항우울제 사용의 원칙

Who should be treated with pharmacotherapy?

•Most second-generation antidepressants as first-line treatments for patients with a major depressive episode of moderate or greater severity (as determined by symptom scales and/or functional impairment).

•First-line treatments for individuals with depression of mild severity include psychoeducation, self-management, and psychological treatments.

•Pharmacological treatments can be considered for mild depression in some situations, including patient preference, previous response to antidepressants, or lack of response to nonpharmacological interventions.

Principles of pharmacotherapy management

- Conduct a detailed clinical assessment, including evaluation of suicidality, bipolarity, comorbidity, concomitant medications, and symptom specifiers/dimensions.
- Discuss evidence-based pharmacologic and nonpharmacologic treatment options.
- Elicit patient preference in the decision to use pharmacological treatment.
- Evaluate previous treatments, including dose, duration, response, and side effects of antidepressant and related medications.

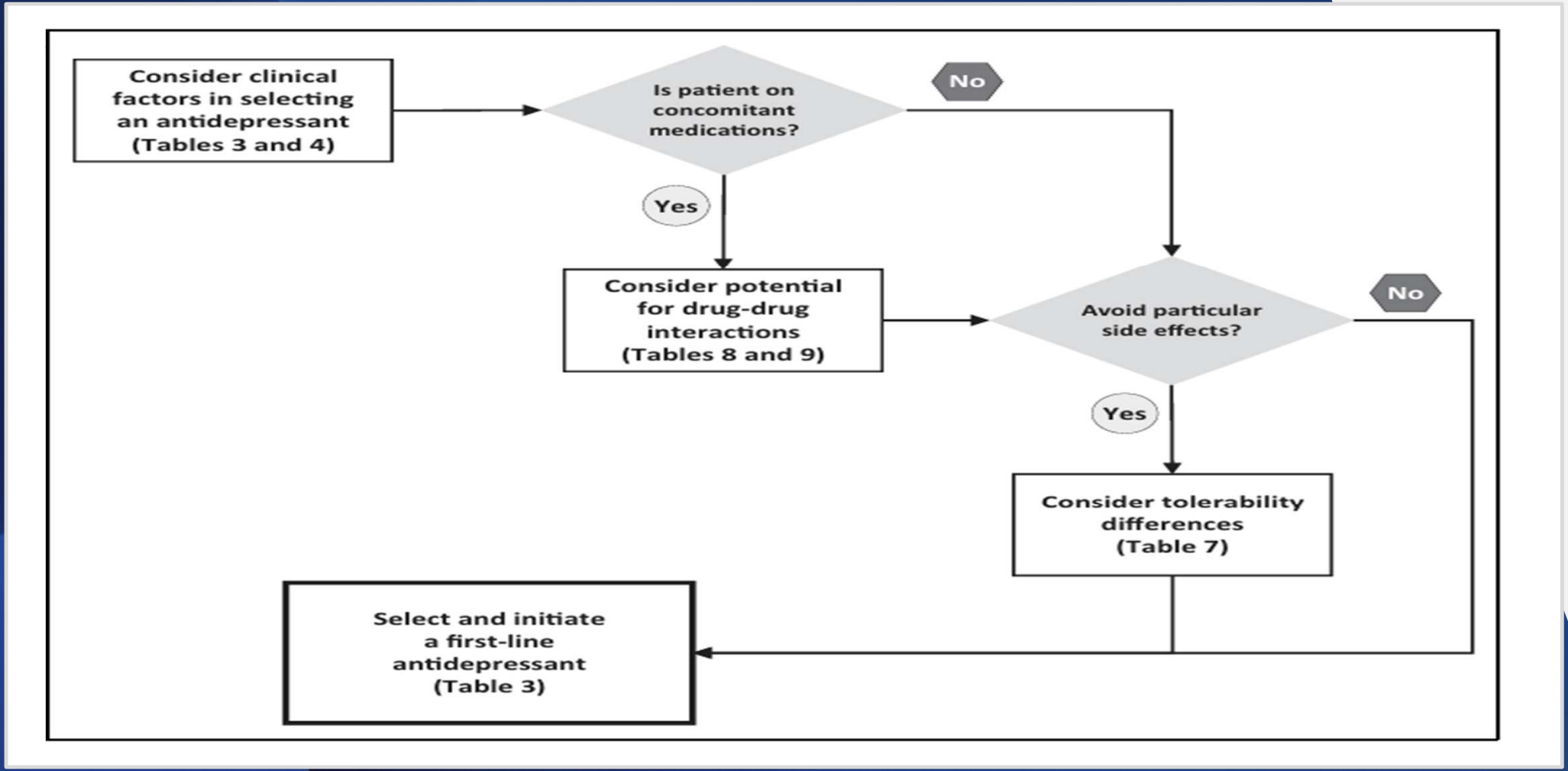
Principles of pharmacotherapy management

•Where clinically indicated, refer for laboratory testing, including lipids, liver function tests, and electrocardiograms.

•Reassess patients for tolerability, safety, and early improvement no more than 2 weeks after starting a medication. Further follow-up may be every 2 to 4 weeks.

•Follow measurement-based care by using validated rating scales to monitor outcomes and guide clinical decisions.

Summary algorithm for selecting an antidepressant



How do you select an antidepressant?

- First-line recommendations for pharmacotherapy for MDD: SSRIs, SNRIs, agomelatine, bupropion, mirtazapine, and vortioxetine
- Second-line agents: TCAs, quetiapine and trazodone, moclobemide and selegiline, levomilnacipran, and vilazodone
- Third-line recommendations: MAO inhibitors and reboxetine

우리나라 1차 치료 항우울제

권고 내용	권고등급	근거수준	권고도출 자료원
• 주요우울삽화를 갖는 환자에게 약물치료를 권고한다.[a]	I	A	1, 3, 73-83
• 약물치료 뿐만 아니라 정신사회적 중재법(정신치료, 인지행동치료, 대인관계치료, 운동 등)과 병합하여 포괄적인 치료계획을 세울 것을 권고한다.[b]	I	A	1, 3, 73-83
• 항우울제는 임상양상, 공존질환, 이전의 약물치료 병력, 부작용, 약물 상호작용, 환자의 기호 등을 종합하여 선택할 것을 권고한다.[c]	I	A	1, 84-86
• 1차 치료 항우울제는 SSRI (escitalopram, sertraline, fluoxetine, paroxetine 등), SNRI (duloxetine, milnacipran, venlafaxine, desvenlafaxine 등), mirtazapine, agomelatine, bupropion, vortioxetine에서 선택할 것을 권고한다.	I	A	1, 19, 87-99
• 급성기 치료에서 관해에 이르면 재발방지를 위해 유지치료 시행을 고려할 수 있다.	IIb	B	1, 134-138

How do you select an antidepressant?

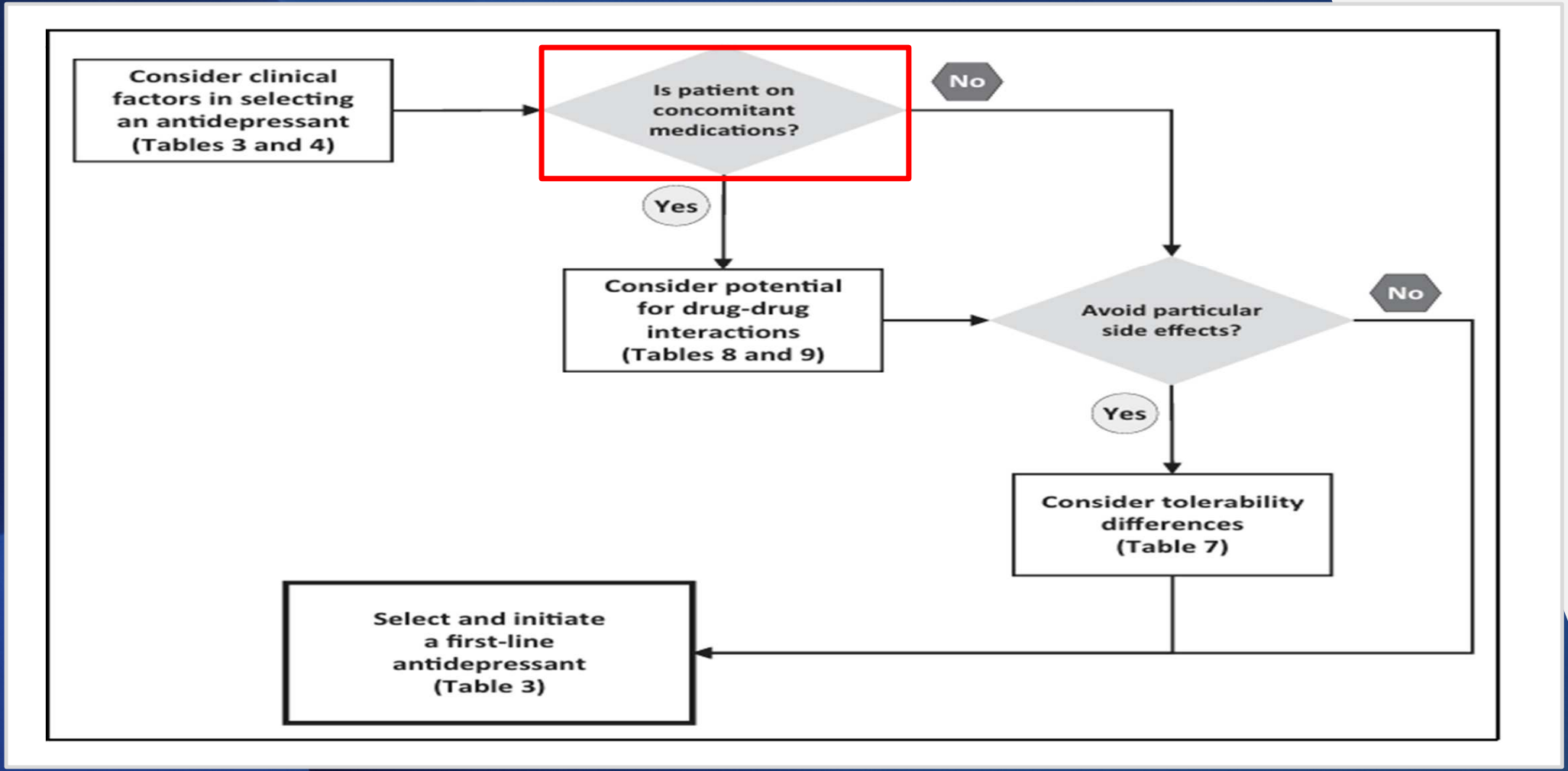
Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level I Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	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)[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 I Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

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

- Selecting an antidepressant involves an individualized needs assessment for each patient.

Summary algorithm for selecting an antidepressant



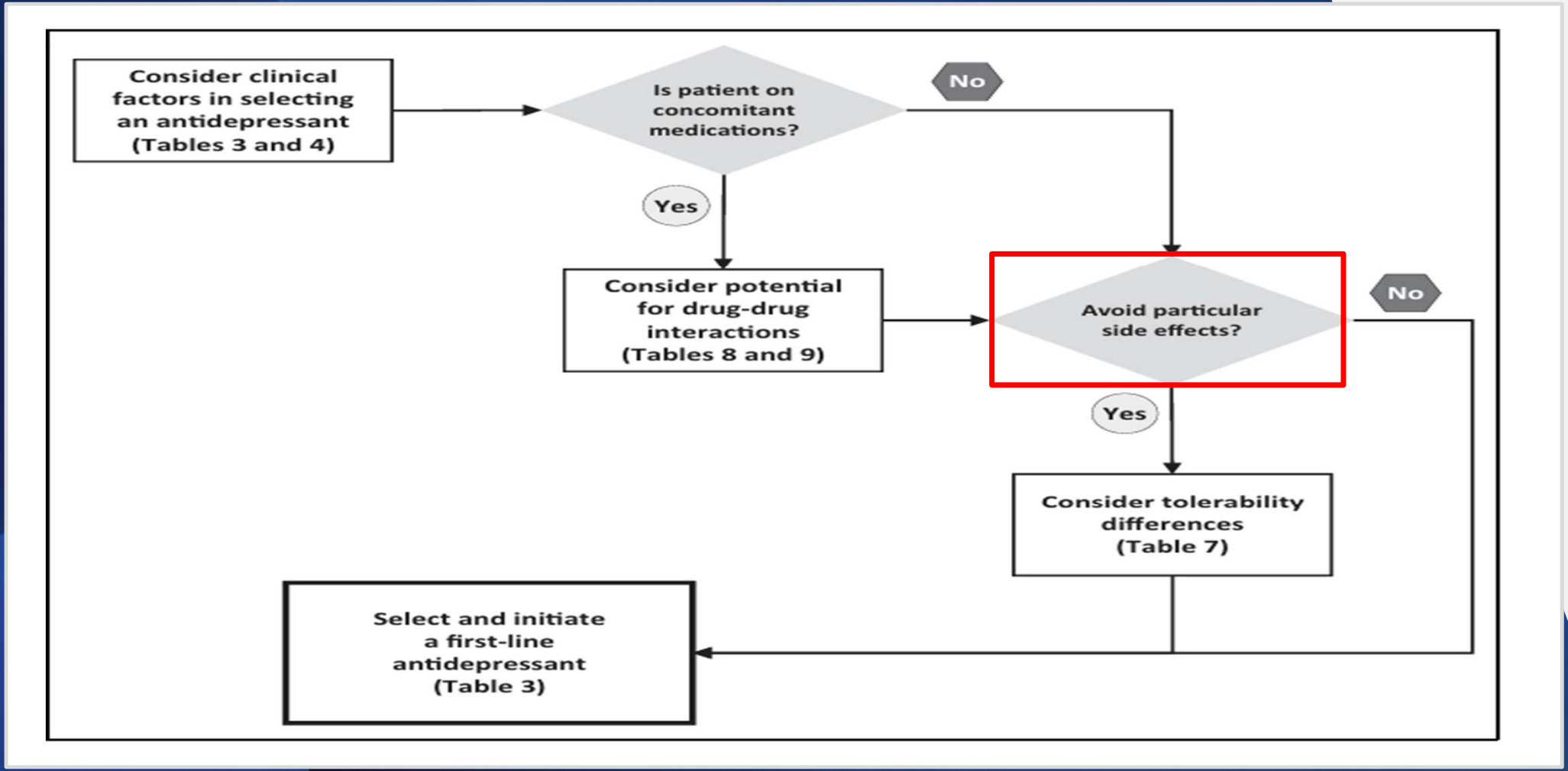
Drug Interactions

Cytochrome P450 Inhibition of	Increases Serum Levels of These CYP Substrates	
CYP1A2	• **Agomelatine** • Caffeine • **Clozapine** • **Duloxetine** • Mexiletine	• Naproxen • **Olanzapine** • **Risperidone** • Tacrine • Theophylline • Warfarin
CYP2C19	• Antiarrhythmics • Antiepileptics (diazepam, phenytoin, phenobarbital) • Indomethacin	• Omeprazole • Primidone • Propanolol • Warfarin
CYP2D6	• Tricyclic antidepressants • Beta-blockers (metoprolol, propranolol) • Codeine and other opioids (reduces effect) • **Olanzapine**	• **Risperidone** • **Vortioxetine** • Tamoxifen (reduces effect) • Tramadol
CYP3A4	• Amiodarone • Antiarrhythmics (quinidine) • Antihistamines (astemizole, chlorpheniramine) • Calcium channel antagonists (e.g., diltiazem, verapamil) • **Haloperidol** • HIV protease inhibitors • Statins • Immune modulators (cyclosporine, tacrolimus)	• **Levomilnacipran** • Macrolide antibacterials (clarithromycin, erythromycin) • **Methadone** • **Phenothiazines** • **Quetiapine** • Sildenafil • Tamoxifen • **Vilazodone**

Newer Antidepressants and Atypical Antipsychotics

Potential for Drug-Drug Interaction	Antidepressants	Atypical Antipsychotics
Minimal or low potential	• Citalopram • Desvenlafaxine • Escitalopram • Mirtazapine • Venlafaxine	• Paliperidone
Moderate potential	• Agomelatine (1A2 substrate[a]) • Bupropion (2D6 inhibitor) • Duloxetine (2D6 inhibitor; • 1A2 substrate[a]) • Levomilnacipran (3A4 substrate) • Sertraline (2D6 inhibitor) • Vilazodone (3A4 substrate) • Vortioxetine (2D6 substrate)	• Aripiprazole (2D6, 3A4 substrate) • Olanzapine (1A2 substrate[b]) • Risperidone (2D6, 3A4 substrate)
Higher potential	• Fluoxetine (2D6, 2C19 inhibitor) • Fluvoxamine (1A2, 2C19, 3A4 inhibitor) • Moclobemide (MAO inhibitor precautions[c]) • Paroxetine (2D6 inhibitor) • Selegiline (MAO inhibitor precautions[c])	• Clozapine (3A4, 1A2 substrate) • Lurasidone (3A4 substrate) • Quetiapine (3A4 substrate)

Summary algorithm for selecting an antidepressant



Prevalence of Adverse Events

	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

How long do you wait for a response?

- Early improvement is correlated with response and remission at 6 to 12 weeks.
- Increasing the antidepressant dose for nonimprovers at 2 to 4 weeks if the medication is tolerated and switching to another antidepressant if tolerability is a problem.

How Long Do You Continue an Antidepressant?

•Patients 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 to Consider Longer Term Maintenance Treatment with Antidepressants

-Frequent, recurrent episodes

-Severe episodes (psychosis, severe impairment, suicidality)

-Chronic episodes Presence of comorbid psychiatric or other medical conditions

-Presence of residual symptoms

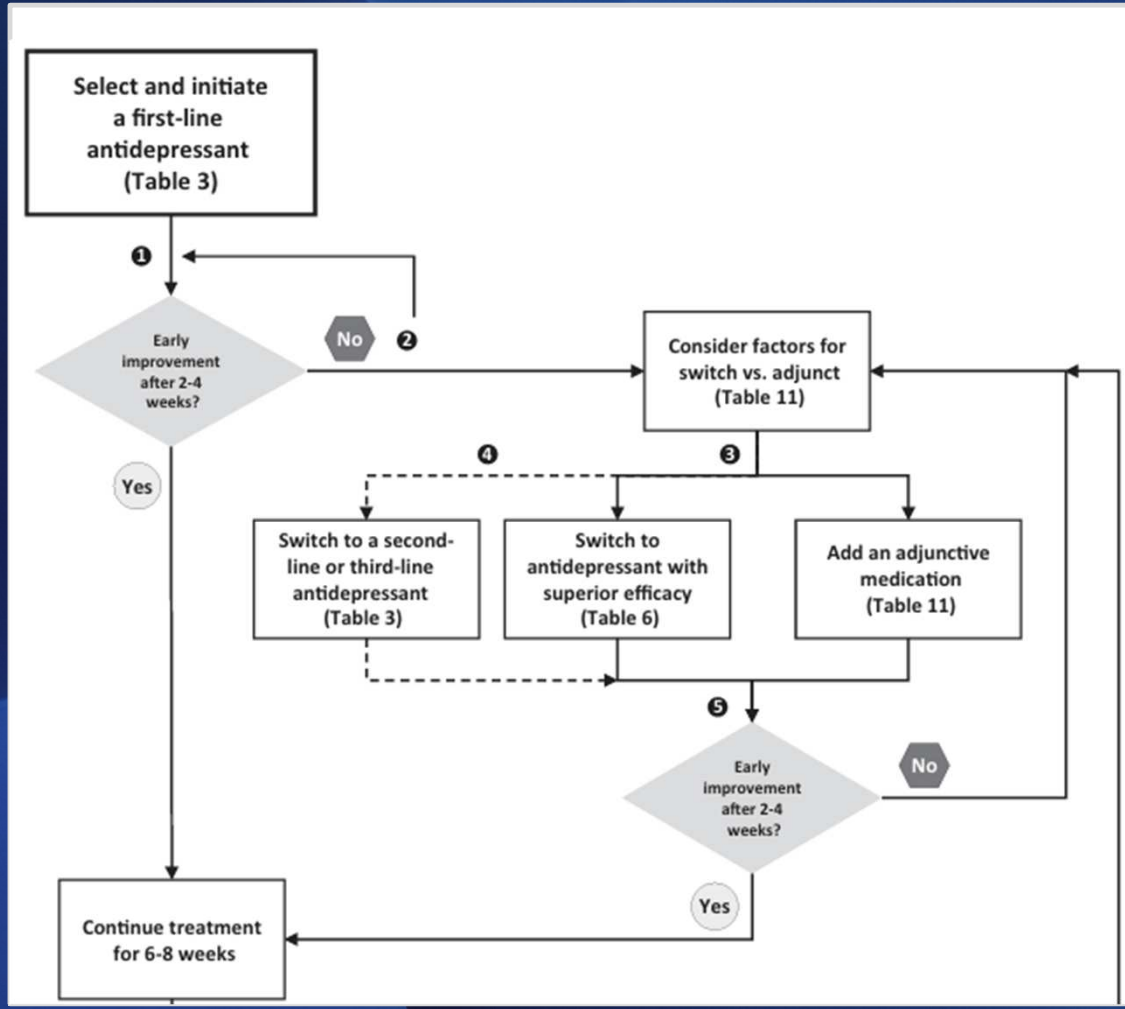
-Difficult-to-treat episodes

How Long Do You Continue an Antidepressant?

•Discontinuation symptoms, described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly.

•Slowly tapering the dose over several weeks when discontinuing antidepressants.

Managing inadequate response

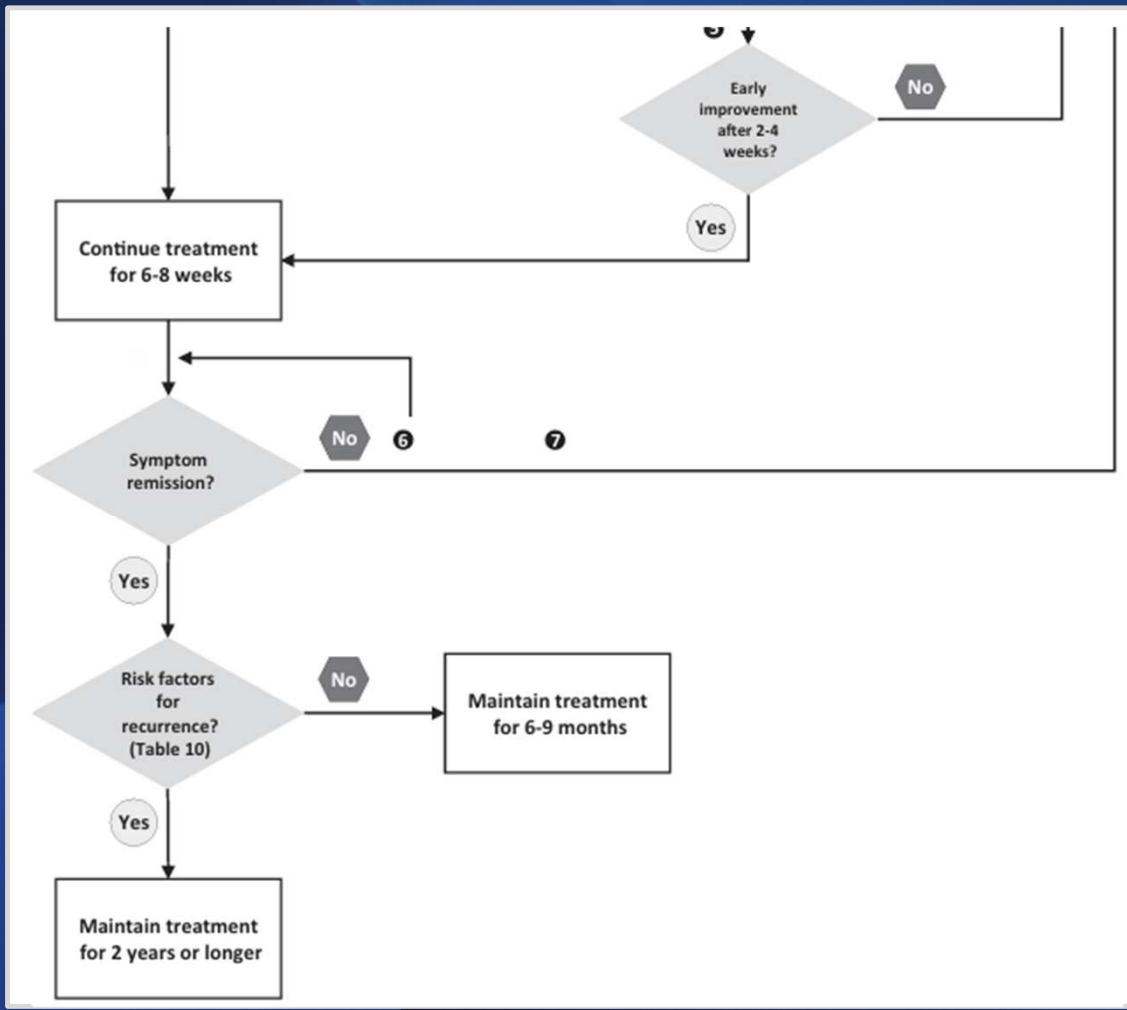


(1)Monitor outcomes using measurement-based care.
(2)Depending on tolerability, first optimize antidepressant by increasing dose.
(3)For early treatment resistance, consider adjunctive use of psychological and neurostimulation treatments.
(4)After failure of 1 or more antidepressants, consider switch to asecond-line or third-line antidepressant.
(5) For more resistant depressions, consider longer evaluation periods for improvement.

Antidepressants for superior efficacy

Antidepressant	Comparator medications
Escitalopram	Citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine
Mirtazapine	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Sertraline	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Venlafaxine	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Agomelatine	Fluoxetine, sertraline
Citalopram	Paroxetine

Managing inadequate response



(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.

Adjunctive medications

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.

Factors to Consider in Choosing between Switching or Adding an Adjunctive Medication

Consider switching to another antidepressant when:	**It is the first antidepressant trial.** **There are poorly tolerated side effects to the initial antidepressant.** **There is no response (<25% improvement) to the initial antidepressant.** **There is more time to wait for a response (less severe, less functional impairment).** **Patient prefers to switch to another antidepressant.**
Consider an adjunctive medication when:	There have been 2 or more antidepressant trials. The initial antidepressant is well tolerated. There is partial response (>25% improvement) to the initial antidepressant. There are specific residual symptoms or side effects to the initial antidepressant that can be targeted. There is less time to wait for a response (more severe, more functional impairment). Patient prefers to add on another medication.