Major depressive disorder

- ✓ The essential feature of major depressive disorder is a clinical course that is characterized by one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes.

- ✓ Dysthymic disorder is a chronic disturbance of mood involving depressed mood and at least two other symptoms, and it is generally less severe than major depressive disorder.

PATHOPHYSIOLOGY:

- Biogenic amine hypothesis. Depression may be caused by decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5-HT), and dopamine (DA). Postsynaptic changes in receptor sensitivity. Studies of many antidepressants have demonstrated that desensitization or downregulation of NE or 5-HT1A receptors may relate to onset of antidepressant effects.

- Dysregulation hypothesis. This theory emphasizes a failure of homeostatic regulation of neurotransmitter systems, rather than absolute increases or decreases in their activities. Effective antidepressants are theorized to restore efficient regulation to these systems.

- 5-HT/NE link hypothesis. This theory suggests that there is a link between 5-HT and NE activity, and that both the serotonergic and noradrenergic systems are involved in the antidepressant response.

- The role of DA. Several reviews suggest that increased DA neurotransmission in the mesolimbic pathway may be related to the mechanism of action of antidepressants.

CLINICAL PRESENTATION:

✓Emotional symptoms may include diminished ability to experience pleasure, loss of interest in usual activities, sadness, pessimistic outlook, crying spells, hopelessness, anxiety (present in almost 90% of depressed outpatients), feelings of guilt, and psychotic features (e.g., auditory hallucinations, delusions).

• Physical symptoms may include fatigue, pain (especially headache), sleep disturbance, appetite disturbance (decreased or increased), loss of sexual interest, and GI and cardiovascular complaints (especially palpitations).

• Intellectual or cognitive symptoms may include decreased ability to concentrate or slowed thinking, poor memory for recent events, confusion, and indecisiveness.

• Psychomotor disturbances may include psychomotor retardation (slowed physical movements, thought processes, and speech) or psychomotor agitation.

DSM-IV-TR Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly caused by a general medical condition or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

D. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

DIAGNOSIS:

- Major depression is characterized by one or more episodes of major depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

- Symptoms must have been present nearly every day for at least 2 weeks. Patients with major depressive disorder may have one or more recurrent episodes of major depression during their lifetime.

- When a patient presents with depressive symptoms, it is necessary to investigate the possibility of a medical-, psychiatric-, and/or drug-induced cause.

- Depressed patients should have a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determinations.

Common Medical Conditions, Substance Use Disorders, and Medications Associated with Depressive Symptoms

General medical conditions

Endocrine diseases
- Hypothyroidism
- Addison's or Cushing's disease

Deficiency states
- Pernicious anemia
- Wernicke encephalopathy
- Severe anemia

Infections
- AIDS
- Encephalitis
- Human immunodeficiency virus
- Mononucleosis
- Sexually transmitted diseases
- Tuberculosis

Collagen disorder
- Systemic lupus erythematosus

Metabolic disorders
- Electrolyte imbalance
  - Hypokalemia
  - Hyponatremia
- Hepatic encephalopathy

Cardiovascular disease
- Coronary artery disease
- Congestive heart failure
- Myocardial infarction

Neurologic disorders
- Alzheimer's disease
- Epilepsy
- Huntington's disease
- Multiple sclerosis
- Pain
- Parkinson's disease
- Poststroke

Malignant disease

Substance use disorders (including intoxication and withdrawal)
- Alcoholism
- Marijuana abuse and dependence
- Nicotine dependence
- Opiate abuse and dependence (e.g., heroin)
- Psychostimulant abuse and dependence (e.g., cocaine)

Drug therapy

Antihypertensives
- Clonidine
- Diuretics
- Guanethidine sulfate
- Hydralazine hydrochloride
- Methyldopa
- Propranolol
- Reserpine

Hormonal therapy
- Oral contraceptives
- Steroids/adrenocorticotropic hormone

Acne therapy
- Isotretinoin

Other

Interferon-β_{1a}

DESIRED OUTCOME:

- The goals of treatment of the acute depressive episode are to eliminate or reduce the symptoms of depression, minimize adverse effects, ensure compliance with the therapeutic regimen, facilitate a return to a premorbid level of functioning, and prevent further episodes of depression.

TREATMENT:

NONPHARMACOLOGIC TREATMENT

- The efficacy of psychotherapy and antidepressants is considered to be additive. Psychotherapy alone is not recommended for the acute treatment of patients with severe and/or psychotic major depressive disorders.

- For uncomplicated nonchronic major depressive disorder, combined treatment may provide no unique advantage. Cognitive therapy, behavioral therapy, and interpersonal psychotherapy appear to be equal in efficacy.

- Electroconvulsive therapy (ECT) is a safe and effective treatment for major depressive disorder. It is considered when a rapid response is needed, risks of other treatments outweigh potential benefits, there has been a poor response to drugs, and the patient expresses a preference for ECT.

- A rapid therapeutic response (10 to 14 days) has been reported. Relative contraindications include increased intracranial pressure, cerebral lesions, recent myocardial infarction, recent intracerebral hemorrhage, bleeding, and otherwise unstable vascular conditions.

- Adverse effects of ECT include confusion, memory impairment (retrograde and anterograde), treatment emergent mania, headache, nausea, muscle aches, and cardiovascular dysfunction. Relapse rates during the year following ECT are high unless maintenance antidepressants are prescribed.

- Bright light therapy (i.e., the patient looking into a 10,000-lux intensity light box for about 30 min/day) may be used for patients with seasonal affective disorder and as adjunctive use for major depression.

PHARMACOLOGIC THERAPY—GENERAL THERAPEUTIC PRINCIPLES:

- In general, antidepressants are equal in efficacy in groups of patients when administered in comparable doses.

- Factors that influence the choice of antidepressant include the patient's history of response, history of familial response, concurrent medical conditions, presenting symptoms, potential for drug–drug interactions, comparative side-effect profiles of various drugs, patient preference, and drug cost.

- Between 65% and 70% of patients with major depression improve with drug therapy.

- Psychotically depressed individuals generally require either ECT or combination therapy with an antidepressant and an antipsychotic agent.

- The acute phase of treatment lasts 6 to 10 weeks, and the goal is remission (i.e., absence of symptoms).

- The continuation phase lasts 4 to 9 months after remission. The goal is to eliminate residual symptoms or prevent relapse.

- ✓The maintenance phase lasts at least 12 to 36 months, and the goal is to prevent recurrence of a separate episodes of depression.

- ✓Some clinicians recommend lifelong maintenance therapy for persons at greatest risk for recurrence (i.e., persons younger than 40 years with two or more prior episodes and persons of any age with three or more prior episodes).

- ✓Educating the patients and their support systems regarding the delay in antidepressant effects (typically 2 to 4 weeks) and the importance of adherence should occur before therapy is started and throughout treatment.

- The selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of 5-HT into the presynaptic neuron. They are generally chosen as first line antidepressants because of their safety in overdose and improved tolerability compared to earlier agents.

- Tricyclic antidepressants (TCAs) are effective for all depressive subtypes, but their use has diminished because of the availability of equally effective therapies that are safer on overdose and better tolerated. In addition to inhibiting the reuptake of NE and 5-HT, they also block adrenergic, cholinergic, and histaminergic receptors.

- The monoamine oxidase inhibitors (MAOIs) **phenelzine** and **tranylcypromine** increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the monoamine oxidase (MAO) enzyme system. Both drugs are nonselective inhibitors of MAO-A and MAO-B.

Selegiline is available as a transdermal patch for treatment of major depression. It inhibits MAO-A and MAO-B in the brain, but has reduced effects on MAO-A in the gut.

The triazolopyridines **trazodone** and **nefazodone** are antagonists at the 5-HT2 receptor and inhibit the reuptake of 5-HT. They can also enhance 5-HT1A neurotransmission. They have negligible affinity for cholinergic and histaminergic receptors.

- **Bupropion's** most potent neurochemical action is blockade of DA reuptake; it blocks the reuptake of NE to a lesser extent.

- The serotonin-norepinephrine reuptake inhibitors include **venlafaxine** and **duloxetine**. Venlafaxine is an inhibitor of 5-HT and NE reuptake and a weak inhibitor of DA reuptake. **Desvenlafaxine** (Pristiq) was recently approved by the FDA. The dose is 50 mg once daily.

- **Maprotiline and amoxapine** are inhibitors of NE reuptake, with less effect on 5-HT reuptake.

- **Mirtazapine** enhances central noradrenergic and serotonergic activity through the antagonism of central presynaptic α2-adrenergic autoreceptors and heteroreceptors. It also antagonizes 5-HT2 and 5-HT3 receptors. It also blocks histamine receptors.

- **St. John's wort**, an herbal nonprescription medication containing hypericum, may be effective for mild to moderate depression, but it is associated with several drug–drug interactions. Its potency, purity, and manufacture are not regulated by the FDA.

- As depression is a potentially life-threatening disease, all antidepressant treatments should be overseen by a trained healthcare professional.

Adult Dosages for Currently Available Antidepressant Medications[a]

Generic Name	Trade Name	Suggested Therapeutic Plasma Concentration (ng/mL)	Initial Dose (mg/day)	Usual Dosage Range (mg/day)
Selective serotonin reuptake inhibitors				
Citalopram	Celexa		20	20–60
Escitalopram	Lexapro		10	10–20
Fluoxetine	Prozac		20	20–60
Fluvoxamine	Luvox		50	50–300
Paroxetine	Paxil		20	20–60
Sertraline	Zoloft		50	50–200
Serotonin/norepinephrine reuptake inhibitors				
Venlafaxine	Effexor		37.5–75	75–225
Duloxetine	Cymbalta		30	30–90
Aminoketone				
Bupropion	Wellbutrin		150	150–300
Triazolopyridines				
Nefazodone	Serzone		100	200–600
Trazodone	Desyrel		50	150–300
Tetracyclics				
Mirtazapine	Remeron		15	15–45
Tricyclics				
Tertiary amines				
Amitriptyline	Elavil	120–250[b]	25	100–300
Clomipramine	Anafranil		25	100–250
Doxepin	Sinequan		25	100–300
Imipramine	Tofranil	200–350[c]	25	100–300
Secondary amines				
Desipramine	Norpramin	100–300[c]	25	100–300
Nortriptyline	Pamelor	50–150	25	50–200
Monoamine oxidase inhibitors				
Phenelzine	Nardil		15	30–90
Selegiline (transdermal)	Emsam		6[d]	6–12[d]
Tranylcypromine	Parnate		10	20–60

Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Side-Effect Profile of Antidepressant Drugs

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]
	Norepinephrine	*Serotonin*				
Selective serotonin reuptake inhibitors						
Citalopram	0	++++	0	+	0	++
Escitalopram	0	++++	0	0	0	0
Fluoxetine	0	+++	0	0	0	++
Fluvoxamine	0	++++	0	0	0	++
Paroxetine	0	++++	+	+	0	++
Sertraline	0	++++	0	0	0	++
Serotonin/norepinephrine reuptake inhibitors						
Venlafaxine[b]	++++	++++	+	+	0	++
Duloxetine[c]	++++	++++	+	0	+	0
Aminoketone						
Bupropion[d]	+	0	+	0	0	++++
Triazolopyridines						
Nefazodone	0	++	0	+++	+++	++
Trazodone	0	++	0	++++	+++	++
Tetracyclics						
Mirtazapine	0	0	+	++	++	0

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]
	Norepinephrine	*Serotonin*				
Tricyclics						
Tertiary amines						
Amitriptyline	++	++++	++++	++++	+++	+++
Clomipramine	++	+++	++++	++++	++	++++
Doxepin	++	++	+++	++++	++	+++
Imipramine	+++	+++	+++	+++	++++	+++
Secondary amines						
Desipramine	++++	+	++	++	++	++
Nortriptyline	+++	++	++	++	+	++
Monoamine oxidase inhibitors						
Phenelzine	++	++	+	++	++	+
Selegiline	0	0	0	+	++	0
Tranylcypromine	++	+	+	+	++	+

Pharmacokinetic Properties of Antidepressants

Generic Name	Elimination Half-Life (hours)[a]	Time of Peak Plasma Concentration (hours)	Plasma Protein Binding (%)	Percentage Bioavailable	Clinically Important
Selective serotonin reuptake inhibitors					
Citalopram	33	2–4	80	≥80	None
Escitalopram	27–32	5	56	80	None
Fluoxetine	4–6 days[b]	4–8	94	95	Norfluoxetine
Fluvoxamine	15–26	2–8	77	53	None
Paroxetine	24–31	5–7	95	[d]	None
Sertraline	27	6–8	99	36[c]	None
Serotonin/norepinephrine reuptake inhibitor					
Venlafaxine	5	2	27–30	45	*O*-Desmethylvenlafaxi
Duloxetine	12	6	90	50	None
Aminoketone					
Bupropion	10–21	3	82–88	[d]	Hydroxybupropion Threohydrobupropion Erythrohydrobupropio
Triazolopyridines					
Nefazodone	2–4	1	99	20	*Meta*-chlorophenylpip
Trazodone	6–11	1–2	92	[d]	*Meta*-chlorophenylpip

Generic Name	Elimination Half-Life (hours)[a]	Time of Peak Plasma Concentration (hours)	Plasma Protein Binding (%)	Percentage Bioavailable	Clinically Import
Tetracyclics					
Mirtazapine	20–40	2	85	50	None
Tricyclics					
Tertiary amines					
Amitriptyline	9–46	1–5	90–97	30–60	Nortriptyline
Clomipramine	20–24	2–6	97	36–62	Desmethylclomipra
Doxepin	8–36	1–4	68–82	13–45	Desmethyldoxepin
Imipramine	6–34	1.5–3	63–96	22–77	Desipramine
Secondary amines					
Desipramine	11–46	3–6	73–92	33–51	2-Hydroxydesipram
Nortriptyline	16–88	3–12	87–95	46–70	10-Hydroxynortript

Pharmacokinetic Drug Interactions Involving Tricyclic Antidepressants (TCAs)

Elevates plasma concentrations of TCAs

- Cimetidine
  Diltiazem
  Ethanol, acute ingestion
  SSRIs
  Haloperidol
  Labetalol
  Methylphenidate
  Oral contraceptives
  Phenothiazines
  Propoxyphene
  Quinidine
  Verapamil

Lowers plasma concentrations of TCAs

Barbiturates
Carbamazepine
Ethanol, chronic ingestion
Phenytoin

Elevates plasma concentrations of interacting drug

Hydantoins
Oral anticoagulants

Lowers plasma concentrations of interacting drug

Levodopa

Pharmacodynamic Drug Interactions Involving Tricyclic Antidepressants

Interacting	Drug Effect
Alcohol	Increased CNS depressant effects
Amphetamines	Increased effect of amphetamines
Androgens	Delusions, hostility
Anticholinergic agents	Excessive anticholinergic effects
Bepridil	Increased antiarrhythmic effect
Clonidine	Decreased antihypertensive efficacy
Disulfiram	Acute organic brain syndrome
Estrogens	Increased or decreased antidepressant response; increased toxicity
Guanadrel	Decreased antihypertensive efficacy
Guanethidine	Decreased antihypertensive efficacy
Insulin.	Increased hypoglycemic effects
Lithium	Possible additive lowering of seizure threshold
Methyldopa	Decreased antihypertensive efficacy; tachycardia; CNS stimulation
Monoamine oxidase.	Increased therapeutic and possibly toxic effects of both drugs; hypertensive inhibitors crisis; delirium; seizures; hyperpyrexia; serotonin syndrome
Oral hypoglycemics	Increased hypoglycemic effects
Phenytoin.	Possible lowering of seizure threshold and reduced antidepressant response

PECIAL POPULATIONS:

Elderly Patients:

• Prominent symptoms of depression in the elderly are loss of appetite, cognitive impairment, sleeplessness, anergia, fatigue, and loss of interest in and enjoyment of the normal pursuits of life.

- The **SSRIs** are often selected as first-choice antidepressants in elderly patients.
- In healthy elderly patients, cautious use of a secondary amine **TCA** (**desipramine** or **nortriptyline**) may be appropriate because of their defined therapeutic plasma concentration ranges, well-established efficacy, and well-known adverse-effect profiles.
- **Bupropion** and **venlafaxine** may also be chosen because of their milder anticholinergic and less frequent cardiovascular side effects.

Children and Adolescents:

- Symptoms of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.

- Data supporting efficacy of antidepressants in children and adolescents are sparse. **Fluoxetine** is the only antidepressant that is FDA approved for treatment of depression in patients less than 18 years of age.

- The FDA has established a link between antidepressant use and suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults 18 to 24 years old.

- All antidepressants carry a black box warning providing cautions in the use of all antidepressants in this population, and the FDA also recommends specific monitoring parameters.

- ✓Several cases of sudden death have been reported in children and adolescents taking **desipramine.**

- ✓A baseline electrocardiogram (ECG) is recommended before initiating a TCA in children and adolescents, and an additional ECG is advised when steady-state plasma concentrations are achieved.

- ✓TCA plasma concentration monitoring is critical to ensure safety.

Pregnancy:

- As a general rule, if effective, nondrug approaches are preferred when treating depressed pregnant patients.

- One study showed that pregnant women who discontinued antidepressants were five times more likely to relapse during their pregnancy than were women who continued treatment.

- No major teratogenic effects have been identified with the **SSRIs** or **TCAs.** However, evaluations to date suggest a possible association of **fluoxetine** with low birth weight and respiratory distress.

- Another study reported a six fold greater likelihood of the occurrence of persistent pulmonary hypertension of newborn infants exposed to an SSRI after the twentieth week of gestation.

- The risks of untreated depression in pregnancy should be considered. These included low birth weight, maternal suicidality, potential for hospitalization or marital discord, poor prenatal care, and difficulty caring for other children.

REFRACTORY PATIENTS:

- Most "treatment-resistant" depressed patients have received inadequate therapy.
- Issues to be considered in patients who have not responded to treatment include the following:
- (1) Is the diagnosis correct?
- (2) Does the patient have a psychotic depression?
- (3) Has the patient received an adequate dose and duration of treatment?
- (4) Do adverse effects preclude adequate dosing?
- (5) Has the patient been compliant with the prescribed regimen?
- (6) Was treatment outcome measured adequately?
- (7) Is there a coexisting or pre existing medical or psychiatric disorder?
- (8) Was a stepwise approach to treatment used?
- (9) Are there other factors that interfere with treatment?

- The STAR*D study showed that one in three depressed patients who previously did not achieve remission with an antidepressant became symptom-free with the help of an additional medication (e.g., **bupropion sustained release**), and one in four achieved remission after switching to a different antidepressant (e.g., **venlafaxine XR**).

- The current antidepressant may be stopped, and a trial initiated with an agent of unrelated chemical structure (e.g., **mirtazapine** or **nortriptyline)**.

- Alternatively, the current antidepressant may be augmented (potentiated) by the addition of another agent (e.g., **lithium, T3**), or an **atypical antipsychotic** (e.g., **risperidone**). Risperidone has been shown to be effective in combination with **fluvoxamine, paroxetine,** or **citalopram** in treatment-resistant depression. **Olanzapine** and **fluoxetine** have been found to be safe and effective in treatment-resistant depression.

- The practice guideline of the American Psychiatric Association recommends that after 6 to 8 weeks of antidepressant treatment, partial responders should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT.

- For those with no response, options include changing to another antidepressant or the addition of psychotherapy or ECT.

- Several monitoring parameters, in addition to plasma concentrations, are useful in managing patients. Patients must be monitored for **adverse effects, remission** of previously documented target symptoms, and **changes in social or occupational functioning**. Regular monitoring should be assured for several months after antidepressant therapy is discontinued.

- Patients given **venlafaxine** should have **blood pressure** monitored regularly. Patients older than age 40 years should receive a pretreatment ECG before starting TCA therapy, and follow-up ECGs should be performed periodically.

- Patients should be monitored for emergence of suicidal ideation after initiation of any antidepressant, especially in the first few weeks of treatment.

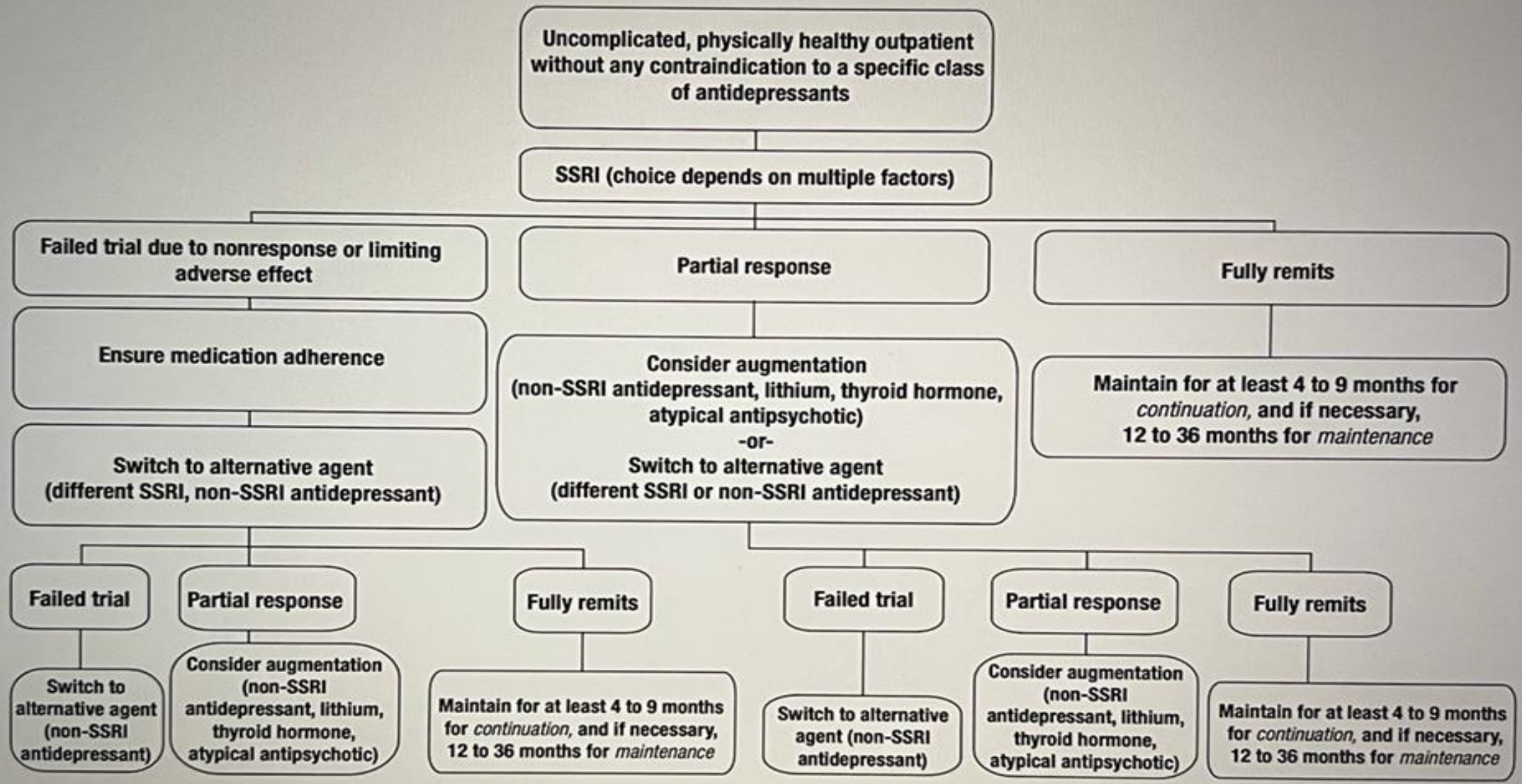

FIGURE 70-1. Algorithm for treatment of uncomplicated major depression. (SSRI, selective serotonin reuptake inhibitor.)