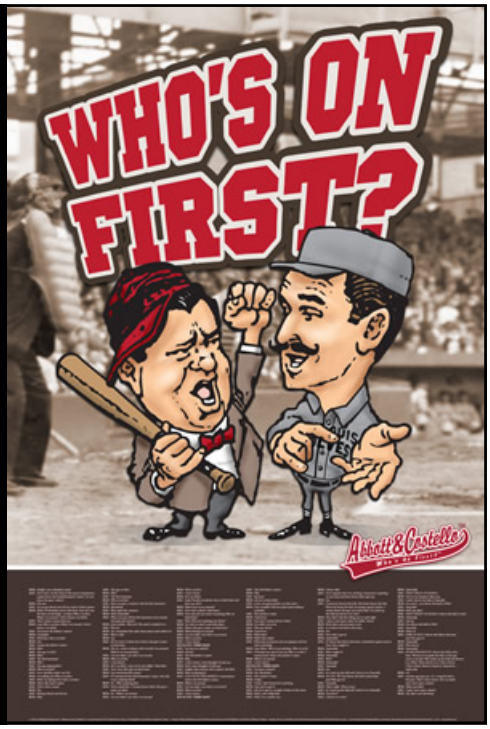


Table 3. Summary Recommendations for Antidepressants.

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level I Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[a] (Tolvon)	α_2-Adrenergic agonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic agonist; 5-HT_2 antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} agonist; 5-HT_{1B} partial agonist; 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 antagonist	10-20 mg
Second line (Level I Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[g]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[a] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; 5-HT_2 antagonist	150-300 mg
Vilazodone (Viibryd)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} partial agonist	20-40 mg (titrate from 10 mg)
Third line (Level I Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

Kennedy, S. et al. The Canadian Journal of Psychiatry 2016, Vol. 61(9) 506-509

How do you choose?

What are the clinical factors that influence antidepressant selection?

Physician Survey: Factors Influencing the Choice of Antidepressant

- Presence of specific symptoms: 52.3%
- Avoid specific side-effect: 48.7%
- Presence of co-morbidity: 45.6%
- Failure with previous medication trial: 25.9%
- Good previous response to antidepressant: 17%
- **Once daily dosing: 15.1%**
- Good response in a family member: 4%
- Patient's interest in a specific medication: 5.2%

Zimmerman, Am J Psychiatry 2004

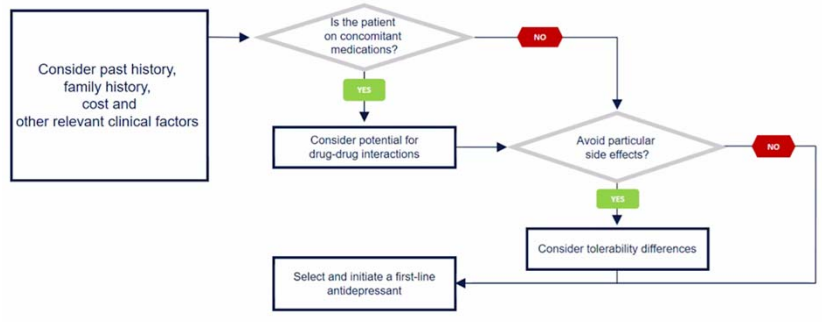
Choosing between antidepressants:

Table 4. Factors to Consider in Selecting an Antidepressant.

Patient Factors	Medication Factors
• Clinical features and dimensions • Comorbid conditions • Response and side effects during previous use of antidepressants • Patient preference	• Comparative efficacy • Comparative tolerability (potential side effects) • Potential interactions with other medications • Simplicity of use • Cost and availability

- Kennedy, S. et al. The Canadian Journal of Psychiatry 2016, Vol. 61(9) 506-509

CANMAT choosing antidepressants

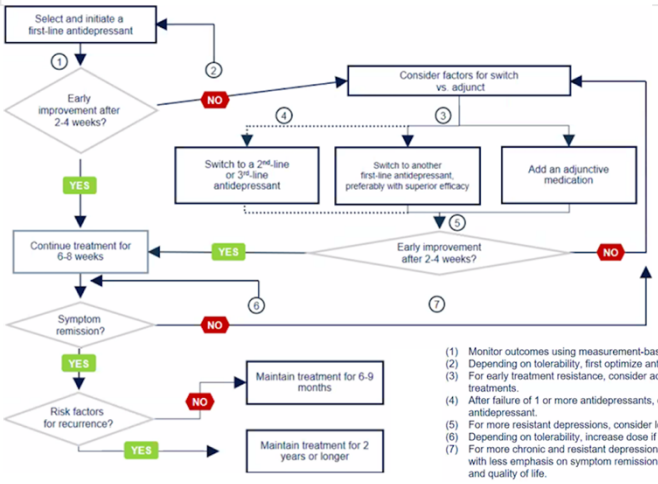


Kennedy SH et al. CANMAT Guidelines Can J Psychiatry 2016 61 (9) 540-560

Other Considerations: Summary

- **Chronic pain and prominent somatic symptoms:**
  - Duloxetine
  - venlafaxine, des-venlafaxine,
  - bupropion (fatigue)
  - levo-milnacipran (pain and fatigue)
- **Drug interactions:**
  - Citalopram, escitalopram
- **Poor sleep, weight loss:**
  - Mirtazapine, quetiapine, trazodone
- **Sexual side effects:**
  - Bupropion, mirtazapine, vortioxetine
- **Cognitive dysfunction:**
  - Vortioxetine (level 1), duloxetine and bupropion (level 2)
- **Pregnancy and breastfeeding:**
  - Avoid paroxetine

Optimizing Pharmacotherapy



Kennedy SH et al. CANMAT Guidelines Can J Psychiatry 2016 61 (9) 540-560

(1) Monitor outcomes using measurement-based care.
(2) Depending on tolerability, first optimize antidepressant by increasing dose.
(3) For early treatment resistance, consider adjunctive use of psychological and neurostimulation treatments.
(4) After failure of 1 or more antidepressants, consider switch to a second-line or third-line antidepressant.
(5) For more resistant depressions, consider longer evaluation periods for improvement.
(6) Depending on tolerability, increase dose if not at maximal doses.
(7) For more chronic and resistant depressions, consider a chronic disease management approach, with less emphasis on symptom remission and more emphasis on improvement in functioning and quality of life.

Dealing with Partial Response…

- Adjunctive aripiprazole: 2-5 mg qd
- Adjunctive quetiapine: 25-300 mg qHS
- Combination SSRI (or SNRI) + bupropion
- Combination SSRI (or SNRI) + mirtazapine
- Adjunctive brexpiprazole: 0.25- 2 mg qd
- Adjunctive stimulants or modafinil
- Adjunctive lithium (suicidality, ?bipolar spectrum)
- Review possible medical comorbidities: OSA, thyroid, anemia, EtOH or substance abuse

Basic Management Principles

1. First-line antidepressant
   - Target the symptoms
   - Avoid side effects
2. Second antidepressant of a different class
3. Adjunctive therapy
4. Neuromodulation (rTMS, ECT, ketamine)
5. Experimental strategies (VNS, DBS)

Appropriate psychotherapy

Unmet Needs

- No reliable clinical data to link patients to best first-line treatment
- >10% of patients do not tolerate pharmacotherapy
- Difficult to target symptom clusters
- Onset of action remains slow (weeks not days)
- ~ 1/3 of patients with treatment resistance
- **More systematic overall approach in treatment resistant patients**

What is Treatment Resistant Depression (TRD)?

- Usually means failure of 2 adequate trials of pharmacotherapy and/or psychotherapy
- Adequate = good dose for reasonable amount of time
- More useful in research
- Stems from STAR*D
- Inflection point after which similar treatments unlikely lead to sustained remission (<5%)

What is Treatment Resistant Depression (TRD)?

- Term borrowed from infectious diseases
- Denotes a poor response to antidepressants with a monoaminergic mechanism of action
- Not a diagnosis
- Poorly defined
- Poorly studied
- Competing with newer concept of ”Difficult to Treat Depression”

“Difficult to Treat Depression”

- Depression that continues to cause a significant amount of burden despite the usual treatment efforts
- The concept recognizes:
  - Limited efficacy of current treatments
  - Complexity of cases
  - Challenge of matching the best treatment to patients
  - Chronicity of MDD and focus on rehabilitation
  - Potential for comorbidities
  - Benefits of a more global approach

McAllister-Williams RH et al. Journal of Affective Disorders 267 (2020) 264-282

DDT vs TRD: conceptual differences

Table 1. A comparison of concepts.

Term	Treatment-resistant depression (TRD)	Difficult-to-treat depression
Positioning	Opposition to …	Collaborative concept (patient, family, physician)
Model	Acute illness model	Chronic illness model
Approach	Mainly biological Biomedical: cure	Biopsychosocial Capability approach Recovery movement Optimizing symptom control Minimizing impact of symptoms
Endpoint	Categorical (remission or not)	Dimensional (waxing and waning)

Rush AJ et al.: Australian & New Zealand Journal of Psychiatry,2019; 53(2)

Figure 2. Proposed workup of potential difficult-to-treat depression.

- ✓ Confirm primary psychiatric diagnosis
- ✓ Assess adequacy of prior treatment recommendations (dose & duration)
- ✓ Confirm adherence to prior treatment recommendations
- ✓ Consider pharmacogenetics testing or therapeutic blood level monitoring
- ✓ Assess concurrent psychiatric conditions that require remediation
- ✓ Assess current general medical conditions that require remediation
- ✓ Assess for undiagnosed general medical conditions that can cause depressior
- ✓ Evaluate current environmental stressors needing remediation

Rush AJ et al.: Australian & New Zealand Journal of Psychiatry,2019; 53(2)

TRD or Misdiagnosis?

Mixed Depression: The Importance of Searching for Symptoms

Moving from a categorical approach to a dimensional one

DSM-5 was updated to include a new "mixed features" specifier for hypomanic, manic or depressive episodes.

[1]American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4e édition, Text Revision. Arlington, VA, 2000.
[2]American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5e édition. Arlington, VA, 2013.

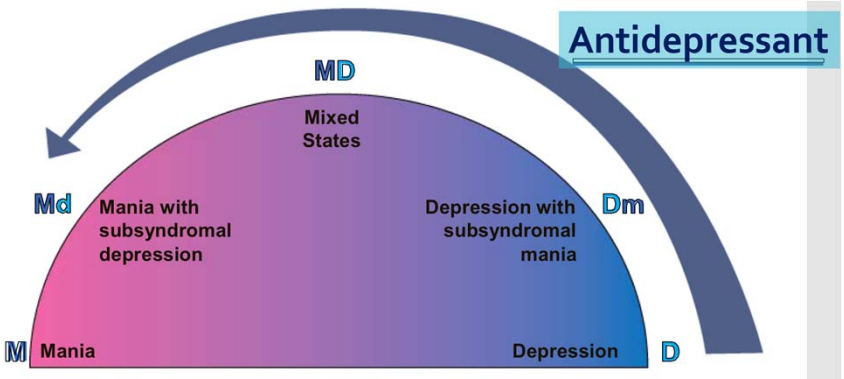
Depression with mixed features

The prognosis for depression with mixed features is worse than for unipolar depression or bipolar depression without mixed characteristics

- Women > men
- Suicidal tendencies
- Early age of onset
- Poor prognosis
- Severity of depression
- Resistance to antidepressants
- Long duration of illness
- Anxiety disorders and substance abuse
- Antidepressant-induced mania
- Family history of bipolar disorder

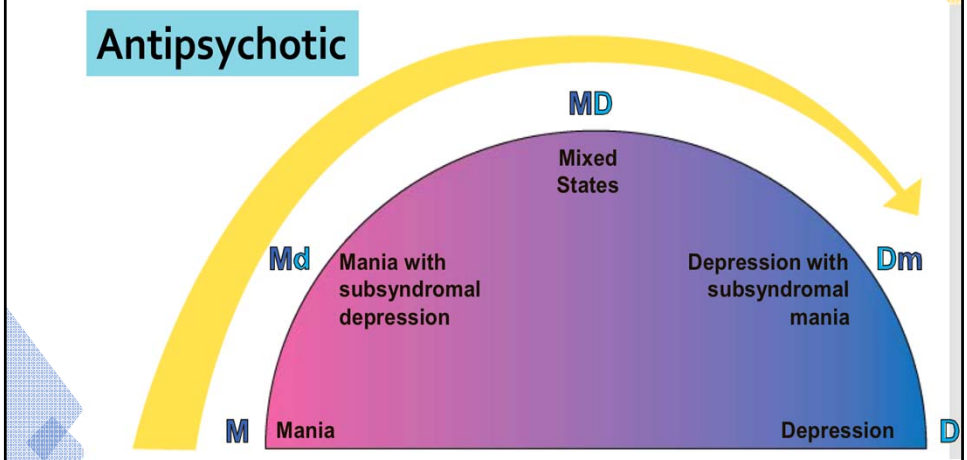
Akiskal HS, Benazzi F. J Affective Disord 2003;73:113-22; Angst J et al. Am J

Formerly:
Presence of depression meant treating with antidepressant

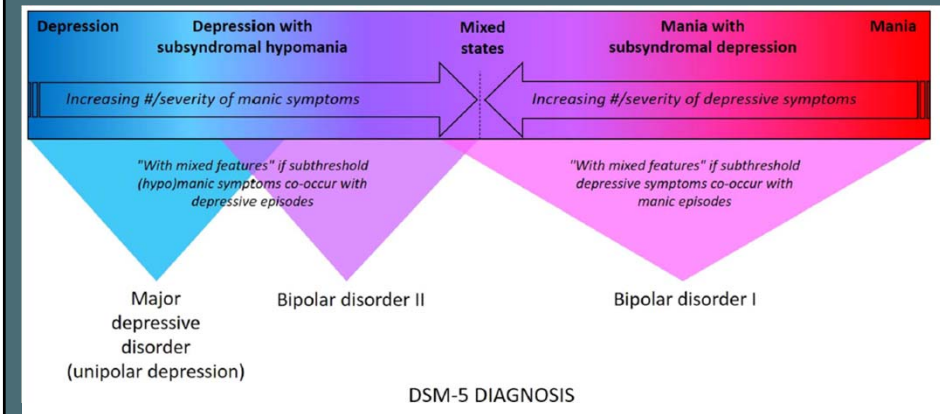


Stahl et al. CNS Spectr. 2017;22(2):203-19.

Current practice:
Presence of hypo/mania means treating with antipsychotic

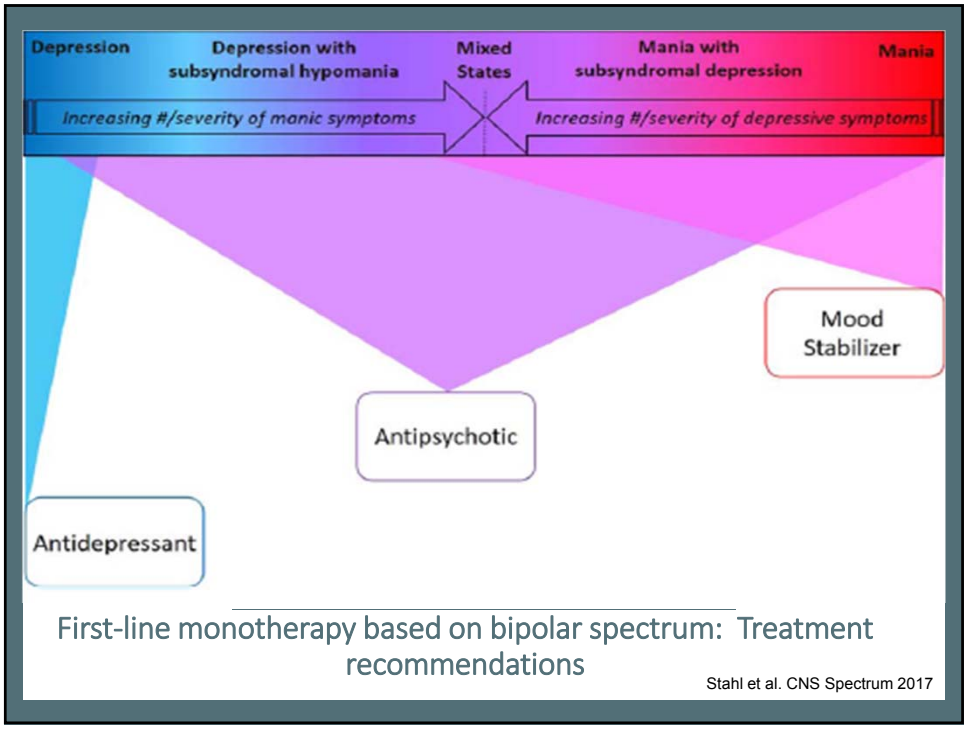


Stahl et al. CNS Spectr. 2017;22(2):203-19.



DSM-5 Dimensional Approach

Stahl et al. CNS Spectrum 2017



First-line monotherapy based on bipolar spectrum: Treatment recommendations

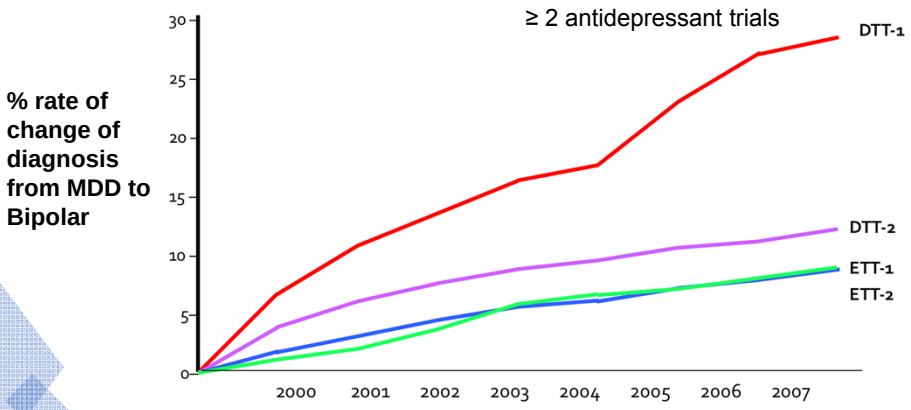
Stahl et al. CNS Spectrum 2017

Mixed States: Conclusions

- Be aware: mixed states manifest themselves in all kinds of forms
- Look for manic symptoms in depressive patients who do not respond adequately to treatment
- Family history and history of psychiatric treatment
- Use various screening tools: MDQ
- Few studies focus on the treatment of mixed episodes
- There are few studies on prophylaxis
- **Does mixed status mean a diagnosis in the bipolar spectrum?**

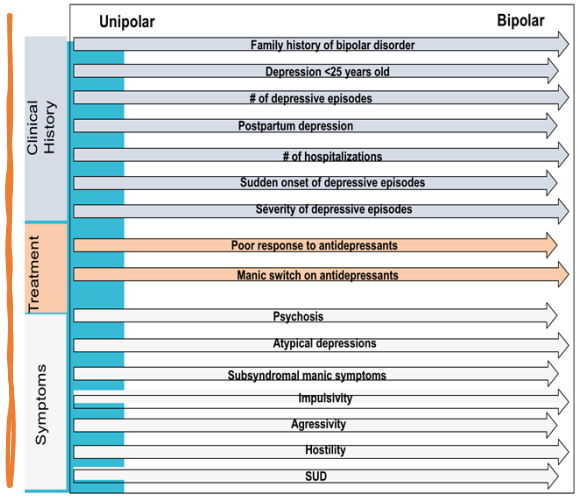
DSM-IV®-TR, APA, 2000.
Hirschfeld RMA, et al. *J Clin Psychiatry.* 2003;64(1):53-59.
Kruger S, et al. *Bipolar Disorders* 2005; 7: 205-215.

Is resistance to antidepressants a predictor of bipolar disorder?



Li CT, Bai YM, Huang YL, et coll. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. Br J Psychiatry 2012; 200(1):45-51.

Suspicion of Bipolarity



Bipolarity Index

https://www.moodtreatmentcenter.com/measurement/

The Bipolarity Index

Directions: Circle the bulleted items that are positive in the patient's history. Score each of the five sections by circling the highest number (0-20) for which there is at least one positive item. The final score is the sum of all five sections.

I. Episode Characteristics	
20	• Acute manic or mixed episode with prominent euphoria, grandiosity or expansiveness and no significant medical or other secondary etiology.
15	• Acute mixed episode or dysphoric or irritable mania with no significant medical or other secondary etiology.
10	• Hypomanic episode with no significant medical or other secondary etiology; or • Cyclothymia with no significant medical or other secondary etiology; or • A manic episode within 12 weeks of starting an antidepressant.
5	• A hypomanic episode within 12 weeks of starting an antidepressant • Episodes with characteristic symptoms of hypomania, but symptoms, duration, or intensity are subthreshold for hypomania; or • A single MDE with psychotic or atypical features (atypical is ≥2 of the following: hypersomnia, hyperphagia or leaden paralysis of limbs); or • Any postpartum depression.
3	• Recurrent unipolar major depressive disorder (≥3 episode); or • History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference or magical thinking).
0	• No history of significant mood elevation, recurrent depression or psychosis.
II. Age of Onset (first affective episode or syndrome)	
20	• 15 to 19 years.
15	• Before age 15 or between age 20 and 30.
10	• 30 to 45 years.
5	• After age 45.
0	• No history of affective illness (no episodes, cyclothymia, dysthymia or bipolar-NOS).
III. Course of Illness & Associated Features	
20	• Recurrent, distinct manic episodes separated by at least 2 months of full recovery.
15	• Recurrent, distinct manic episodes with incomplete inter-episode recovery; or • Recurrent, distinct hypomanic episodes with full inter-episode recovery.
10	• Any substance use disorder (excluding nicotine/caffeine); or • Psychotic features only during acute mood episodes; or • Incarceration or repeated legal offenses related to manic behavior (e.g. shoplifting, reckless driving or bankruptcy).
5	• Recurrent unipolar MDD with ≥3 or more major depressive episodes; or • Recurrent, distinct hypomanic episodes without full inter-episode recovery; or • Borderline personality disorder, anxiety disorder (including PTSD and OCD), eating disorder, or history of ADHD with onset before puberty; or • Engagement in gambling or other risky behaviors with the potential to pose a problem for patient, family or friends; or • Behavioral evidence of perimenstrual exacerbation of mood symptoms.
3	• Baseline hyperthymic personality when not manic or depressed; or • Marriage 3 or more times (including remarriage to the same individual); or • In two or more years, has started a new job and changed jobs after less than a year; or • Has more than two advanced degrees.
0	• None of the above.
IV. Response to Treatment	
20	• Full recovery within 4 weeks of therapeutic treatment with a mood stabilizer.
15	• Full recovery within 12 weeks of therapeutic treatment with a mood stabilizer or relapse within 12 weeks of discontinuing treatment; or • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose.
10	• Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania (exclude worsening that is limited to known antidepressant side effects such as akathisia, anxiety or sedation); or • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment; or • Antidepressant-induced new or worsening rapid-cycling course.
5	• Treatment resistance: lack of response to complete trials of 3 or more antidepressants; or • Affective switch to mania or hypomania with antidepressant withdrawal.
3	• Immediate, near-complete response to antidepressant withdrawal within 1 week or less.
0	• None of the above, or no treatment.
V. Family History	
20	• At least one first-degree relative with clear bipolar disorder.
15	• At least one second-degree relative with clear bipolar disorder; or • At least one first-degree relative with recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
10	• First-degree relative with recurrent unipolar MDD or schizoaffective disorder; or • Any relative with clear bipolar disorder or recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
5	• First-degree relative with clear substance use disorder (excluding nicotine/caffeine); or • Any relative with possible bipolar disorder.
3	• First-degree relative with possible recurrent unipolar MDD; or • First-degree relative with anxiety disorder (including PTSD and OCD), eating disorder or ADD/ADHD.
0	• None of the above or no family history of psychiatric disorders.
	<- Total score (0 – 100). Add the highest number in each section. A score ≥50 indicates a high probability of bipolar disorder.

Aiken CB, Weisler RH, Sachs GS (2015). J Affect Disord;177:59-64.

Bipolarity Index

https://www.moodtreatmentcenter.com/measurement/

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5	• A hypomanic episode within 12 weeks of starting an antidepressant • Episodes with characteristic symptoms of hypomania, but symptoms, duration, or intensity are subthreshold for hypomania; or • A single MDE with psychotic or atypical features (atypical is ≥2 of the following: hypersomnia, hyperphagia or leaden paralysis of limbs); or • Any postpartum depression.
3	• Recurrent unipolar major depressive disorder (≥3 episode); or • History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference or magical thinking).
0	• No history of significant mood elevation, recurrent depression or psychosis.
II. Age of Onset (first affective episode or syndrome)	
20	• 15 to 19 years.
15	• Before age 15 or between age 20 and 30.
10	• 30 to 45 years.
5	• After age 45.
0	• No history of affective illness (no episodes, cyclothymia, dysthymia or bipolar-NOS).
III. Course of Illness & Associated Features	
20	• Recurrent, distinct manic episodes separated by at least 2 months of full recovery.
15	• Recurrent, distinct manic episodes with incomplete inter-episode recovery; or • Recurrent, distinct hypomanic episodes with full inter-episode recovery.
10	• Any substance use disorder (excluding nicotine/caffeine); or • Psychotic features only during acute mood episodes; or • Incarceration or repeated legal offenses related to manic behavior (e.g. shoplifting, reckless driving or bankruptcy).
5	• Recurrent unipolar MDD with ≥3 or more major depressive episodes; or • Recurrent, distinct hypomanic episodes without full inter-episode recovery; or • Borderline personality disorder, anxiety disorder (including PTSD and OCD), eating disorder, or history of ADHD with onset before puberty; or • Engagement in gambling or other risky behaviors with the potential to pose a problem for patient, family or friends; or • Behavioral evidence of perimenstrual exacerbation of mood symptoms.
3	• Baseline hyperthymic personality when not manic or depressed; or • Marriage 3 or more times (including remarriage to the same individual); or • In two or more years, has started a new job and changed jobs after less than a year; or • Has more than two advanced degrees.
0	• None of the above.
IV. Response to Treatment	
20	• Full recovery within 4 weeks of therapeutic treatment with a mood stabilizer.
15	• Full recovery within 12 weeks of therapeutic treatment with a mood stabilizer or relapse within 12 weeks of discontinuing treatment; or • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose.
10	• Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania (exclude worsening that is limited to known antidepressant side effects such as akathisia, anxiety or sedation); or • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment; or • Antidepressant-induced new or worsening rapid-cycling course.
5	• Treatment resistance: lack of response to complete trials of 3 or more antidepressants; or • Affective switch to mania or hypomania with antidepressant withdrawal.
3	• Immediate, near-complete response to antidepressant withdrawal within 1 week or less.
0	• None of the above, or no treatment.
V. Family History	
20	• At least one first-degree relative with clear bipolar disorder.
15	• At least one second-degree relative with clear bipolar disorder; or • At least one first-degree relative with recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
10	• First-degree relative with recurrent unipolar MDD or schizoaffective disorder; or • Any relative with clear bipolar disorder or recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
5	• First-degree relative with clear substance use disorder (excluding nicotine/caffeine); or • Any relative with possible bipolar disorder.
3	• First-degree relative with possible recurrent unipolar MDD; or • First-degree relative with anxiety disorder (including PTSD and OCD), eating disorder or ADD/ADHD.
0	• None of the above or no family history of psychiatric disorders.
	<- Total score (0 – 100). Add the highest number in each section. A score ≥50 indicates a high probability of bipolar disorder.

Aiken CB, Weisler RH, Sachs GS (2015). J Affect Disord;177:59-64.

Screening for Bipolar Disorder with the MDQ

- Serves as an initial screen for bipolar I
- Positive screen result
  - Yes to ≥7 of 13 items in Question 1, *and*
  - Yes to Question 2, *and*
  - "Moderate" or "Serious" problem on Question 3
- However, the MDQ is a starting point and should not be presumptive of a diagnosis of BPD
- The MDQ is meant to identify mania
- Clinicians need to conduct a thorough patient interview

		YES	NO
1.	Has there ever been a period of time when you were not your usual self and...		
	...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐
	...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
	...you felt much more self-confident than usual?	☐	☐
	...you got much less sleep than usual and found you didn't really miss it?	☐	☐
	...you were much more talkative or spoke faster than usual?	☐	☐
	...thoughts raced through your head or you couldn't slow your mind down?	☐	☐
	...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
	...you had much more energy than usual?	☐	☐
	...you were much more active or did many more things than usual?	☐	☐
	...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
	...you were much more interested in sex than usual?	☐	☐
	...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
	...spending money got you or your family into trouble?	☐	☐
2.	If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please circle one response only.* YES NO		
3.	How much of a problem did any of these cause you — like being unable to work; having family, money, or legal troubles; getting into arguments or fights? *Please circle one response only.* No problem Minor problem Moderate problem Serious problem		

Hirschfeld RM, et al. Am J Psychiatry. 2000;157(11):1873-1875.

The Rapid Mood Screener (RMS): A Novel and Pragmatic Screener for Bipolar I Disorder

Item	Response	
1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	Yes	No
2. Did you have problems with depression before the age of 18?	Yes	No
3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Yes	No
4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	Yes	No
5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	Yes	No
6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	Yes	No

McIntyre RS, et al. Curr Med Res Opin. 2020.

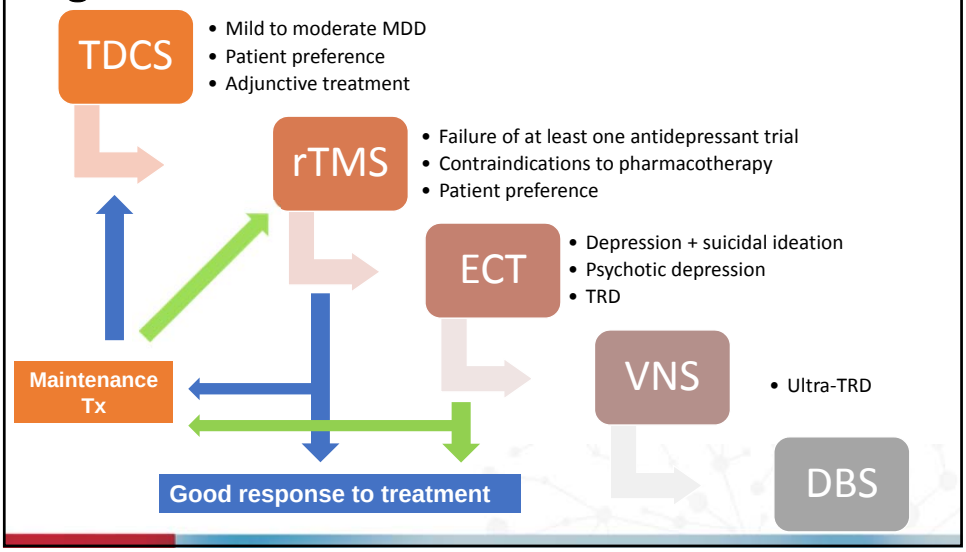
Neuromodulation: CANMAT 2016 Recommendations

Table 2. Summary of Neurostimulation Treatment Recommendations for Major Depressive Disorder.

Neurostimulation	Overall Recommendation	Acute Efficacy	Maintenance Efficacy	Safety and Tolerability
rTMS	First line (for patients who have failed at least 1 antidepressant)	Level 1	Level 3	Level 1
ECT	Second line First line in some clinical situations (see Table 5)	Level 1	Level 1	Level 1
tDCS	Third line	Level 2	Level 3	Level 2
VNS	Third line	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3
MST	Investigational	Level 3	Not known	Level 3

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

TRD: Neuromodulation Treatment Algorithm



What novel treatments are being investigated?

Novel treatments under investigation

- Ketamine model:
  - NMDA receptors
  - Rapid effect
  - IV ketamine, intranasal esketamine
  - GluN2B antagonists (CERC-301)
- Rapastinel: GLYX-13 (targets glycine co-agonist site on the NMDA receptor)
- Targeting metabotropic glutamate (mGlu) receptors: basimglurant
- Drugs targeting the endocannabinoid system
- Psilocybin: NEJM 384;15 April 15, 2021

Ketamine

- Rapid effect
- Anti-suicidal properties
- Adverse effects:
  - Hallucinations
  - Dreams
  - Out-of-body experiences (dissociative properties)
- Well tolerated but…"Clinicians giving ketamine for depression should be fully trained in ketamine administration"
- IV
- IM
- PO
- **Intranasal: both racemic and esketamine**

Conclusions

A large percentage of patients with MDD are not treated to remission

This leads to poor functional outcomes and a high risk of relapse

There remain many unmet needs in multiple symptom domains of MDD

Future treatments will focus on non-monoaminergic mechanisms


merci
thank you
gracias
obrigado
danke
go raibh maith agat
grazie
sukriya
bedankt
arigatô
ngiyabonga
dakujem
mochchakkeram
terima kasih
dank je
sagolun
chokrane
dziękuję
謝謝
takk
tapadh
teşekkür ederim
hvala
taiku
mauruuru
спасибо
мерси
ありがとう
Баярлалаа
ευχαριστώ
vinaka
barka
tau
kia ora
grazzi
dekuji
tanemirt
mersi
diolch
dhanyavad
spas
teşekkü ederim
welalin
gratias ago
matondo
dhanyavadagalu
kop khun
najis tuke
paldies
faafetai lava
kam sah hamnida
nanni
asante
rahmet
kop khun krap
mercé
leat
nandri
krap
didi madloba
mahalo
хвала
sobodi
dankon
manana
dankie
kiitos
tenki
murakoze
tack
aciü
djere dieuf