Mental Disorders (Anxiety, Depression)

PATIENT PROFILE CALENDAR 2017

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Depression

Anxiety

Learning Objectives

Mental Disorders

- List the major symptoms of depression/ anxiety
- Recommend an appropriate therapy for both depression and anxiety based on treatment phase and patient history
- Evaluate response to therapy and treatment side effect
- Identify the role of the community pharmacist in counseling patient with depression/ anxiety

DEPRESSION: Introduction

- Prevalence
  - Highly prevalent throughout the world and appears to be increasing
- Estimated lifetime prevalence is 12 percent
  - Developed countries like United States and Europe ➔ 18%
  - Developing countries like Peoples' Republic of China, Mexico, and Brazil ➔9%
- World Health Organization
  - Unipolar major depression as the 11th greatest cause of disability and mortality in the world
- United States
  - Major depression ranks second among all diseases and injuries as a cause of disability, and persistent depressive disorder (dysthymia) as the 20th

- Following recovery:
  - From one episode ➔ Estimated rate of recurrence over two years is > 40%
  - From two episodes ➔ Risk of recurrence within five years is approximately 75%

DEPRESSION: Diagnosis

A. Five (or more) of the following symptoms have been present during the same two-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 attributable to another medical condition.

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FIFTH EDITION

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- 1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)
- 2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
- 3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)
- 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 (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)
- 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 episode is not attributable to the direct physiological effects of a substance or to another medical condition.

NOTE: Criteria A through C represent a major depressive episode.

NOTE: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic or hypomanic episode.

DEPRESSION: Neurobiology

Serotonin

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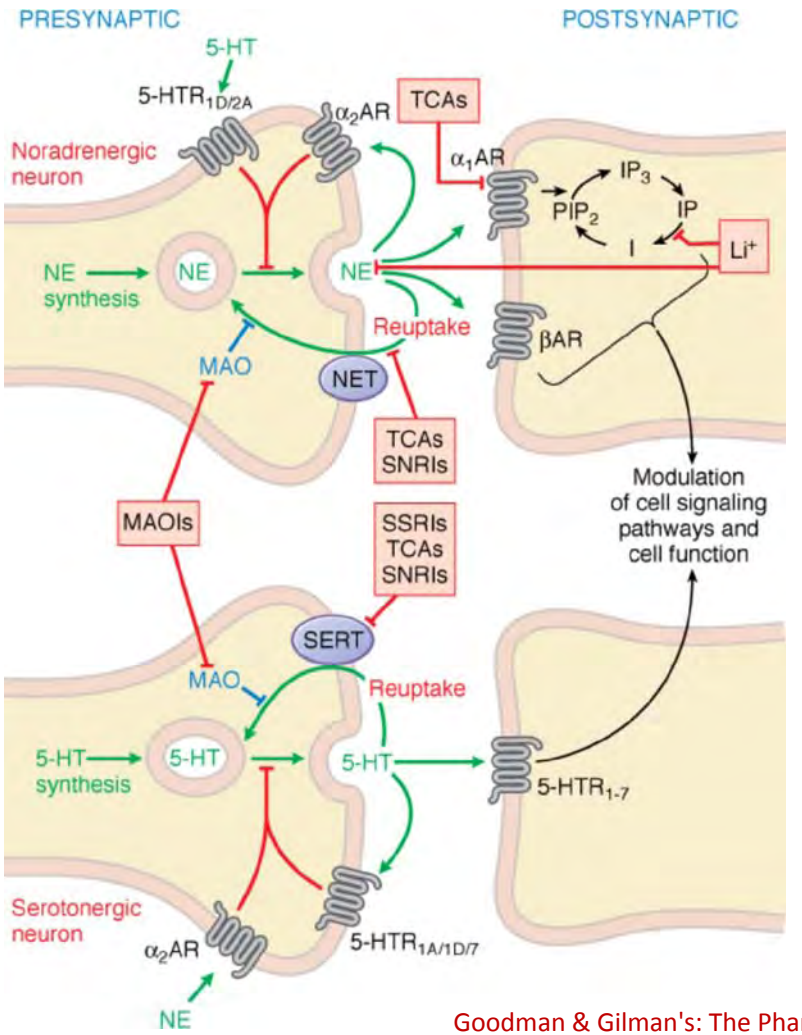

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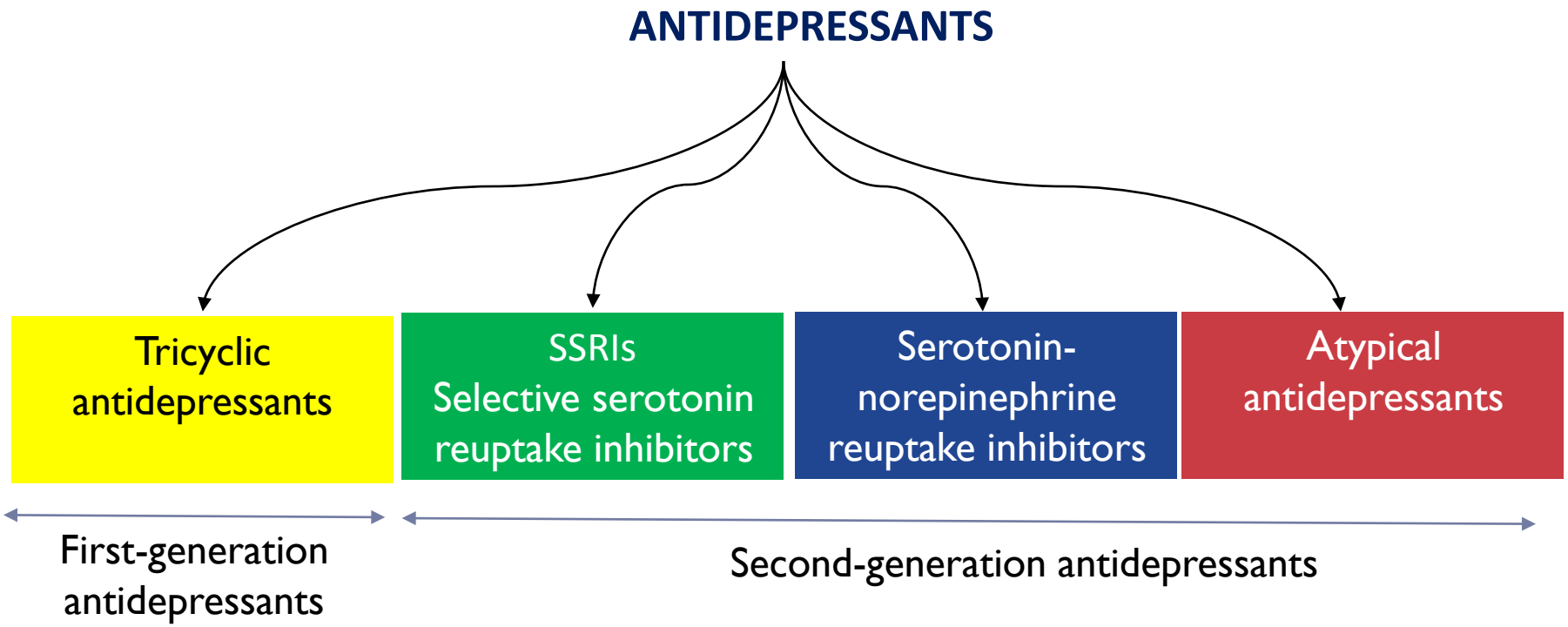
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e

DEPRESSION: Treatment and Management

- Psychotherapy + Pharmacotherapy



Others:

-Monoamine oxidase inhibitors (MAOIs)

-Serotonin modulators

DEPRESSION: Treatment and Management

Tricyclic antidepressants

TCA	Type of amine	MOA	MOA: blocks	Half life (h)	DDI	Metabolism and elimination
Amitriptyline	Tertiary	More potent in blocking reuptake of 5-HT compared with NE	H 1 and M1	24 hours	Substrate	Liver
Clomipramine	Tertiary		H 1 and M1	24 hours		Liver
Doxepin	Tertiary		Strongest H1	24 hours		Liver
Imipramine	Tertiary		Alpha, H1, and M1	24 hours		Liver (has active metab: desip)
Trimipramine	Tertiary		H1	24 hours		Liver
Desipramine	Secondary	More potent in blocking reuptake of NE than 5-HT	Less H1 and M1	24 hours		Liver (is the active metab of imipramine)
Nortriptyline	Secondary		Less H1 and M1	24 hours		Liver (is the active metab of amitrip)
Protriptyline	Secondary		Less H1 and M1	24 hours		Liver
Maprotiline	Tetracyclic		H1	24 hours		Liver
Amoxapine	Different	More Potent NE reuptake inhibitor than 5-HT and blocks postsynaptic DA receptors	DA	8 hours		Liver

DEPRESSION: Treatment and Management

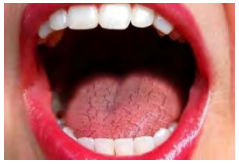
Tricyclic antidepressants

- Use
  - 1958 ➔ TCAs were first-line treatment for depression for 30 years, until SSRIs were introduced
  - Major depression, panic attacks, generalized anxiety disorder, post-traumatic stress disorder, bulimia nervosa, smoking cessation, chronic daily headache and neuropathy
  - Taken once a day, usually at bedtime because of sedating side effects
  - Response may not occur until four or more weeks have elapsed after a therapeutic dose has been achieved
  - Sufficient duration (eg, 6 to 12 weeks) before determining whether the medications have sufficiently relieved symptoms

DEPRESSION: Treatment and Management

Tricyclic antidepressants

- Side effects
  - Tertiary amines: ++++ side effects vs secondary amines
    - More anticholinergic side effects (eg, constipation or blurred vision) + highly sedating (central effects on histamine)
  - Heart block, ventricular arrhythmias, and sudden death ➔ screening for cardiac conduction system disease, which precludes the use of these medications
    - > 40 years: ECG; < 40 years: no ECG required if no history of cardiac disease
  - Orthostatic hypotension (alpha block)
  - Anticholinergic effects ➔ blurred vision, constipation, dry mouth (which may lead to dental caries), urinary retention, tachycardia, ocular crisis in patients with narrow-angle glaucoma, confusion and delirium
  - Antihistaminic effects ➔ sedation, increased appetite leading to weight gain, confusion, and delirium
  - Decreased seizure threshold, sexual dysfunction, diaphoresis, and tremor



DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

SSRIs	Half life (h)	DDI	Metabolism and elimination
Citalopram	1 day	None	Liver
Escitalopram	1 day	None	Liver
Fluoxetine	1 – 3 days + active metabolite: norfluoxetine (4 – 16 days)	2D6 (potent), 2C9, 2C19, 2B6, and 3A4	Liver
Fluvoxamine	15 hours	1A2 (potent), 2C19 (potent), 2B6, 2C9, and 3A4	Liver
Paroxetine	1 day	2D6 (potent) and 2B6 (potent)	Liver
Sertraline	1 day	2D6 (potent at doses > 200 mg per day), 2B6, 2C9, 2C19, and 3A4	Liver

DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

- Use
  - Frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose
- Pharmacology
  - SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy
  - SSRIs are selective in that they have relatively little affinity for other types of receptors
- Efficacy
  - There is no compelling evidence that one SSRI is more efficacious than another
  - Choice is based upon cost, individual patient tolerance, and clinician experience

DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

- Side effects
  - Sexual dysfunction ➔ anorgasmia in women and erectile dysfunction in men, and increase ejaculation latency in men
  - Drowsiness
  - Weight gain ➔ improved appetite, increased carbohydrate craving, and changes in serotonin 2C receptor activity
  - Insomnia
  - Anxiety
  - Dizziness
  - Headache
  - Dry mouth
  - Observational studies suggest SSRIs may increase the risk of diabetes, abnormal bleeding, and bone loss




DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

- Switching between antidepressants
  - Cross-tapering is the best technique
  - Dose of the current antidepressant is gradually reduced over a one to two week period or longer, while the dose of the new antidepressant is gradually increased to therapeutic range over the same time period

DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

- Discontinuation of antidepressants
  - Antidepressant dose should be reduced by 25% per week so as to minimize the occurrence of discontinuation side effects
  - Taper over two to four weeks
  - Discontinuation syndrome
    - Abrupt cessation of SSRIs
    - Symptoms ➔ dizziness, nausea, fatigue, muscle aches, chills, anxiety, and irritability
    - Symptoms are mild with fluoxetine (long half-life) and can be particularly severe with paroxetine

DEPRESSION: Treatment and Management

SSRIs
Selective serotonin reuptake inhibitors

- Serotonin syndrome
  - Potentially life-threatening condition associated with increased serotonergic activity in the central nervous system
  - Caused by overstimulation of central and peripheral serotonin receptors
    - It can occur after initiating or increasing a single serotonergic drug
  - Clinical features include:
    - Anxiety, agitation, delirium, diaphoresis, tachycardia, hypertension, hyperthermia, gastrointestinal distress, tremor, muscle rigidity, myoclonus, and hyperreflexia

DEPRESSION: Treatment and Management

Serotonin-norepinephrine reuptake inhibitors

SNRIs	Half life (h)	DDI	Metabolism and elimination
Desvenlafaxine	9 – 11 hours	None	Renal and hepatic
Duloxetine	10 – 12 hours	Inhibits CYP2D6	Renal and hepatic
Milnacipran	8 – 10 hours	None	Renal and hepatic
Venlafaxine	5 hours parent 11 hours active metabolite (desvenlafaxine)	None	Renal and hepatic

DEPRESSION: Treatment and Management

Serotonin-norepinephrine reuptake inhibitors

- Use
  - Initial treatment of major depression, treatment resistant depression, and other disorders
  - Duloxetine may be used in diabetic peripheral neuropathy and fibromyalgia

- Pharmacology
  - Initially blocking presynaptic serotonin and norepinephrine transporter proteins ➔ Inhibits reuptake of these neurotransmitters and leads to increased stimulation of post-synaptic receptors
  - Little or no effect on dopaminergic, cholinergic, histaminergic, or alpha1-adrenergic receptors

DEPRESSION: Treatment and Management

Serotonin-norepinephrine reuptake inhibitors

- Side effects
  - Nausea ➔ Administer with food to reduce nausea
  - Dizziness
  - Diaphoresis

  - Desvenlafaxine ➔ weight loss / HTN / Nausea
  - Duloxetine ➔ CI in uncontrolled angle closure glaucoma
  - Milnacipran ➔ CI in uncontrolled angle closure glaucoma / HTN
  - Venlafaxine ➔ XR formulation is used because of less nausea / HTN / Overdose can cause hypertension, hypotension, cardiac arrhythmias, seizures, serotonin syndrome, and death

DEPRESSION: Treatment and Management

Atypical antidepressants

Atypical antidepressants	Half life (h)	DDI	Metabolism and elimination
Agomelatine (not available in the United States)	1 – 2 hours	None	Liver
Bupropion	14 hours parent 21 – 51 hours active metabolite	Inhibit CYP 2D6	Liver and kidney
Mirtazapine	20 – 40 hours parent 25 hours active metabolite	None	Liver and kidney

DEPRESSION: Treatment and Management

Atypical antidepressants

- Use
  - Used in patients with inadequate responses or intolerable side effects during first-line treatment with SSRIs
  - First-line treatment if the drug has a desirable characteristic
    - Agomelatine ➔ major depression + insomnia
    - Bupropion ➔ major depression, seasonal affective disorder, ADHD, tobacco dependence, hypoactive sexual disorder, and obesity
    - Mirtazapine ➔major depression, generalized anxiety disorder, and tension type headaches

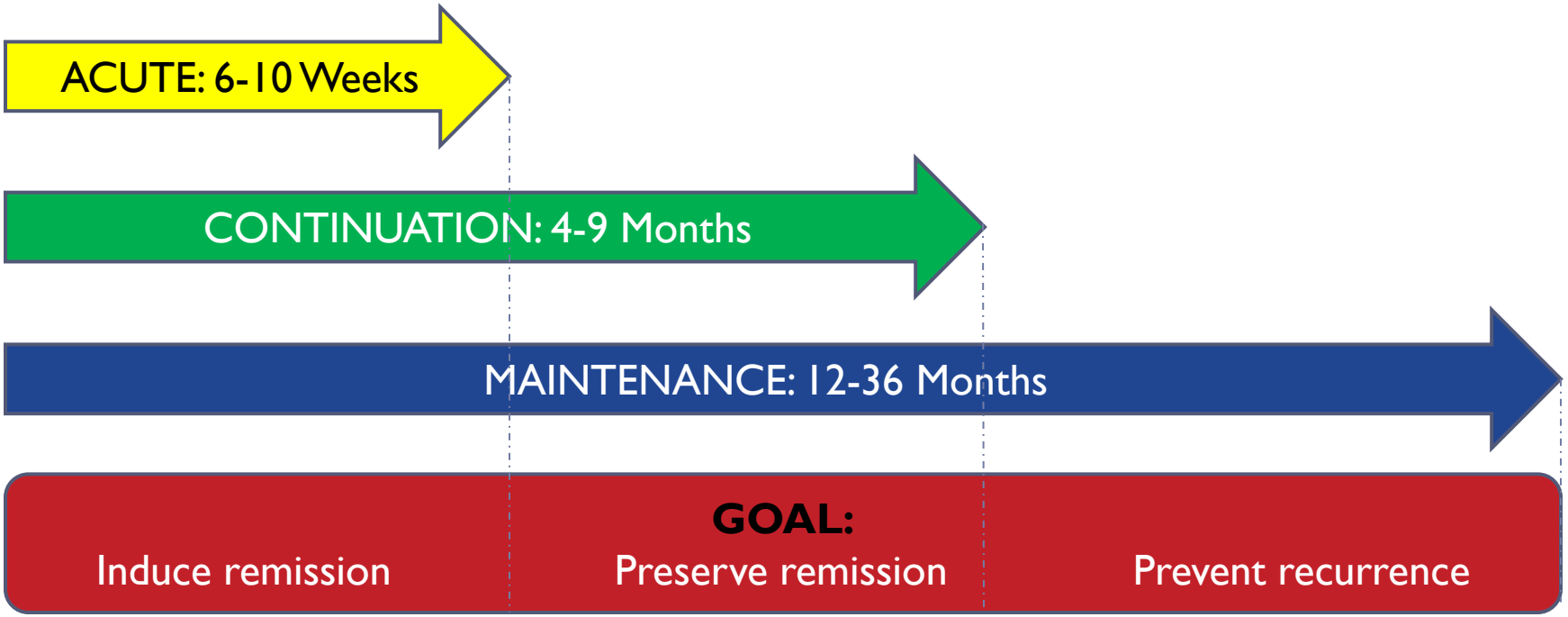
DEPRESSION: Treatment and Management

Atypical antidepressants

- Side effects

Agomelatine	Bupropion	Mirtazapine
Dizziness	Seizures Dry mouth Nausea Insomnia Dizziness Anxiety Dyspepsia	Dry mouth Drowsiness Sedation Appetite increase Weight increase

DEPRESSION: Treatment approach



- If no response at therapeutic doses in 8 – 12 weeks: OPTIONS:
  - Switch to an agent from the same class
  - Switch to an agent from a different class
  - If failure after 2 different agents from different classes
    - Augmentation therapy
    - Electroconvulsive therapy
    - Combination therapy

DEPRESSION: Special Populations

- Pregnancy
  - Pregnancy does not protect against depression
  - Weigh risks vs. benefits
  - SSRIs and Bupropion among the safer options
  - Consider d/c therapy prior to conception

- Elderly
  - Start at lower doses
  - Avoid TCAs
  - Reserve MAOIs for resistant/atypical patients
  - SSRIs, Bupropion, Venlafaxine

- Pediatrics
  - Antidepressants increase the risk of suicidal thinking/behavior in children, adolescents and young adults
  - Antidepressants have a Black Box warning from the FDA
  - Monitor patients closely
  - Fluoxetine approved for pediatrics

ANXIETY: Introduction

- United States ➔ Lifetime prevalence of GAD of 5.1 to 11.9%
- Europe ➔ Lifetime prevalence of 4.3 to 5.9%
- One of the most common mental disorders in primary care settings and is associated with increased use of health services
- Twice as common in women as it is in men
- Several disorders
  - **Generalized anxiety disorder (GAD)**
  - **Panic disorder with or without agoraphobia**
  - **Obsessive compulsive disorder (OCD)**
  - **Post traumatic stress disorder (PTSD)**
  - **Social phobia**
  - **Specific phobia**
  - **AND more…**

ANXIETY: GAD-Diagnosis

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety that are difficult to control, cause significant distress and impairment, and occur on more days than not for at least six months.

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FIFTH EDITION

DSM-5™

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance)
- B. The individual finds it difficult to control the worry
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past six months):

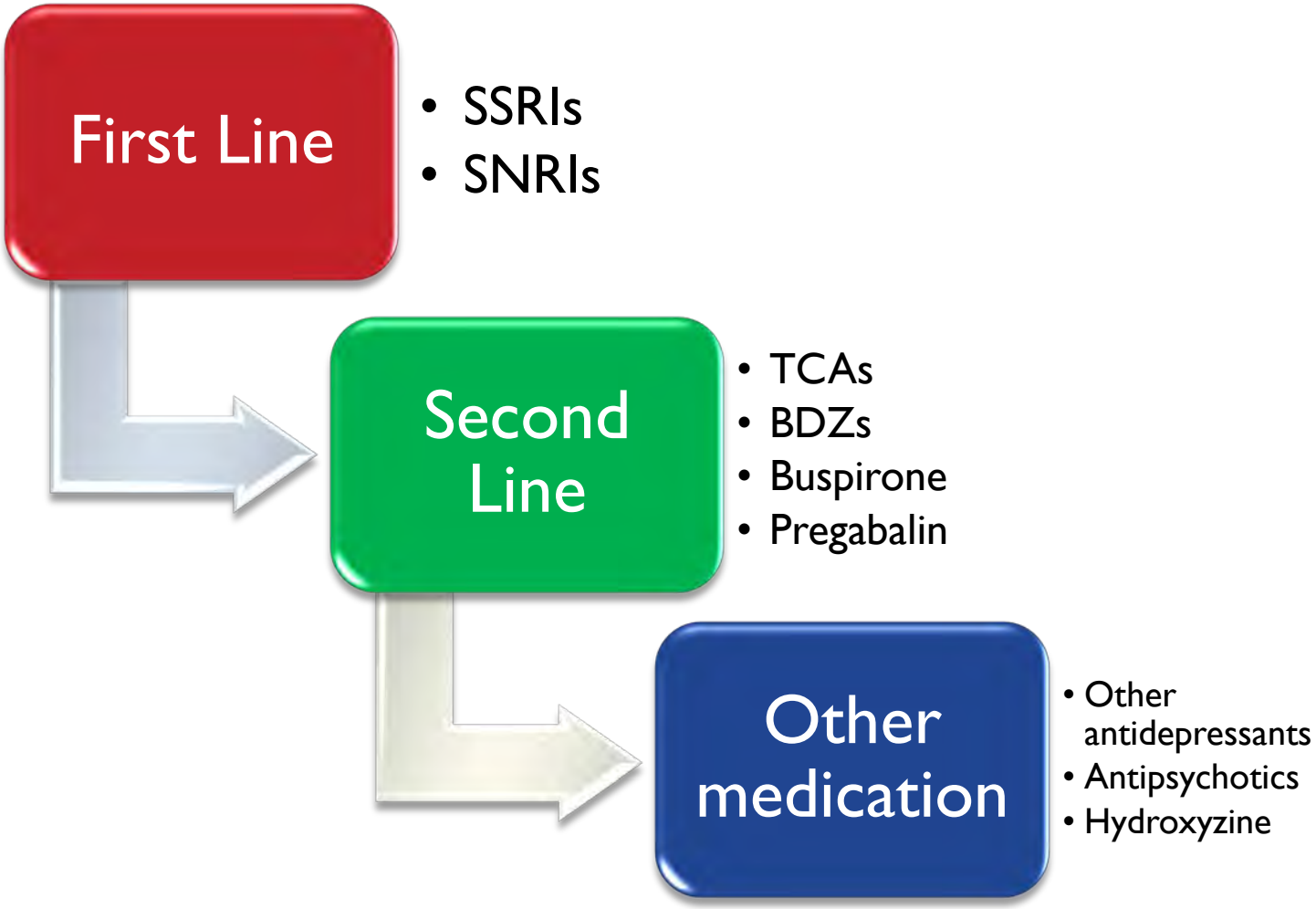
Note: Only one item is required in children.

1. Restlessness or feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

- D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- E. The disturbance is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication) or another medical condition (eg, hyperthyroidism)
- F. The disturbance is not better explained by another mental disorder

1.American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

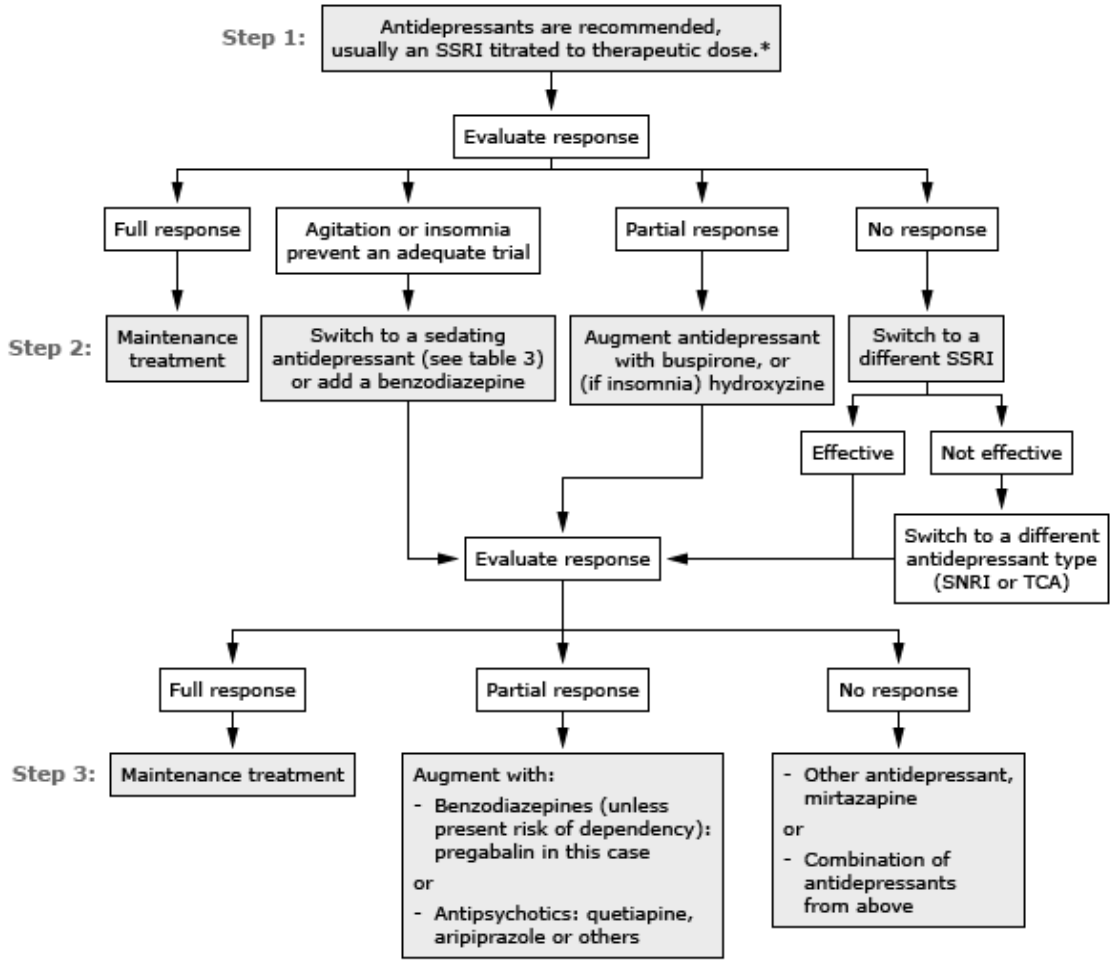
ANXIETY: Treatment and management



ANXIETY

Treatment ALGORITHM

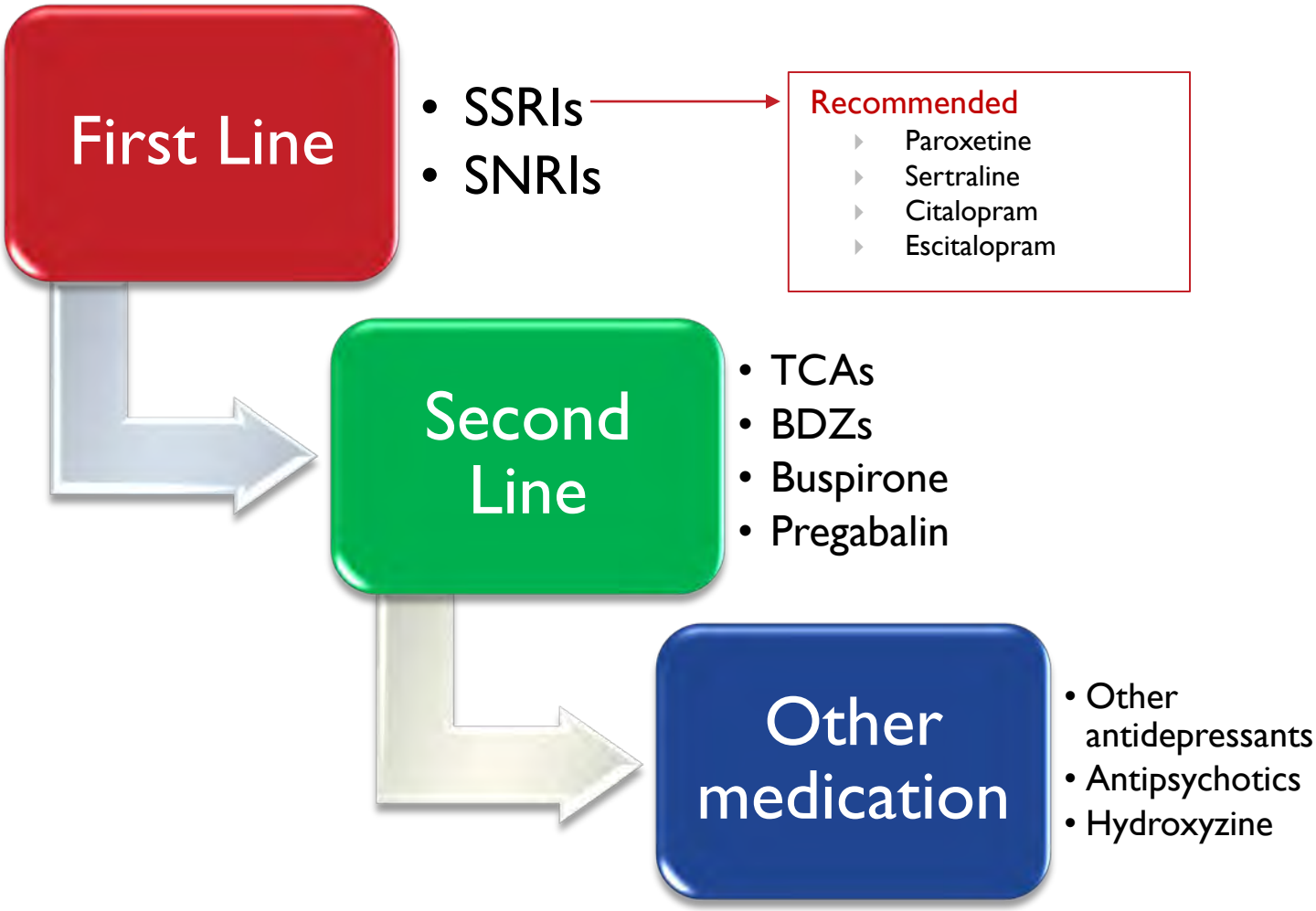
Algorithm for stepped pharmacotherapy for generalized anxiety disorder



Cognitive behavioral therapy can be used as an alternative first-line treatment or in combination with medications. The choice between pharmacotherapy and CBT may be based on availability and patient preference.

* A benzodiazepine such as lorazepam can be used if needed to manage anxiety before the SSRI takes effect

ANXIETY: Treatment and management



ANXIETY: Treatment and management

GAD

Treatment

& Medication

I st Line

Pharmacology of medicines for treatment of adults with generalized anxiety disorder (GAD)

Drug	Initial daily oral dose (mg)*	Daily oral dose range (mg)*	Primary metabolism Δ	Effect on metabolism of other drugs Δ	Selected characteristics relevant to treatment of adults with GAD
Selective serotonin reuptake inhibitor (SSRI) antidepressants Applies to all SSRIs: Onset of effect may be delayed 2-4 weeks or more. Adverse effects among the SSRIs include: Nausea, diarrhea, insomnia/agitation, somnolence, impaired sexual function, and hyponatremia. Adverse effects of individual agents are presented in a separate table in UpToDate.					
Citalopram	10	10 to 40	CYP3A4, 2C19	None	▪ Lower risk of insomnia/agitation ▪ Few drug interactions ▪ Appears to prolong QT interval with increasing blood levels
Escitalopram	5 to 10	10 to 20	CYP3A4, 2C19	None	▪ Lower risk of insomnia/agitation ▪ Few drug interactions
Sertraline	50	50 to 150	Limited (minor CYP2C9, 2D6, and 3A4)	Inhibits CYP2B6, 2C19, 2D6	▪ Greater risk of insomnia/agitation ▪ More frequent diarrhea and other gastrointestinal complaints
Paroxetine	20	20 to 50	CYP2D6	Inhibits CYP2B6, 2D6	▪ Mildly sedating ▪ Weakly anticholinergic ▪ Lower risk of insomnia/agitation ▪ Withdrawal symptoms if not tapered
Fluoxetine	20	20 to 60	CYP2D6, 2C9, and several minor	Inhibits CYP2D6, 2C19	▪ Greater risk of insomnia/agitation ▪ No withdrawal symptoms if not tapered ▪ Takes weeks to reach steady blood levels due to long half-life
Fluvoxamine	50	100 to 300	CYP1A2, 2D6	Inhibits CYP1A2, 2C19	▪ Lower risk of insomnia/agitation ▪ Withdrawal symptoms if not tapered ▪ Significant drug interactions

ANXIETY: Treatment and management

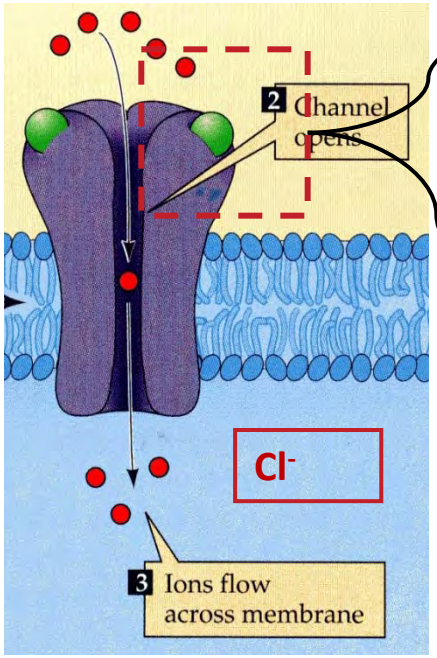
GAD Treatment & Medication:

2nd Line

- Benzodiazepines
  - Reduction of emotional and somatic symptoms within minutes to hours
  - Given during acute, maintenance, or long-term treatment of GAD
  - Monotherapy (if no comorbid depression)

  Or
  - More common ➔ Adjunct to antidepressant
    - Acute management of anxiety and worry during the period before SSRIs or SNRIs take effect
    - Counteract the initial agitation often caused by the SSRI
    - When patient responds to the SSRI ➔ Taper off benzodiazepine gradually

ANXIETY: Treatment and management

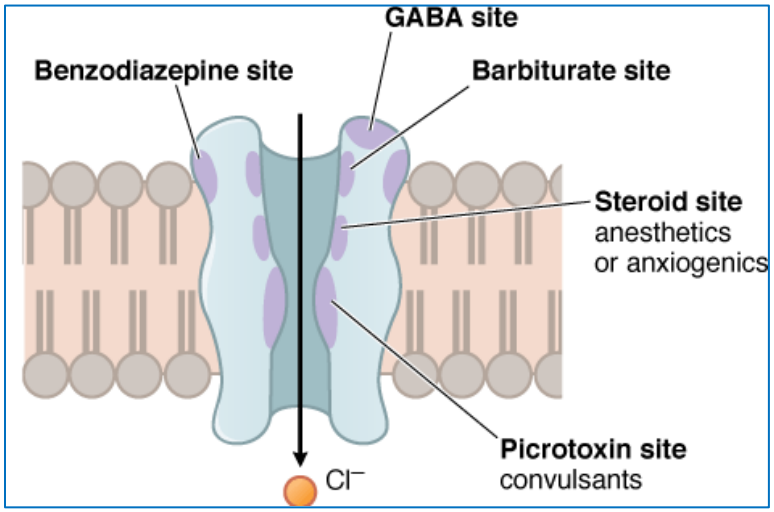


su **β:** GABA

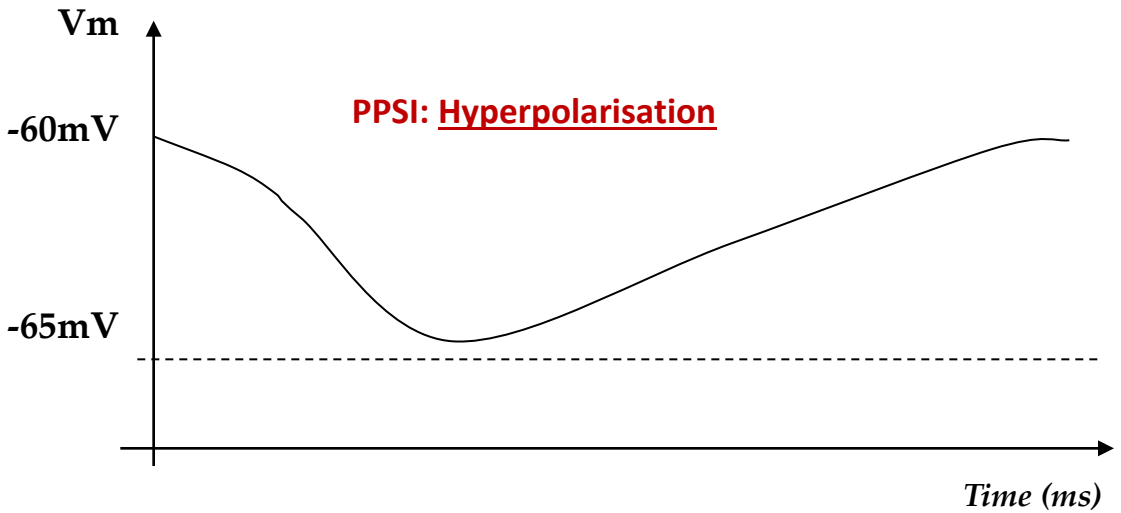
su **α:** BZD

barbiturates

(other site)

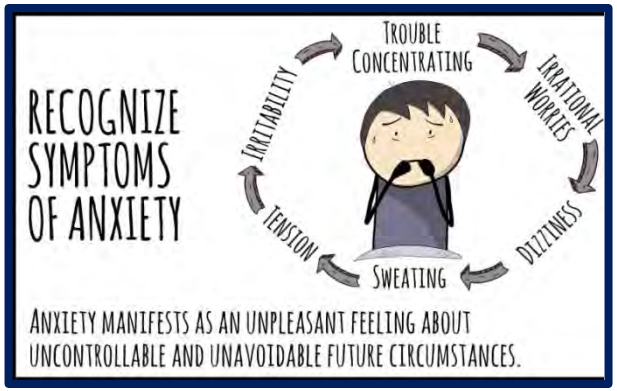


GABA RECEPTORS



PPSI: Hyperpolarisation

ANXIETY: Treatment Strategy & Duration



- ✓ **Time to effect is ~ 4 weeks**: Concomitantly administered benzodiazepine
  - ➢ Treat agitation and anxiety
- ⌘ If **partial** response
  - ➢ Increase dose
- ✕ If **no improvement after 6 – 8 weeks** on a therapeutic dose
  - ➢ Taper off and switch to a different SSRI
- ✕ If **no response to 2nd SSRI**
  - ➢ Go to 2nd line or augment SSRI
- ✓ If **effective** antidepressant
  - ➢ Continue AD for at least 12 months
- ⌀ If **relapse** following termination of an effective medication
  - ➢ Extend length of treatment
- ⌀ **After two relapses when tapering off** the medication
  - ➢ Ongoing maintenance treatment should be considered

Depression

Anxiety

Take Home messages

Mental Disorders

- Identify people at risk of mental disorders, support them and guide them
- Never prescribe treatment without medical assessment (psychiatrist, etc.)
- Counsel about onset of action, side effects occurrence, DDI and treatment duration
- Promote smoking cessation, and rational use of alcohol
- Involve patients in the treatment plan with a proactive input :
  - Insist on adherence to treatment (medication on time, duration of treatment, correct dose escalation and tapering)
  - Explain the importance of continuing the treatment to reduce relapse
  - Promote healthy eating, active lifestyle, exercising

Depression

Anxiety

Case studies

Mental Disorders

Mona is a 56 year old obese woman, with history of hypertension, anemia and arrhythmia. She presented to the psychiatry clinics with complaints of depressed mood, fatigue, insomnia, decreased concentration and recurrent thoughts of death with no attempts of suicide. She has been diagnosed with moderate depression. **Which of the following is the best choice of therapy?**

A. Mirtazapine
B. Lithium
C. Paroxetine
D. Venlafaxine
E. Imipramine

Mona is a 56 year old obese woman, with history of hypertension, anemia and arrhythmia. She presented to the psychiatry clinics with complaints of depressed mood, fatigue, insomnia, decreased concentration and recurrent thoughts of death with no attempts of suicide. She has been diagnosed with moderate depression. Which of the following is the best choice of therapy?

A. Mirtazapine
B. Lithium
C. **Paroxetine**
D. **Venlafaxine**
E. Imipramine

A 36 year old woman presents with symptoms of major depression that are unrelated to a general medical condition, bereavement, or substance abuse. She is not taking any over the counter of prescription medications. Drug treatment is to be initiated with fluoxetine. In your information to the patient, you would tell her that:

A. It is preferable that she does not take it in the evening
B. Headache and nausea can sometimes occur
C. She should tell you if she anticipates using other prescription drugs
D. The antidepressant effects of fluoxetine may take 2 weeks or more to become effective
E. All of the above

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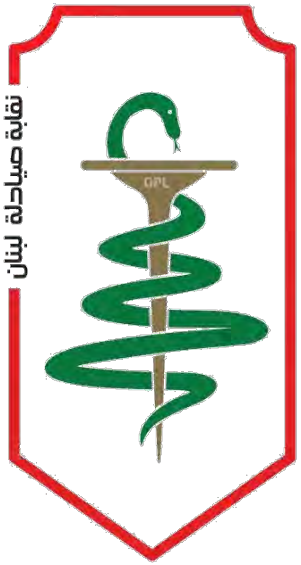
E. **All of the above**

D S is a 45 years old married lady and mother to 3 children. She is still on the same living pattern since years however she is becoming highly irritable for the past months. Her family recognized that and advised her to visit the psychiatry clinic where she was diagnosed with generalized anxiety disorder. Her past medication history reveals: omega 3 capsule daily, omeprazole 20 mg qd, and paracetamol prn. The physician prescribed escitalopram 10 mg daily. The patient had a partial response after 3 weeks from starting the drug and then her case deteriorated back after another 4 weeks. What should your advice as a clinical pharmacist be for this patient at the time being?

A. Switch her to paroxetine
B. Add buspirone to her current therapy
C. Augment her therapy with hydroxyzine
D. Add clonazepam to her current therapy
E. Keep her management as it is since the patient needs more time for an adequate trial



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R, a 23-year-old woman, a PharmD student, comes to your pharmacy and complains about an excessive worry, associated sometimes with an overwhelming fear when it comes to the exams period. She explains that she had similar episodes during the past years but she managed to control them before. She is very worried if the symptoms will continue to recur and she came to ask you for an advice. It is noteworthy to add that one of her parents had the Brugada syndrome (Congenital QT prolongation) and died from Tdp. Which of the following can be considered a first line option for the management of her condition?

A. Escitalopram + Lorazepam
B. Fluoxetine + Clomipramine
C. Sertraline + Lorazepam
D. Sertraline + Buspirone
E. Clomipramine + Buspirone

R, a 23-year-old woman, a PharmD student, comes to your pharmacy and complains about an excessive worry, associated sometimes with an overwhelming fear when it comes to the exams period. She explains that she had similar episodes during the past years but she managed to control them before. She is very worried if the symptoms will continue to recur and she came to ask you for an advice. It is noteworthy to add that one of her parents had the Brugada syndrome (Congenital QT prolongation) and died from Tdp. Which of the following can be considered a first line option for the management of her condition?

A. Escitalopram + Lorazepam
B. Fluoxetine + Clomipramine
C. **Sertraline + Lorazepam**
D. Sertraline + Buspirone
E. Clomipramine + Buspirone

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What do you recommend as a next step?

A. Taper off benzodiazepine gradually after 2-4 weeks

B. Taper off the SSRI gradually after 2-4 weeks

C. Continue using the combination for 3 months

D. Stop both medications after the exams period

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