UNIVERSITY OF ALBERTA

Major Depressive Disorder

Mental Health Assessment and Prescribing by Alberta Pharmacists (MAP-AP) Study Group

REB ID Pro00093776

Learning Objectives

1. Describe the epidemiology and the impacts of Major Depressive Disorder (MDD)
2. Describe the diagnosis and clinical assessment for a patient with MDD
3. Describe patient administered monitoring tool (e.g., PHQ-9) to manage MDD
4. Compare and contrast different pharmacotherapy options
5. Summarize the step-wise approach to managing MDD

Epidemiology

- MDD affects 350 million people (5%) worldwide

- In Canada[1]:
  - Annual prevalence of Major Depressive Episodes (MDE) in general population is 4.5%
  - More than 1.5 million Canadians aged 15+ experienced a MDE in past year
  - Estimated lifetime prevalence of MDE is 11.3%
  - Lifetime prevalence of MDD is 9.9%

1. Kennedy et al. CJP. 2016: 1-21.

Epidemiology

- Up to 50% of patients with MDD are untreated[2]
- Peak age of onset: 20-40 years old[4]
- Higher incidence in females (2:1)[4]
- Inversely related to age[1]

1. Kennedy et al. CJP. 2016: 1-21.
2. Lecrubier. J Clin Psychiatry. 2007; 68 Suppl 2: 36-41
3. Patten. Can J Psychiatry. 2006;51:84-90
4. Kennedy et al. J Affect Disord 2009;117:S1-S64.

Impacts of MDD

- Quality of Life:
  - Depressive disorders were the second leading cause of disability worldwide (Global Burden of Disease Study 2010)

- Occupational Costs:
  - WHO Mental Health Survey (2010) participants with depression had a yearly mean of 34.4 ‘‘days out of role’’
  - Short and long-term disability episodes

Impacts of MDD

- Economic burden:
  - MDD in USA ~US $210.5 billion (2010)
  - Health Canada: Depression and distress cost Canadians at least $14.4 billion annually in treatment, medication, lost productivity, and premature death (2001)

- Social impairment
  - Strain on personal relationships

How is MDD diagnosed?

- Duration: ≥ 2 weeks
- Five or more of the following:
  1. Depressed mood*
  2. ↓ Interest or pleasure*
  3. Weight loss/gain (>5% change in 1 month)
  4. ↑/↓sleep
  5. Psychomotor agitation/retardation
  6. ↓ Energy
  7. Guilt/worthlessness
  8. ↓ Concentration/decisiveness
  9. Suicidal ideation (+/-plan)

*MUST include #1 and/or #2

Symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Episode is NOT attributable to the physiological effects of a substance or another medical condition.

Absence of history of manic or hypomanic episode

MDD: Severity

- Severity of MDD is based on number and severity of symptoms (Sx) & degree of functional disability
- Symptoms can be mild, moderate, or severe
- Note: the Nature of symptoms (e.g., suicidal ideation) should also be considered in assessing severity of MDD

MDD: Severity

- MILD
  - Few (if any) symptoms beyond the minimum required to make the diagnosis
  - Sx distressing but manageable
  - Minor social and/or occupational functional impairment

- MODERATE
  - More than minimum criteria met
  - Greater functional impairment (inbetween mild and severe)

- SEVERE
  - Excess of criteria beyond requirement for diagnosis.
  - Sx are seriously distressing and unmanageable.
  - Marked interference with social and/or occupational functioning

MDD: Assessment

- Assessment for MDD is comprised of the following:
  - Clinical Presentation (SIGECAPS*)
  - History of Presenting Illness
  - Medication History
  - Family & Social History
  - Functional Overlap

Assessment: Clinical Presentation

S	Sleep disorder ↑ or ↓
I	Interest deficit (anhedonia)
G	Guilt (worthlessness, hopelessness, regret)
E	Energy deficit
C	Concentration deficit
A	Appetite disorder ↑ or ↓
P	Psychomotor retardation or agitation
S	Suicidality

Note:

- No two patients will have the same presentation
- Consider ethnic, religious, and cultural factors
- Consider life event stressors

Abraham et al. Am J Psychiatry. 2006

Assessment: History of Presenting Illness

- Timing
  - Preceding psychosocial stressors (e.g., major life events, mourning)
  - Prodromal symptoms (e.g., social withdrawal, fatigue, mood swings)
  - Episodes of symptoms/ episodes over time
  - Seasonality of symptoms

- Functional impairments
  - Work, life, relationships, sleep (collateral/ insight from others)
  - Hospitalizations

Assessment: History of Presenting Illness

- Concurrent Psych Disorders
  - Bipolar-hypomania or mania (length of time)
  - Anxiety
  - Suicidal ideation/tendencies
  - Psychotic symptoms
  - Hospitalizations

- General Medical Disorders associated with MDD
  - Chronic disease (DM, COPD, Stroke, CVD, Obesity, thyroid disorders)
  - Infectious disease (AIDS)
  - Cancer
  - Neuro (stroke, parkinson dx, dementia, MS)

Assessment: Medication Hx

- Several medications are associated with depression

- Antihypertensives:
  - ACE-I, clonidine, diuretics, guanethidine, hydralazine, methyldopa, digoxin, propranolol, reserpine
- Hormonal therapy:
  - OC, steroids, CS, tamoxifen, GnRH agonists, finasteride
- Anticonvulsants:
  - Levetiracetam, phenobarbital, primidone, phenytoin, tiagabine, vigabatrin
- Acne therapy:
  - Isotretinoin, Tetracycline
- Others:
  - Interferon (B-1a, alpha), apremilast, varenicline, levodopa, efavirenz, substance of abuse (alcohol, amphetamines, cocaine, marijuana, opioids, benzodiazepines), acetazolamide, antibiotics

Assessment: Family Hx

- 2-3 x higher risk if a parent or a sibling is diagnosed with MDD
- 4-5x higher risk if a parent or a sibling has recurrent depression or was diagnosed with MDD early in life (childhood to twenties)
- Family Hx of bipolar disorder
- Family Hx can help with directing treatment planning (e.g., consider antidepressants that were effective for family members)

Assessment: Social Hx

- Concurrent Substance use
  - Smoking, ETOH, recreational drugs
- Social Supports
- Psychosocial Stressors
  - Significant loss/bereavement
  - Interpersonal conflict
  - Financial difficulties
  - Life changes
  - Abuse
  - Trauma

Assessment: Review of Systems

CNS	● Headache ● Vague aches and pains ● Memory: pseudodementia, global memory loss ● Speech ○ little or no spontaneity, monosyllabic, long pauses, soft low monotone, non-linear thought pattern, difficulty getting to the point
PSYCH	● Mood & affect: depressed, irritable, frustrated, sad, constricted ● Thought content and process ○ Delusions and hallucinations, pervasive negative view & hopelessness, obsessive rumination, worthlessness, guilt, somatic preoccupations, indecisiveness, poverty of content ● Suicidal thinking
MSK	● Back pain
ENDO	Hypothyroidism ● Can contribute to depressive symptoms

Patient Monitoring Tool for MDD: PHQ-9

- Patient Health Questionnaire (PHQ)
- 9 Items/Questions
  - Patient Self Administered
  - Each item scored out of 3
  - Reviews criteria that has bothered the patient in the past 2 weeks
  - Expected completion ≤ 3 minutes

- Addresses DSM-IV criteria, valid for dx of MDD in primary care (vs. HAM-D)
  - 82% sensitivity (95% CI 77-86%)
  - 83% specificity (95% CI 76-88%)

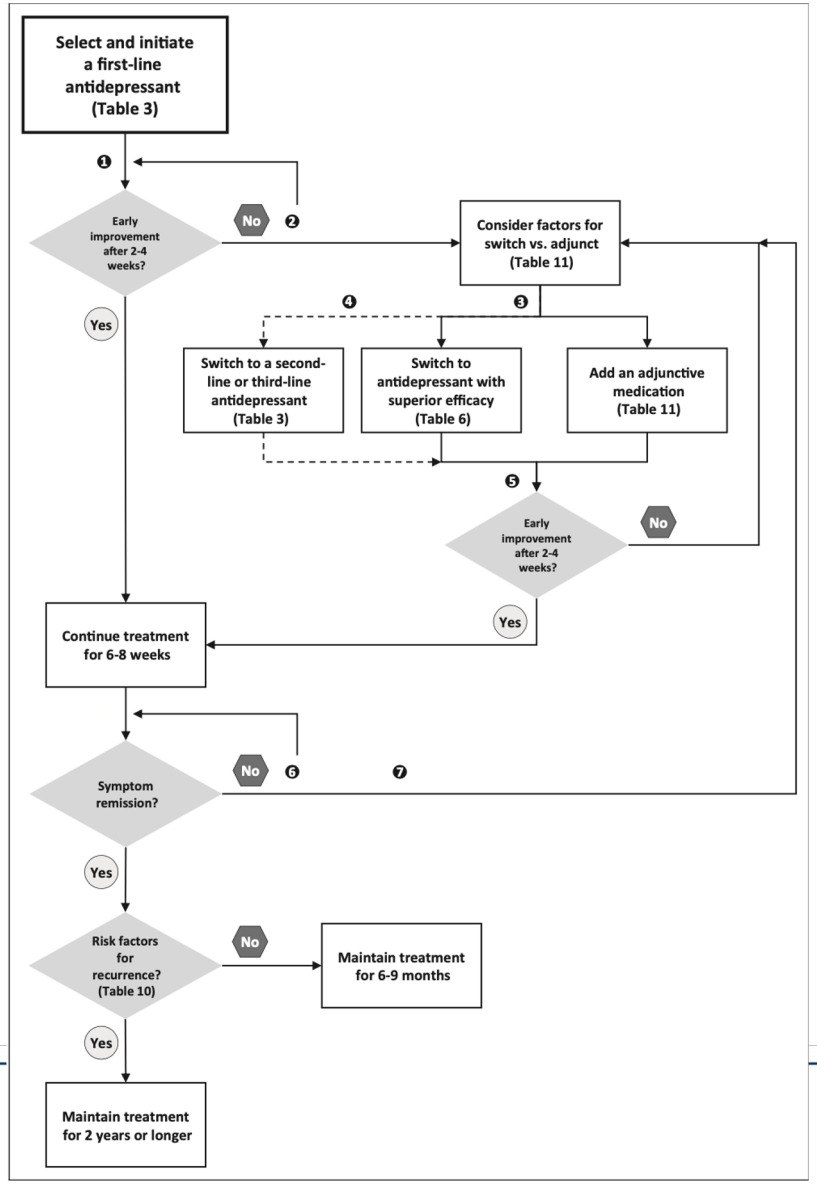
PHQ-9: Items

		Not at all	Several days	More than half the days	Nearly every day
1.	Little interest or pleasure in doing things	0	1	2	3
2.	Feeling down, depressed, or hopeless	0	1	2	3
3.	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4.	Feeling tired or having little energy	0	1	2	3
5.	Poor appetite or overeating	0	1	2	3
6.	Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7.	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8.	Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9.	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

PHQ-9: Scoring

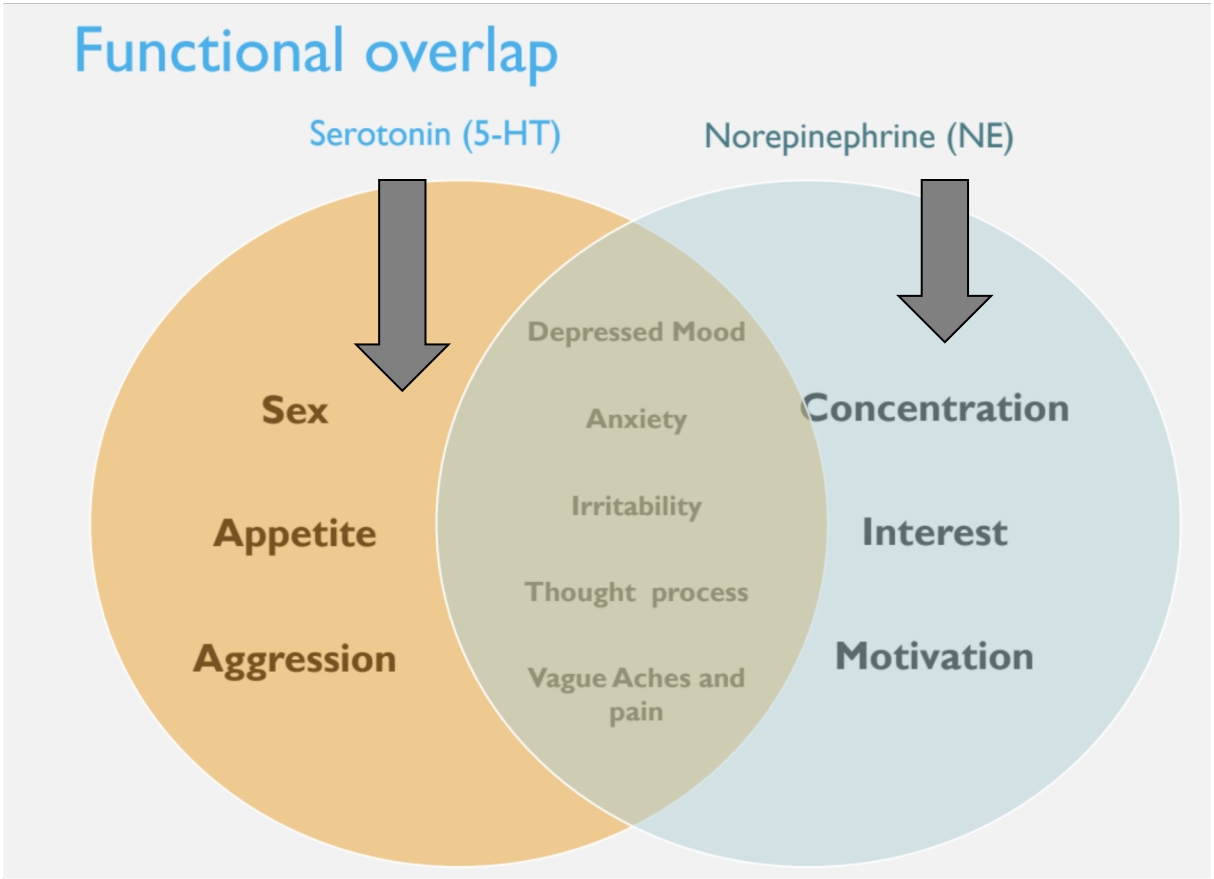
Score	Depression Severity
0-4	None - Minimal
5-9	Mild
10-14	Moderate
15-19	Moderately Severe
20-27	Severe

Overview: Management of MDD



Pharmacotherapy: MDD

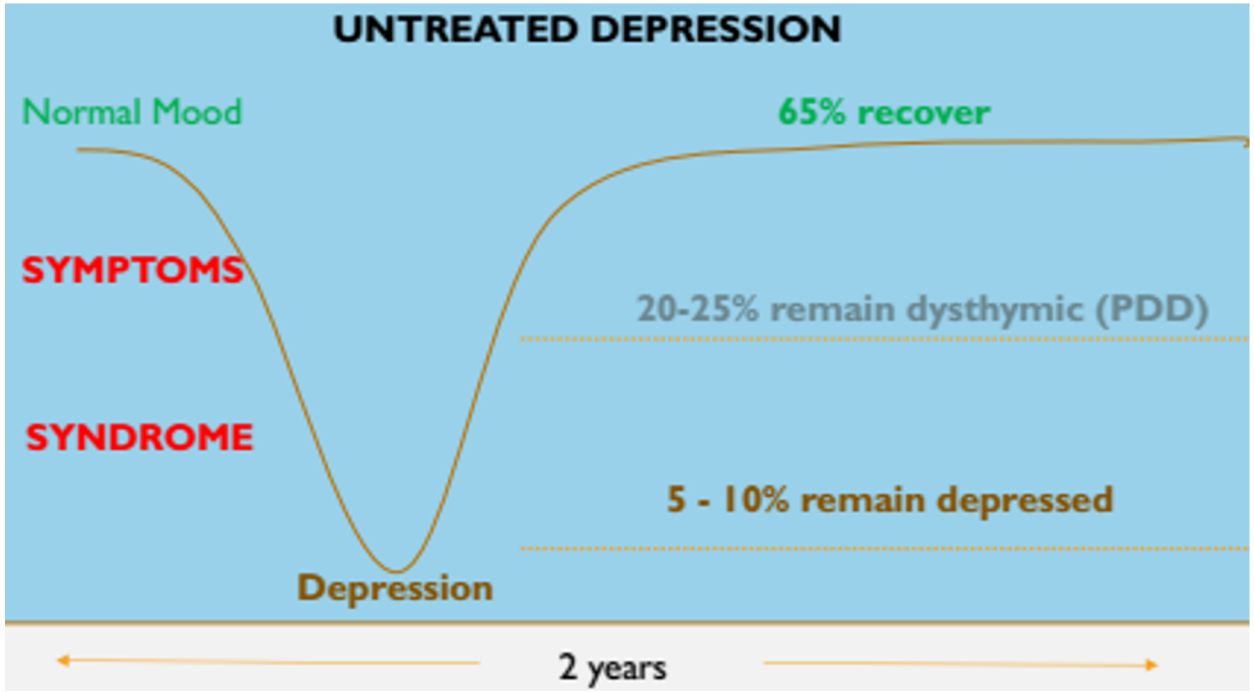
- Neurotransmitters (NT) responsible for certain symptoms
- Monoamine theory: MDD is caused by functional deficits of the monoamine NT at certain sites in brain
- Patient presentation can be helpful in identifying the NT they may be lacking



Ref: Adapted from: Stahl SM. In: Essential Psychopharmacology: Neuroscientific Basis and Practical Applications: 2nd ed. Cambridge University Press 2000.

MDD: Treatment vs. No Treatment

- Untreated, episodes typically last 6 months or longer
- Treated, median time to recovery is 20 weeks (APA, 2010)
- Consider collateral risks
  - Losing job, suicide risk, relationships affected

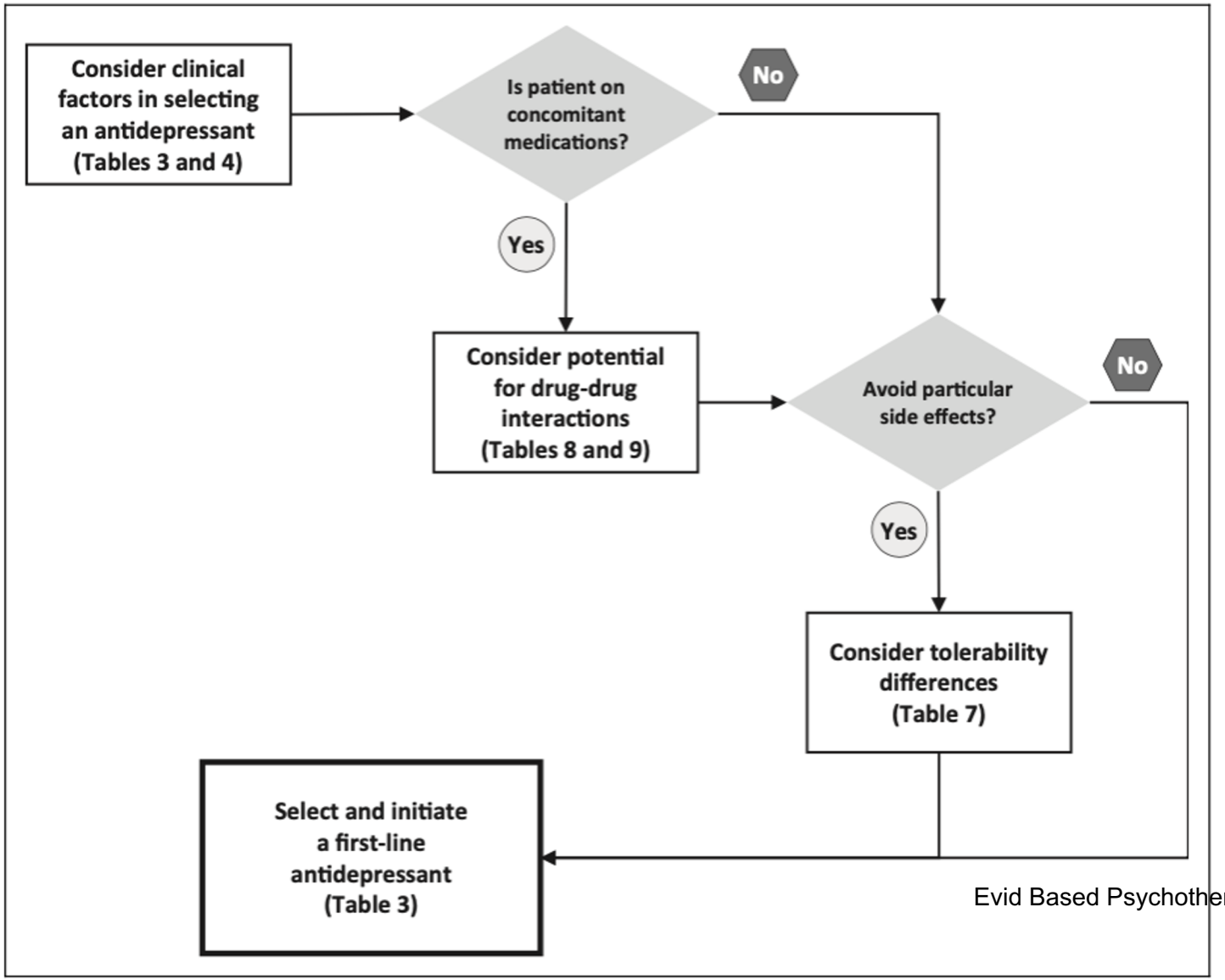


Adapted from: Am J Psych 2000 Apr; 157 (4 suppl) 1- 45

MDD: Goals of Therapy

Acute Phase (8-12 weeks since the initial diagnosis)	Maintenance Phase (6-24+ months, once patient reached remission)
Symptom remission Restore function	Restoration to full function and quality of life Prevent recurrence
At all phases...	
Prevent consequence(s) of illness Prevent/ minimizes adverse effects of medications	

MDD: Pharmacotherapy initiation



Evid Based Psychother. 2015;15:147

MDD: Pharmacotherapy initiation

- CANMAT Guideline (p. 544)
- Pharmacotherapy options
  - Participants will bring in their prescription to your pharmacy

- Non-Pharm options
  - Psychotherapy: mild-moderate severity
    - Meta-analysis demonstrates psych + meds > meds alone
  - Exercise: at least 30 minutes moderate intensity 3x/week
  - Neurostimulation: ECT is 2nd line

MDD: First Line Pharmacotherapy

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

MDD: Second & Third Line Pharmacotherapy

Second line (Level 1 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)[e]	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 1 Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

5-HT, 5-hydroxytryptamine (serotonin); MAO, monoamine oxidase; MT, melatonin; NDRI, noradrenaline and dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Not available in Canada.

[b]Available as sustained-release (SR) and extended-release (XL) versions.

[c]Available as rapid-dissolving (RD) version.

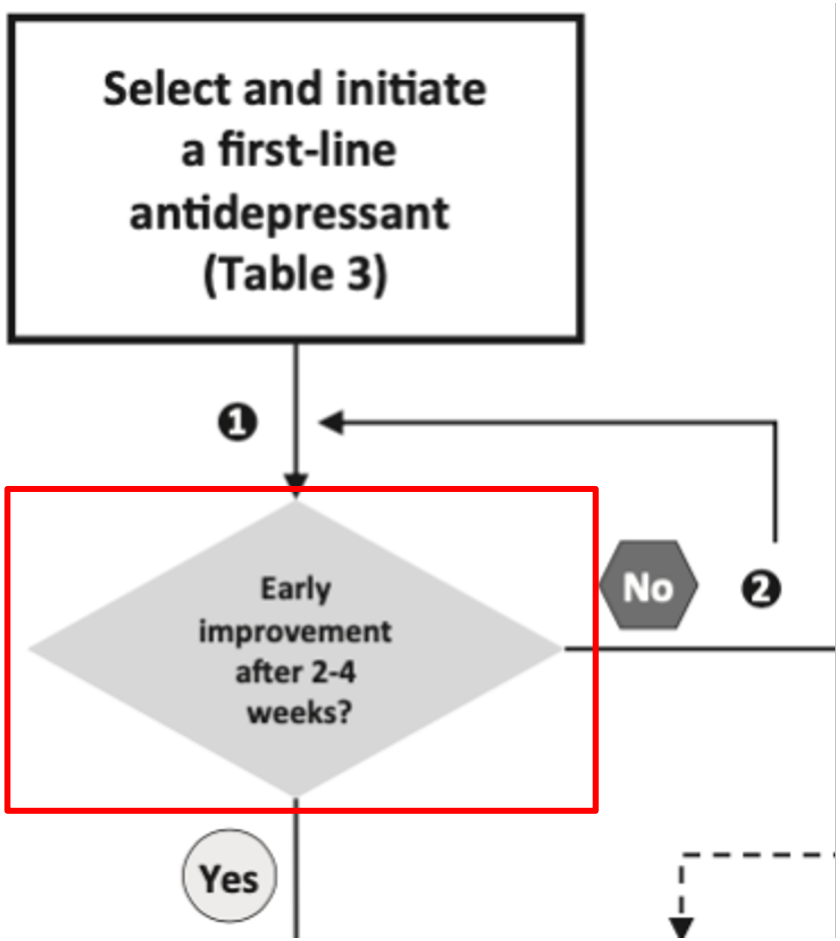
[d]Available as controlled-release (CR) version

[e]Available as extended-release (XR) version.

[f]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.

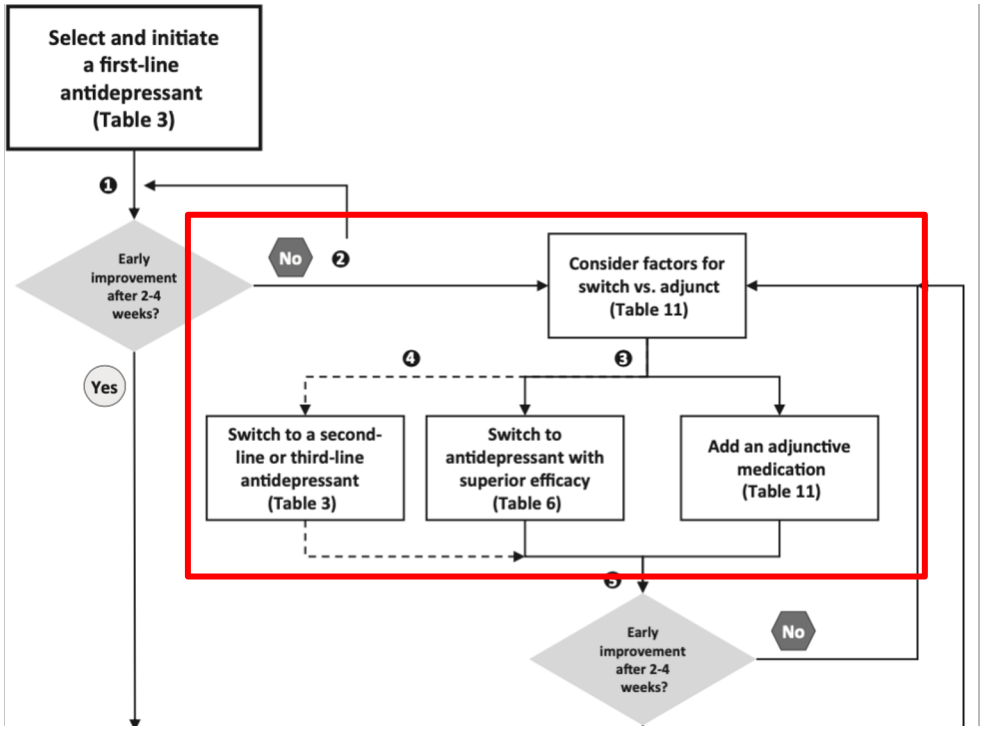
MDD: Management

- CANMAT Guideline (p. 551)
- Early improvement (≥20% reduction in symptom score) to a first-line agent should be apparent within 1-4 weeks of achieving a (potentially) therapeutic dose



MDD: Management

- If this does NOT occur, consider:
  - Increasing dose (if Rx well tolerated)
  - Switching agents (if Rx poorly-tolerated)
  - + consider adding adjunct medications, psychological or neurostimulation treatments



MDD: Adjunctive medications

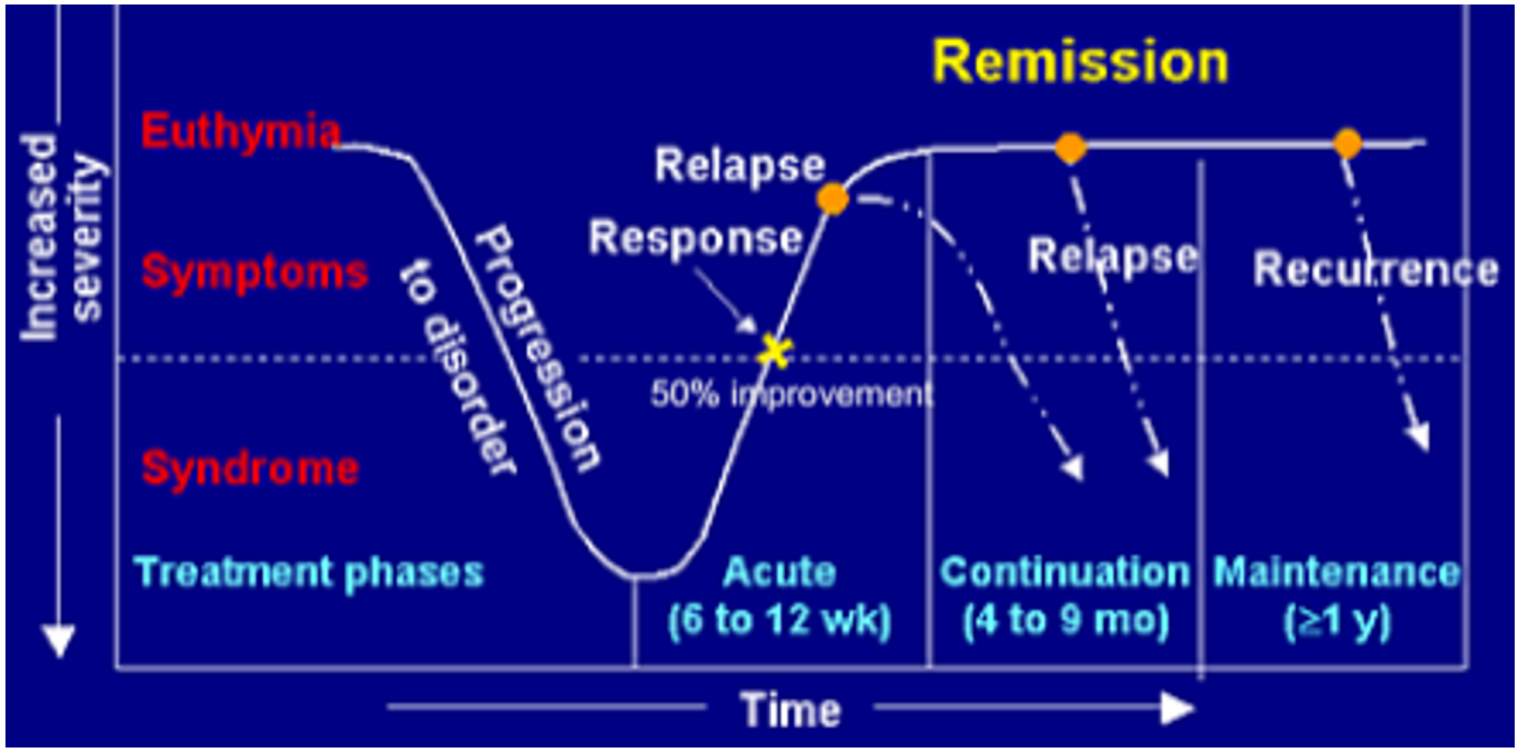
Table 11. Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

MDD: Expected Course

- MDD is a medical condition with a high rate of relapse
- Consider risk factors of patients for long-term maintenance of MDD



MDD: Monitoring response

Level of Response	% Reduction from Baseline Rating Scale Score
Early Response	≥ 20%* *Within 1-4 weeks of achieving potentially therapeutic dose
Response	≥ 50%
Partial Response	25-49%
Non-response	<25%
Remission	Goal* *No longer meets diagnostic criteria

Note: in the MAP-AP Study, one secondary outcome is difference in % of participants achieving response using the PHQ-9

MDD: Monitoring response

- Full therapeutic effect may not be evident for 4-6 (even 8) weeks
  - Some response may be seen as early as 2 weeks
  - Average time to remission (complete Sx relief) is ~ 6-8 weeks

- Follow-up visits every 1-3 months
  - Evaluate efficacy
  - Checking in every 1-2 weeks for adverse effects, and check for suicide risk

Note: in the MAP-AP Study, one secondary outcome is difference in % of participants achieving response using the PHQ-9

MDD: Course of Therapy

- Treat a minimum of 6-9 months after recovery
  - NOTE: higher relapses/recurrent when stopped within 6 months
  - Patients with risk factors for recurrent may require 2+yrs

- When stopping, taper drug over 2-3 months
  - If relapse, treat 3-6 more months

Monitoring: Common adverse effects

CNS	Headache, dizziness somnolence, insomnia
PSYCH	Nervousness, anxiety, agitation
HEENT	Dry mouth
GI/GU	Nausea, constipation, anorexia
MSK	Tremor

Monitoring: Medication-Specific Adverse Effects

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.

[a]Data from all indications.
[b]Data from 50-mg dose.
[c]C, common effects, ≥1% and <10%.
[d]Data from 100- to 150-mg dose.
[e]Data from 40-mg dose.
[f]Data from 10-mg dose.

References

1. Kennedy 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. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 61(9), 540–560.
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Monitoring: Suicide Ideation

- Ongoing evaluation PRN for RISK
- Ask about suicidal thoughts, intent, plans, means, and behaviors
- Identify specific psychiatric symptoms (for example, psychosis, severe anxiety, substance use) or general medical conditions that may increase likelihood of acting on suicidal ideas
- Assess past (especially recent) suicidal behavior
- Ask about current stressors and potential protective factors (for example, positive reasons for living, strong social support)
- Ask about family history of suicide or mental illness

Monitoring: Suicide ideation

- If detected, ask directly for IDEATION and INTENT
  - Do you feel that life is worth living?
  - Do you wish you were dead?
  - Do you ever think about ending your life? If yes, then ask
  - Do you currently have a plan? If yes, then ask
  - What is your plan; be specific, what method would you use?
  - Do you have access to a way to carry out your plan?
  - What keeps you from harming yourself?

- IF RISK of immediate harm to themselves or others→ urgent referral to specialist mental health services (AHS Access Mental Health brochure)