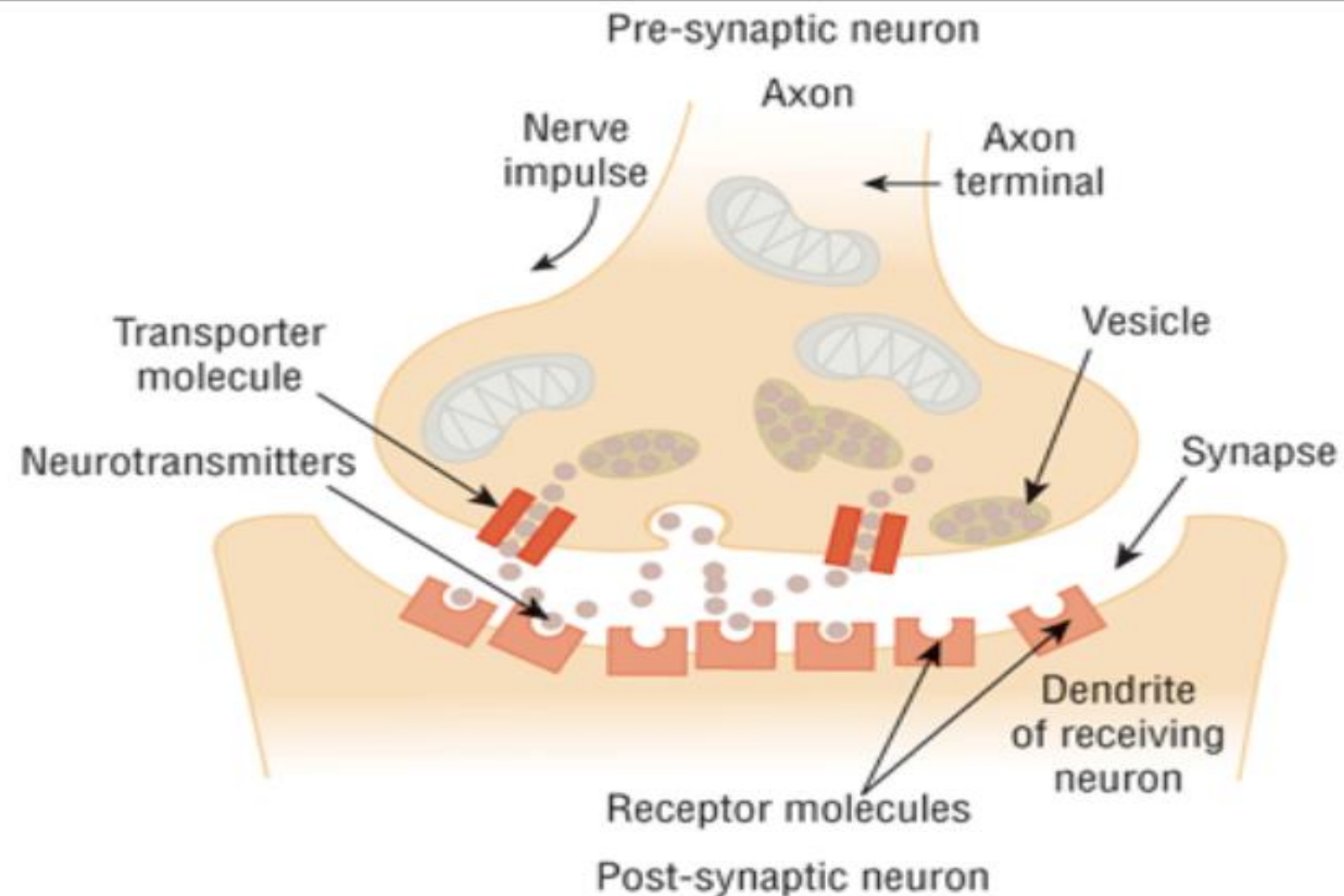


Major Depressive Disorder (MDD)



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LEARNING OBJECTIVES

LO

Upon completion of the chapter, the reader will be able to:

1. Explain the etiology and pathophysiology of major depressive disorder (MDD).
2. Identify the signs and symptoms of MDD.
3. Outline the treatment goals for a patient with MDD.
4. Recommend pharmacotherapy given a specific patient with MDD.
5. Develop a monitoring plan for a specific patient with MDD which includes the assessment of efficacy as well as adverse effects.
6. Predict, prevent, identify, and resolve potential drug-related problems.
7. Educate patients and caregivers on the proper use of antidepressant therapy.

Major Depressive Disorder(MDD): is medical condition characterized by one or more depressive episode without history of manic and hyper manic.

- Individuals with major depressive disorder (MDD) experience pervasive symptoms affecting mood, thinking, physical health, work, and relationships.

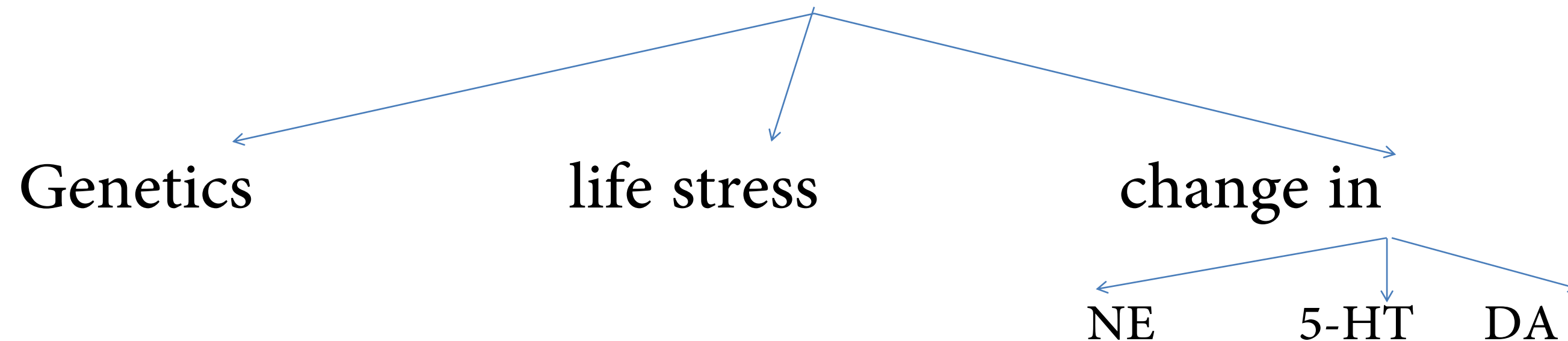
EPIDEMIOLOGY AND ETIOLOGY

- Women are twice as likely as men to experience MDD.
- According to the (WHO), depression is the leading cause of disability.
- The average age of onset is in the midtwenties.
- Symptoms of depression are due to a change in the brain neurotransmitters: norepinephrine (NE), serotonin (5-HT), and dopamine (DA).

Etiology and pathophysiology:

The exact cause remains **unknown**.

The development of MDD is based on :



First-degree relatives are
2-4X

Pathophysiology

- **Biogenic amine hypothesis:** decrease brain level of neurotransmitters (norepinephrine(NE), serotonin (5-HT), and dopamine).
- **The receptor hypothesis** suggests that depression is related to **abnormal functioning** (upregulation) of monoamine neurotransmitter **receptors**.
- **Other Neurobiological Hypotheses**
- **At least three categories** of peripheral hormones are associated with the **pathophysiology of depression**.
 - BDNF is **decreased** in patients with MDD.
 - Proinflammatory cytokines(interleukin-1 β , interleukin-6, and TNF- α .) are **increased** in individuals with MDD.
 - hypothalamic pituitary axis (HPA) is **impaired** in MDD .

CLINICAL PRESENTATION AND DIAGNOSIS

- The diagnosis of a major depressive episode (MDE) requires **the presence of five depressive symptoms for a minimum of 2 weeks** that cause clinically significant effects.
 - The diagnosis of MDD is based on the presence of one or more MDEs during a person's lifetime.

Table 39–1**Clinical Presentation of Depression: Diagnostic Criteria for Major Depressive Episode⁵**

At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning.

- Depressed mood^a
- Markedly diminished interest or pleasure in usual activities^a
- Increase or decrease in appetite or weight
- Increase or decrease in amount of sleep
- Increase or decrease in psychomotor activity (ie, agitation or retardation)
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death, suicidal ideation, or suicide attempt

The symptoms cause clinically significant distress or impairment in functioning.

The symptoms are not due to the direct physiologic effects of a substance or medical condition.

^aOne of these two symptoms must be present.

Table 39–2**Medical Conditions and Medications Associated with Depression^{5,12-15}****Medical disorders**

Hypothyroidism
Cancer
Anemia
Infections
Electrolyte disturbances
Folate deficiency
Neurologic disorders
Cardiovascular disease
Respiratory disease

Medications

CNS depressants (alcohol, benzodiazepines, opioids)
Corticosteroids
Contraceptives
Phenobarbital
Brivaracetam
Levetiracetam
Perampanel
Tiagabine
Topiramate
Vigabatrin
Gonadotropin-releasing hormone agonists
Interferon α
Interleukin 2
Varenicline
Mefloquine
Isotretinoin
Propranolol
Clonidine
Methyldopa
Reserpine

Activate V
Go to Setting

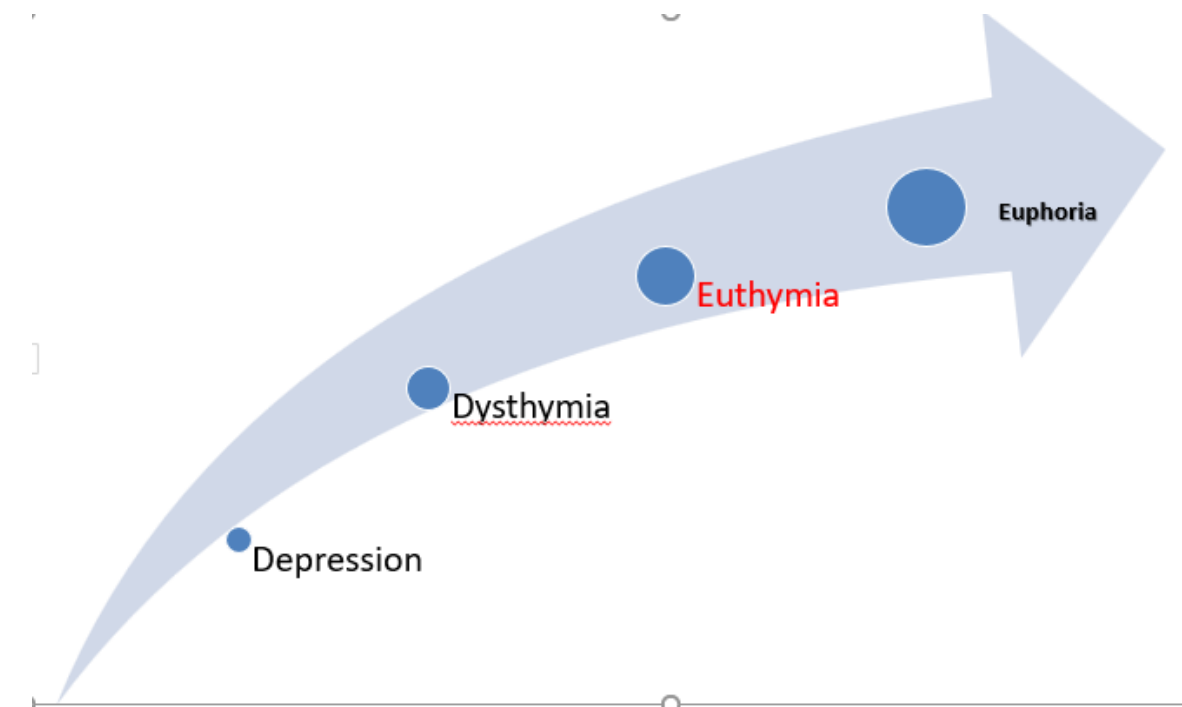
Differential Diagnosis

- MDEs also occur in bipolar disorder. Individuals with bipolar disorder also experience **hypomanic, manic, or mixed episodes during the course of their illness**, but individuals with MDD do not.
- Conditions that may coexist with MDD include anxiety, eating disorders, personality disorders, and substance use disorders.
- MDD is associated with **a 65% increased risk of diabetes in elderly patients**. MDD is also strongly correlated with coronary artery disease.
- Other **medical disorders associated with depression** include: hypothyroidism, cancer, anemia, infections, electrolyte disturbances, folate deficiency, neurologic disorders, and cardiovascular and respiratory disease

Dysthymia

Persistent depressive disorder (dysthymia) : is a chronic form of depression.

- Many symptoms of dysthymia are similar to those of MDD, but they are **chronic and milder**.
- Symptoms must be present for at least 2 years and may include:
 - **sleep and appetite disturbances,**
 - **lack of energy, and**
 - **difficulty making decisions.**
- Individuals with dysthymia are more likely to develop MDD.
- **MDD has a high mortality rate** because approximately 15% of patients ultimately complete suicide.



TREATMENT

- The goal of therapy for patients with MDD is:
 - resolution of **depressive symptoms**,
 - return to **euthymia**, and
 - **prevention of relapse and recurrence** of symptoms.
- *One extremely **important goal** is prevention of **suicide attempts**.*
- Other desired outcomes include normalization of functioning in areas such as work.

Nonpharmacologic Therapy

Psychotherapy:

- Psychotherapy alone is an initial treatment option for mild to moderate cases of depression.
- the combination of psychotherapy and pharmacotherapy can be more effective than either treatment modality alone in cases of severe or recurrent MDD
- helpful for patients with significant
 - Psychosocial stressors,
 - interpersonal difficulties.

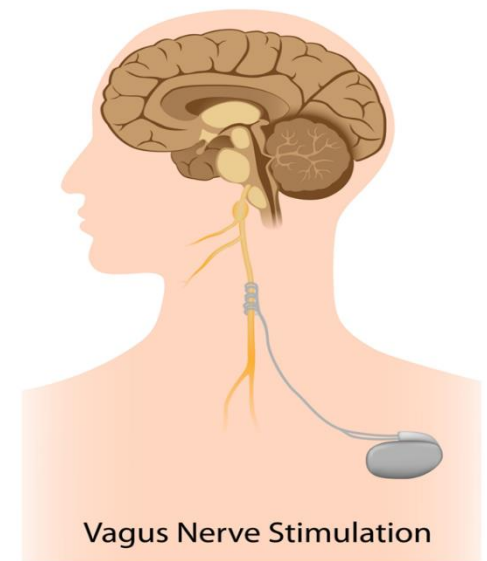
Electroconvulsive therapy (ECT):

- The **response rate is about 80% to 90%** and even exceeds 50% for patients who have failed pharmacotherapy.
- **ECT may be beneficial for MDD that is complicated by**
 - psychotic features,
 - severe suicidality,
 - refusal to eat
 - pregnancy
 - contraindication/non-response to pharmacotherapy.
- Six to 12 treatments are typically necessary with response occurring in 10 to 14 days.
- When ECT is discontinued, antidepressants are initiated to help maintain response.
- side effects are confusion and memory impairment.¹⁶



➤ Vagus nerve stimulation (VNS):

- used for adult patients with **treatment-resistant depression**.
- A **pulse generator** is surgically implanted under the skin of the left chest, and an electrical lead connects the generator to the left vagus nerve. Stimulation of this nerve sends signals to the brain.
- This therapy is intended to be used along with traditional therapies, such as pharmacotherapy and ECT.



➤ Light therapy:

- light intensity of 10,000 lux for 30 minutes daily for up to 6 weeks.

➤ Physical exercise:

- is effective for mild-to-moderate depression. At least 30 minutes of supervised, moderate-intensity exercise, 3 days weekly, for at least 9 weeks has been proven effective.

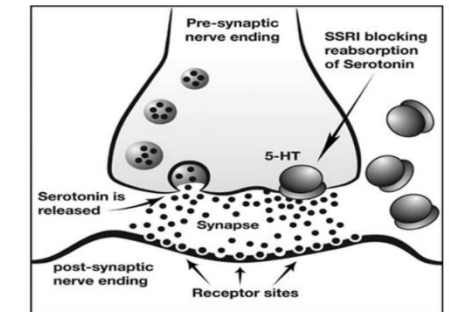
➤ Transcranial magnetic stimulation:

- is a noninvasive, well-tolerated procedure that is FDA approved for use after one failed trial of an antidepressant.

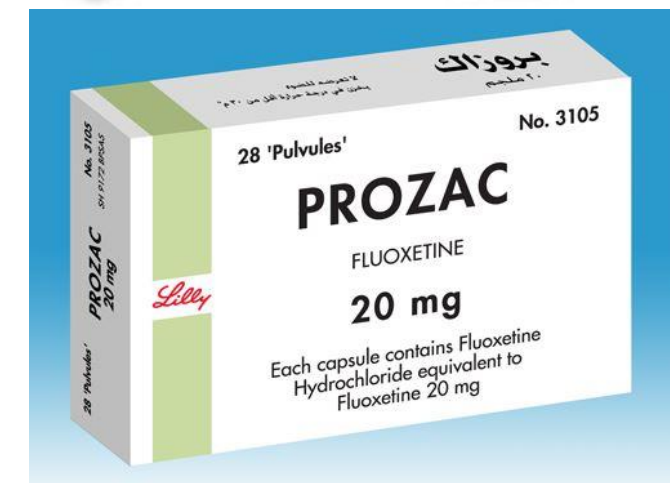


SSRIs

- Selective Serotonin Reuptake Inhibitors: inhibit reuptake of 5-HT into the presynaptic neuron.
- *first-line antidepressants* due to **safety** profile and **tolerability**
 - Citalopram (20-40 mg)
 - Escitalopram (10- 20 mg)
 - Fluoxetine (10-80 mg)
 - Fluvoxamine (50- 300 mg)
 - Paroxetine(10-50 mg)
 - Sertraline (50-200 mg)



Depression CAREPATH
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SNRIs

- **serotonin-norepinephrine reuptake inhibitors (SNRI)**

- Venlafaxine: Higher SRI activity [37.5-375 mg]
- Desvenlafaxine: Higher SRI activity [50- 100ng]
- Duloxetine: balanced SRI and NRI activities [40-60]
- Levomilnacipran: Higher NRI activity [20-120 mg]



Table 39-4

Efficacy and Adverse Effect Profile Based on Pharmacology^{7,9}

Pharmacologic Action

Result

SRI

Antidepressant and antianxiety efficacy (via interaction of 5-HT at 5-HT_{1A} receptors)
 Anxiety, insomnia, sexual dysfunction (via interaction of 5-HT at 5-HT_{2A} receptors)
 Anxiety, anorexia (via interaction of 5-HT_{2C} receptors)
 Nausea, GI problems (via interaction of 5-HT at 5-HT₃ receptors)

NRI

Antidepressant efficacy
 Tremor, tachycardia, sweating, jitteriness, increased blood pressure



➤ ***Norepinephrine Dopamine Reuptake Inhibitor(NDRI)***

- Bupropion : is a NE and DA reuptake inhibitor (NDRI)....may induce seizure.

➤ ***Serotonin Antagonist and Reuptake Inhibitors***

- Nefazodone.... sedative effect and liver toxicity,
- Trazodone (sedation, rarely Priapism)

➤ ***Other Newer Antidepressants***

- Mirtazapine (MRT, NE and 5-HT): is a noradrenergic and specific serotonergic antidepressant (NaSSA). used when **insomnia is associated** with depression (has sedation effect).
- Vilazodone : has SRI and a partial agonist at 5-HT_{1A} receptors
- Vortioxetine : positive effect on memory
- Esketamine : NMDA antagonist
- Brexanolone: has modulation effect on GABA receptors. It causes excessive sedation.



TCAs

- Their use has diminished greatly due to the availability of equally effective therapies that are much safer in overdose and better tolerated.
- TCAs possess both serotonin reuptake inhibition (SRI) and norepinephrine reuptake inhibition (NRI) properties,
- In addition they have affinity to
- Cholinergic, histaminergic, adrenergic .
 - Amitriptyline (tertiary TCAs)
 - Imipramine (tertiary TCAs)
 - Desipramine (secondary TCAs)
 - Nortriptyline (secondary TCAs)
- S/E(ortho. Hypotension, sedation, weight gain ,anticholinergic S/E



MAOIs



- MAOIs increase the concentrations of NE, 5-HT, and DA within the neuronal synapse through inhibition of the MAO enzyme.

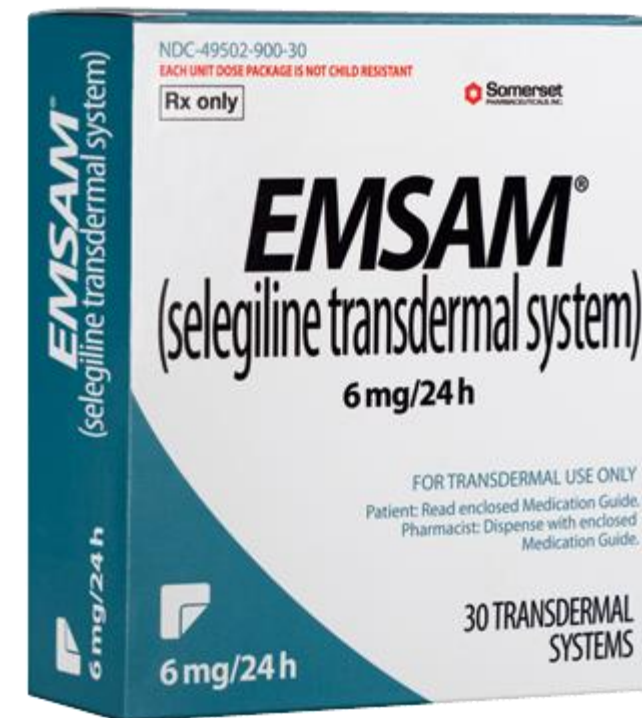
- Phenelzine
- Selegiline
- Tranylcypromines

Side effect :

- postural hypotension
- Anticholinergic side effects(less than TCA)
- Sexual dysfunction
- Cheese reaction

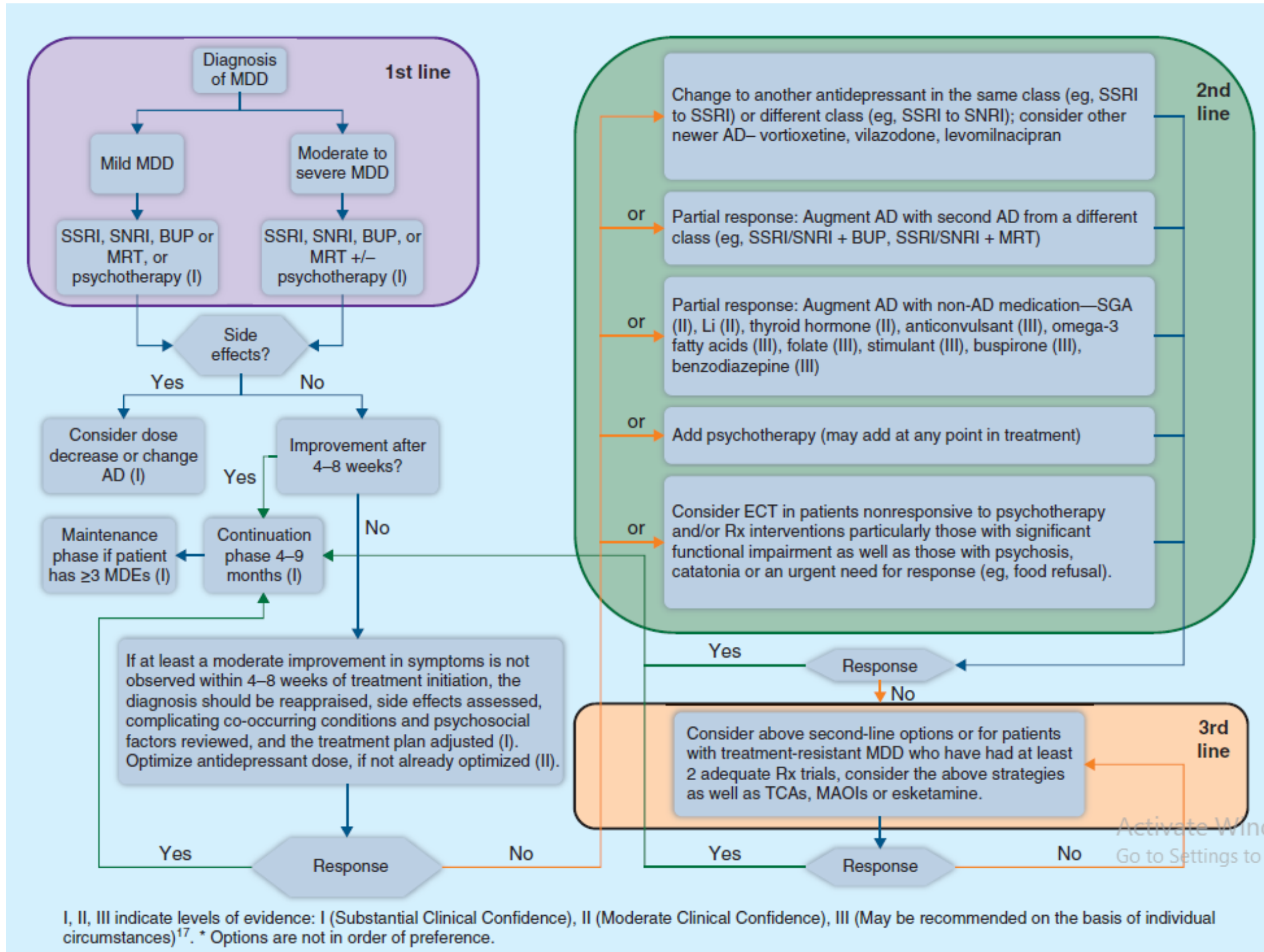
Drug- drug interactions:

- 1-sympathomimetic (ephedrine, pseudoephedrine, phenylephrine) , stimulants (amphetamines, or methylphenidate) or foods rich in tyramine **Hypertensive crisis**.
- 2- serotonergic agent(Serotonergic antidepressants, Meperidine, Dextromethorphan, Tramadol, linezolid, triptans,.. **Serotonin syndrome**



- **Hypertensive crisis** is characterized by
 - sharply elevated blood pressure,
 - occipital headache,
 - stiff or sore neck,
 - nausea, vomiting, and sweating.
- It may result during MAOI therapy if the patient consumes foods rich in a **tyramine** or take **sympathomimetic drugs, or stimulants**
- **Serotonin syndrome**
is characterized by : confusion, **restlessness, fever, abnormal muscle movements**, hyperreflexia, sweating, diarrhea, and shivering.

Selection of Medication



Duration of Therapy

- **There are three *phases of treatment* for patients with MDD:**
 - (1) **the *acute phase***: lasting 6 to 12 weeks in which the goal is remission (i.e., absence of symptoms);
 - (2) **the *continuation phase*** :lasting 4 to 9 months after remission is achieved, in which the goal is to eliminate residual symptoms or prevent relapse (i.e., return of symptoms within 6 months of remission);
 - (3) **the *maintenance phase***: lasting at least 12 to 36 months or lifelong in which the goal is to prevent recurrence.

Managing Partial or No Response

For patients experiencing a partial response,:

- **One option:** **extending the medication** trial and/or using **higher doses** within the recommended dosage range may be helpful.
- **Another option** is **augmentation therapy**, ie, adding another medication that generally is not used as an antidepressant, such as, SGA, **lithium**, **buspirone**, or **triiodothyronine**, omega-3 fatty acids (Ill), folate.
- Second-generation antipsychotics, **aripiprazole**, and **quetiapine** are approved by the FDA for augmenting partial response to antidepressants.
- **A third option** is **combination therapy**, Examples include combining **bupropion** and **SSRIs** or combining **TCAs and SSRIs**, **SSRI + MRT**)



Switching to a different antidepressant is a common strategy for patients who have had **no response** to initial antidepressant therapy, but also is **acceptable in cases of partial response**.

- The olanzapine-fluoxetine combination medication has been approved for treatment-resistant depression. Esketamine (Spravato) nasal spray is also approved for treatment resistant depression.

Discontinuation of Therapy:

- When discontinuing therapy, it is best to gradually taper the antidepressant for two reasons.
 - **Withdrawal syndromes (esp. venlafaxine, paroxetine)**
 - **Return of depression**

Spravato™
(esketamine) III
nasal spray



SPECIAL POPULATIONS



VS



Pregnant

- general rule, if effective, **nondrug approaches** are preferred when treating depressed pregnant patients.
- **Sertraline, fluoxetine, citalopram**, and the **TCAs** have the greatest reproductive safety data and should be **considered first-line treatments** when pharmacotherapy is indicated.
- ECT may also be considered as a treatment option for pregnant patients
- **Paroxetine**... increased risk of congenital malformations, particularly atrial and ventricular septal defects
- Brexanolone is an antidepressant marketed specifically for postpartum depression



Geriatric Patients

- The SSRIs are chosen frequently for geriatric depression because of their overall favorable adverse effect profiles and low toxicity.
- most TCAs are avoided due to problematic anticholinergic, cardiovascular, and sedative properties.
- The TCAs desipramine and nortriptyline are more tolerable in terms of these adverse effects and may be used in geriatric depression.
- Other newer antidepressants, such as bupropion, venlafaxine, nefazodone, and mirtazapine, are alternatives for the treatment of geriatric patients.
- lower starting doses of antidepressants and slow upward titrations as tolerated are recommended for geriatric patients.

Pediatric patients

- Symptoms of depression in childhood include anxiety, and sleep disturbance.
- **Fluoxetine and escitalopram** are the only antidepressant that is FDA approved for treatment of depression in patients less than 18 years of age.
- ***Suicidal Patients:***
- All antidepressants have a black box warning regarding an increase in suicidal thinking and behavior in children and young adults.

Table 39-3

Primary Pharmacologic Actions^a of Antidepressants^{7,11,30}

[illegible]

PHQ-9

Table 39–10

Patient Health Questionnaire-9⁵³

Over the last 2 weeks, how often have you been bothered by any of the following problems?

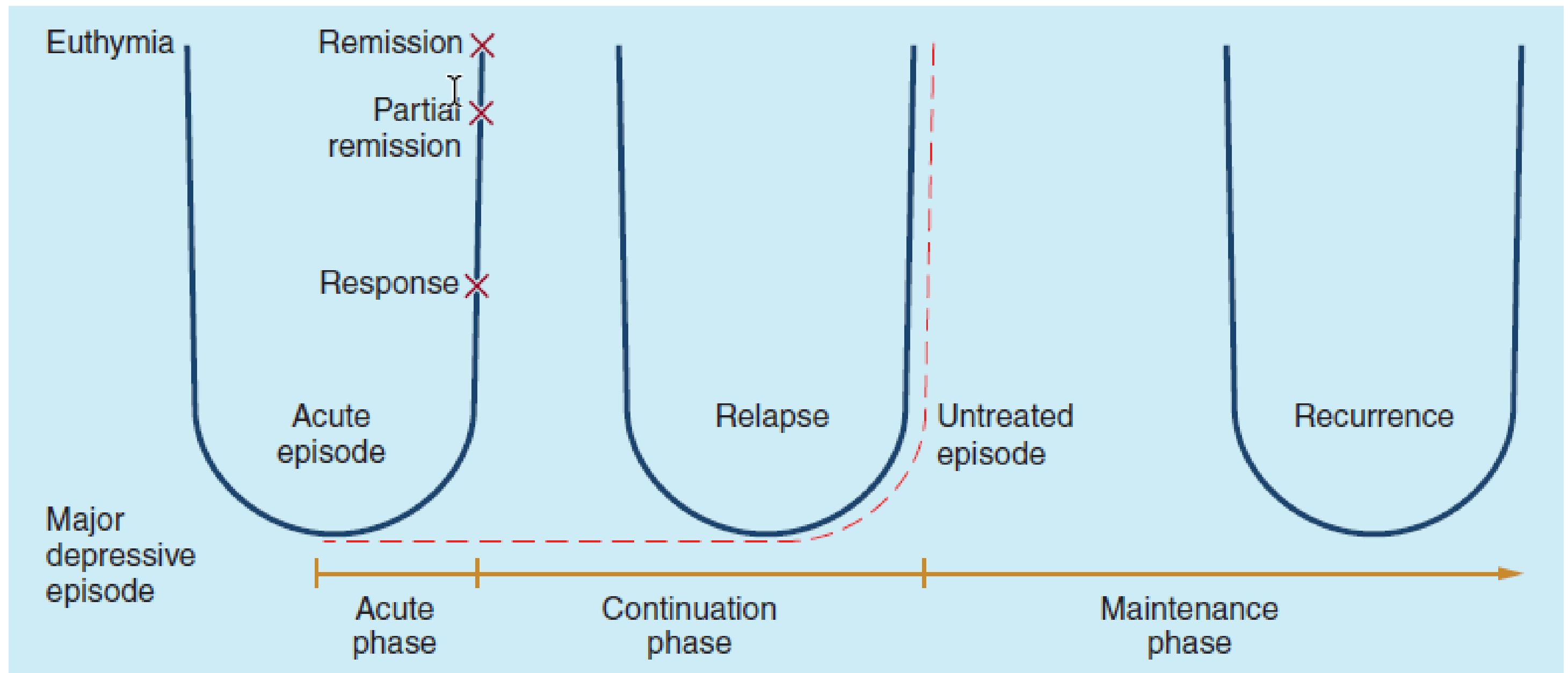
	Not at All	Several Days	More Than Half the Days	Nearly Every Day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching TV	0	1	2	3
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
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Total Score = _____

Depression Severity, PHQ-9 Total Score: 1–4 minimal, 5–9 mild, 10–14 moderate, 15–19 moderately severe, 20–27 severe

If you checked any problems, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

Not Difficult at All Somewhat Difficult Very Difficult Extremely Difficult



The course of depression and phases of treatment.^{7,18}