Anxiety Disorders

- Anxiety disorders include a constellation of disorders in which anxiety and associated symptoms are **irrational** or experienced at a level of severity that impairs functioning.

- The characteristic features are **anxiety** and **avoidance**.

PATHOPHYSIOLOGY:

- *Noradrenergic model. This model suggests that the autonomic nervous* system of anxious patients is hypersensitive and overreacts to various stimuli.

- The **locus ceruleus** may have a role in regulating anxiety, as it activates norepinephrine release and stimulates the sympathetic and parasympathetic nervous systems.

- Chronic noradrenergic overactivity down regulates α2-adrenoreceptors in patients with generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD).

- Patients with social anxiety disorder (SAD) appear to have a hyperresponsive adrenocortical response to psychological stress.

- *γ-Aminobutyric acid (GABA) receptor model.* *GABA is the major inhibitory* neurotransmitter in the CNS. Many antianxiety drugs target the GABAA receptor.

- Benzodiazepines (BZs) enhance the inhibitory effects of GABA, which has a strong regulatory or inhibitory effect on serotonin (5-HT), norepinephrine, and dopamine systems.

- In patients with GAD, BZ binding in the left temporal lobe is reduced.

- Abnormal sensitivity to antagonism of the BZ binding site and decreased binding was demonstrated in panic disorder.

- Growth hormone response to baclofen in patients with generalized SAD suggests an abnormality of central GABAB receptor function.

- Abnormalities of GABA inhibition may lead to increased response to stress in PTSD patients.

5-HT model:

- GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways.

- Patients with SAD have greater prolactin response to buspirone challenge, indicating an enhanced central serotonergic response.

CLINICAL PRESENTATION:

- The diagnostic criteria require persistent symptoms most days for at least 6 months.

- The anxiety or worry must be about a number of matters and is accompanied by at least three psychological or physiologic symptoms.

- The illness has a gradual onset at an average age of 21 years. The course of illness is chronic, with multiple spontaneous exacerbations and remissions.

- There is a high percentage of relapse and a low rate of recovery.

Presentation of Generalized Anxiety Disorder

Psychological and cognitive symptoms

- Excessive anxiety
- Worries that are difficult to control
- Feeling keyed up or on edge
- Poor concentration or mind going blank

Physical symptoms

- Restlessness
- Fatigue
- Muscle tension
- Sleep disturbance
- Irritability

Impairment

- Social, occupational, or other important functional areas
- Poor coping abilities

Symptoms of a Panic Attack

Psychological symptoms

- Depersonalization
- Derealization
- Fear of losing control
- Fear of going crazy
- Fear of dying

Physical symptoms

- Abdominal distress
- Chest pain or discomfort
- Chills
- Dizziness or lightheadedness
- Feeling of choking
- Hot flushes
- Palpitations
- Nausea
- Paresthesias
- Shortness of breath
- Sweating
- Tachycardia
- Trembling or shaking

Presentation of Social Anxiety Disorder

Fears

- Being scrutinized by others
- Being embarrassed
- Being humiliated

Some feared situations

- Addressing a group of people
- Eating or writing in front of others
- Interacting with authority figures
- Speaking in public
- Talking with strangers
- Use of public toilets

Physical symptoms

- Blushing
- "Butterflies in the stomach"
- Diarrhea
- Sweating
- Tachycardia
- Trembling

Types

- Generalized type: fear and avoidance extend to a wide range of social situations
- Nongeneralized type: fear is limited to one or two situations

Presentation of Posttraumatic Stress Disorder

Reexperiencing symptoms

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (e.g., dissociative flashbacks)
- Physiologic reaction to reminders of the trauma

Avoidance symptoms

- Avoidance of conversations about the trauma
- Avoidance of thoughts or feelings about the trauma
- Avoidance of activities that are reminders of the event
- Avoidance of people or places that arouse recollections of the trauma
- Inability to recall an important aspect of the trauma
- Anhedonia
- Estrangement from others
- Restricted affect
- Sense of a foreshortened future (e.g., does not expect to have a career, marriage)

Hyperarousal symptoms

- Decreased concentration
- Easily startled
- Hypervigilance
- Insomnia
- Irritability or angry outbursts

Subtypes

- Acute: duration of symptoms is less than 3 months
- Chronic: symptoms last for longer than 3 months
- With delayed onset: onset of symptoms is at least 6 months posttrauma

Screening questions

- Have you ever experienced a significant trauma in your life?
- Did this experience have a lasting negative impact or change your life?

DIAGNOSIS:

- Evaluation of the anxious patient requires a complete physical and mental status examination; appropriate laboratory tests; and a medical, psychiatric, and drug history.

- Anxiety symptoms may be associated with medical illnesses or drug therapy. About 50% of patients with GAD have irritable bowel syndrome.

- Anxiety symptoms may be present in several major psychiatric illnesses (e.g., mood disorders, schizophrenia, organic mental syndromes, and substance withdrawal).

Common Medical Illnesses Associated with Anxiety Symptoms

Cardiovascular:

Angina, arrhythmias, congestive heart failure, ischemic heart disease, myocardial infarction.

Endocrine and metabolic:

Cushing's disease, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B12 or folate deficiencies.

Neurologic:

Dementia, migraine, Parkinson's disease, seizures, stroke, neoplasms, poor pain control.

Respiratory system:

Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia.

Others:

Anemias, systemic lupus erythematosus, vestibular dysfunction.

DESIRED OUTCOME:

- The desired outcomes of treatment of GAD are to reduce severity, duration, and frequency of the symptoms and to improve overall functioning.

- The goals of therapy of panic disorder include a complete resolution of panic attacks, marked reduction in anticipatory anxiety and phobic fears, elimination of phobic avoidance, and resumption of normal activities.

- The goals of treatment of SAD are to reduce the physiologic symptoms and phobic avoidance, increase participation in desired social activities, and improve quality of life.

- The goals of therapy of PTSD are to decrease core symptoms, disability, and comorbidity and improve quality of life and resilience to stress.

TREATMENT

- For patients with GAD, nonpharmacologic modalities include short-term counseling, stress management, cognitive therapy, meditation, supportive therapy, and exercise.

- GAD patients should be educated to avoid caffeine, stimulants, excessive alcohol, and diet pills.

- Hydroxyzine was effective in 88% of patients for a duration of 3 months.

- Pregabalin produced anxiolytic effects similar to lorazepam, alprazolam, and venlafaxine in acute trials.

- Cognitive behavioral therapy (CBT) is the most effective psychological therapy for GAD patients, and most patients with GAD should have psychological therapy, alone or in combination with antianxiety drugs.

Antidepressants:

- Antidepressants are efficacious for acute and long-term management of GAD. They are considered the treatment of choice for long-term management of chronic anxiety, especially in the presence of depressive symptoms.

- Antianxiety response requires 2 to 4 weeks. Venlafaxine extended release, duloxetine, paroxetine, and escitalopram are FDA approved for treatment of GAD. Sertraline is also effective.

- Acute response and remission rates are approximately 65% and 30%, respectively.

- Imipramine may be used when patients fail to respond to selective serotonin reuptake inhibitors (SSRIs).

- The BZs are the most frequently prescribed drugs for the treatment of **acute anxiety**.

- All BZs are equally effective anxiolytics, and most of the improvement occurs in the first 2 weeks of therapy.

- They are considered to be more effective for **somatic and autonomic symptoms of GAD**, while antidepressants are considered more effective for the psychic symptoms (e.g., apprehension and worry).

- The dose must be individualized. Some patients require longer treatment.

- The elderly have an enhanced sensitivity to BZs and may experience falls when on BZ therapy.

- Buspirone is a 5-HT1A partial agonist that lacks anticonvulsant, muscle relaxant, sedative-hypnotic, motor impairment, and dependence-producing properties.

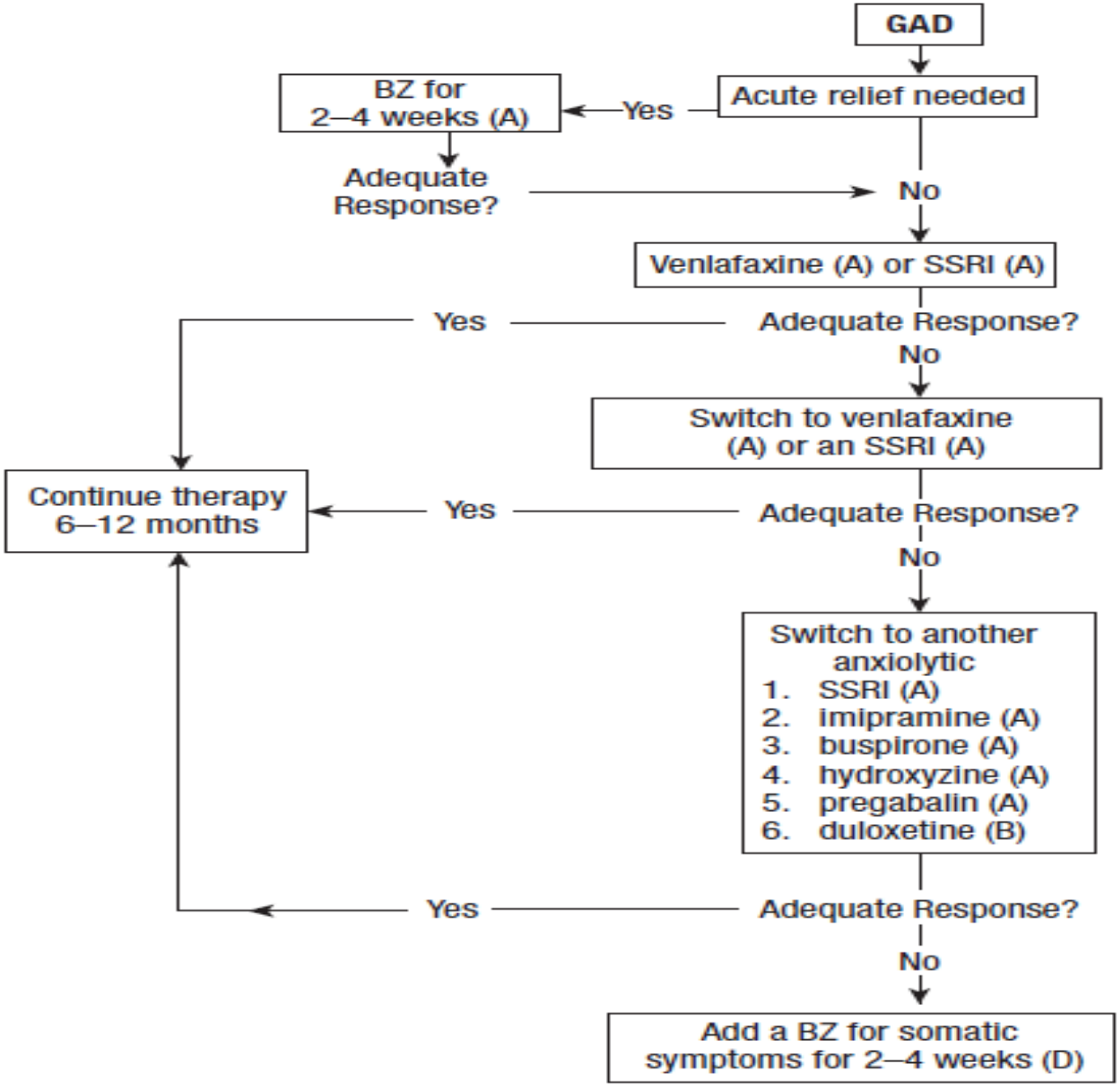
- It is considered a second-line agent for GAD because of inconsistent reports of efficacy, delayed onset of effect, and lack of efficacy for comorbid depressive and anxiety disorders (e.g., panic disorder or SAD).

Benzodiazepine Antianxiety Agents

Generic Name	Brand Name	Approved Dosage Range (mg/day)*a*	Approximate Equivalent Dose (mg)
Alprazolam	Niravam,*c* Xanax, Xanax XR	0.75–4 1–10*d*	0.5
Chlordiazepoxide	Librium	25–100	10
Clonazepam	Klonopin Klonopin Wafers	1–4*d*	0.25
Clorazepate	Tranxene.	7.5–60	7.5
Diazepam	Valium	2–40	5
Lorazepam	Ativan	0.5–10	1
Oxazepam	Serax	30–120	15

- Initially, anxious patients should be monitored once to twice weekly for reduction in anxiety symptoms, improvement in functioning, and side effects.

- The Visual Analog Scale may assist in the evaluation of drug response.


GAD
Acute relief needed
Yes
BZ for 2–4 weeks (A)
Adequate Response?
No
Venlafaxine (A) or SSRI (A)
Adequate Response?
Yes
No
Switch to venlafaxine (A) or an SSRI (A)
Adequate Response?
Yes
Continue therapy 6–12 months
No
Switch to another anxiolytic
1. SSRI (A)
2. imipramine (A)
3. buspirone (A)
4. hydroxyzine (A)
5. pregabalin (A)
6. duloxetine (B)
Adequate Response?
Yes
No
Add a BZ for somatic symptoms for 2–4 weeks (D)

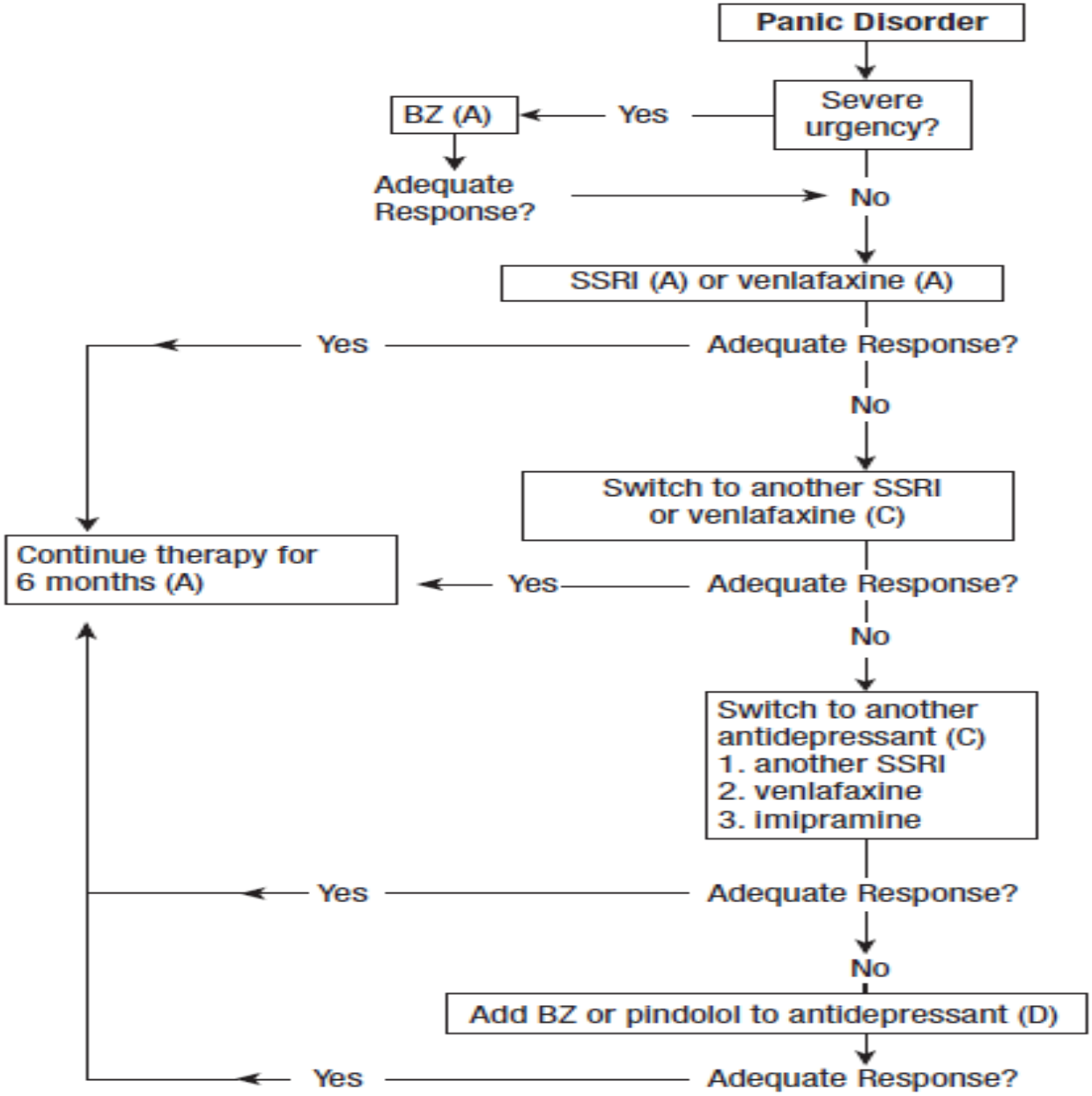
Drugs Associated with Anxiety Symptoms

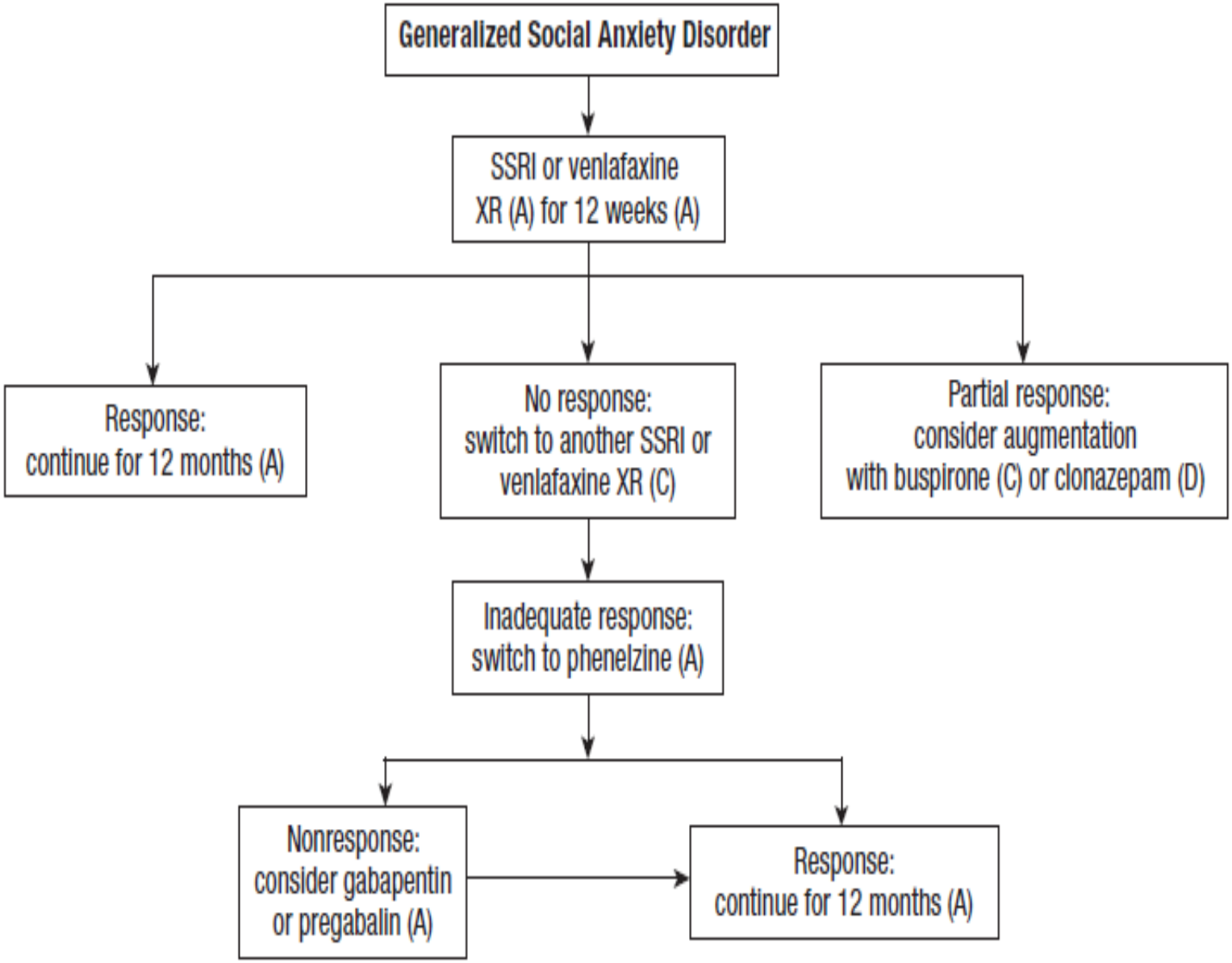
Anticonvulsants: carbamazepine
Antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants
Antihypertensives: felodipine
Antibiotics: quinolones, isoniazid
Bronchodilators: albuterol, theophylline
Corticosteroids: prednisone
Dopa agonists: levodopa
Herbals: ma huang, ginseng, ephedra
Nonsteroidal antiinflammatory drugs: ibuprofen
Stimulants: amphetamines, methylphenidate, caffeine, cocaine
Sympathomimetics: pseudoephedrine
Thyroid hormones: levothyroxine
Toxicity: anticholinergics, antihistamines, digoxin
Withdrawal: alcohol, sedatives

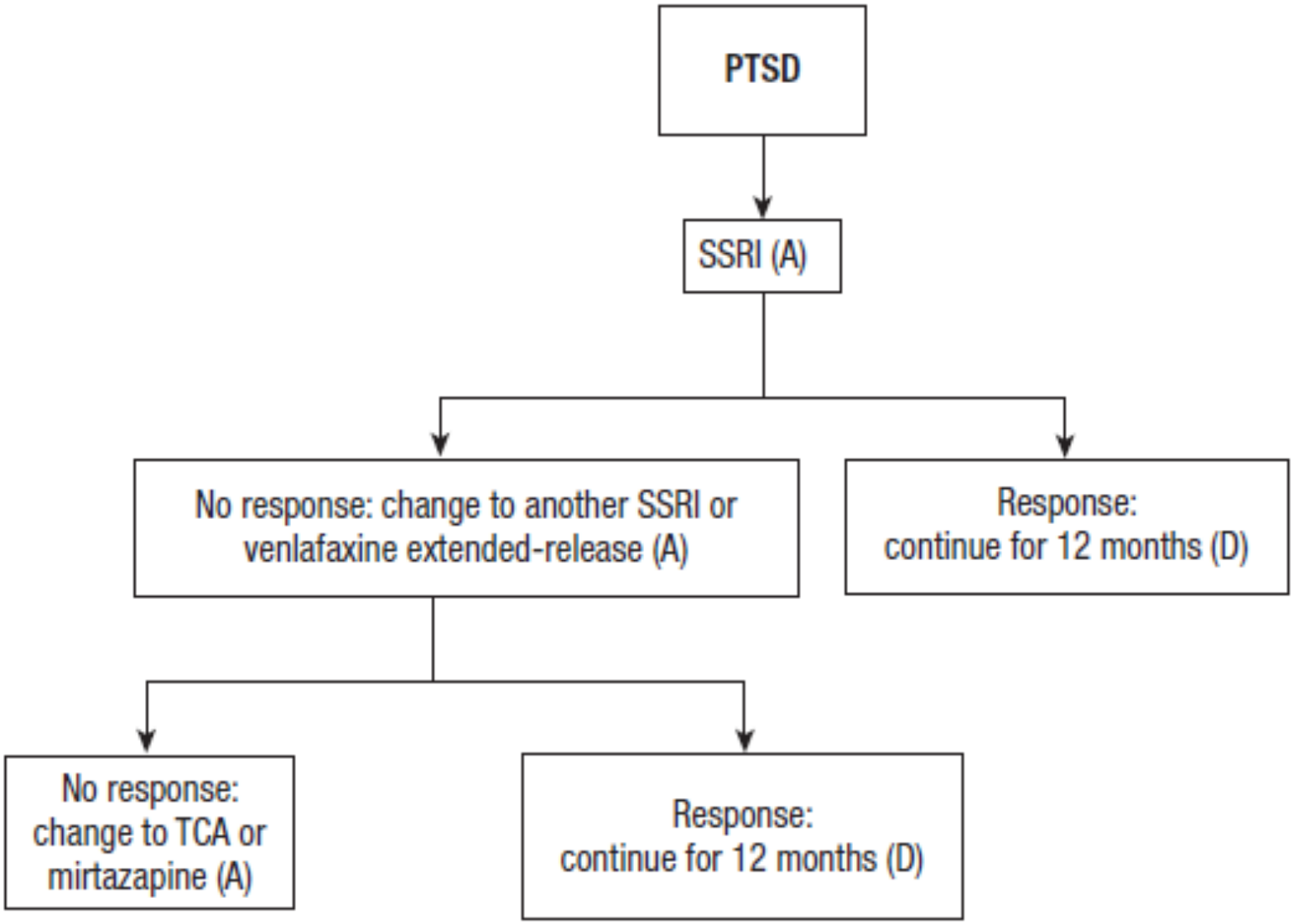
Drug Choices for Anxiety Disorders

Anxiety Disorder	First-Line Drugs	Second-Line Drugs	Alternatives
Generalized anxiety	Duloxetine Escitalopram Paroxetine Venlafaxine XR	Benzodiazepines Buspirone Imipramine Sertraline	Hydroxyzine Pregabalin
Panic disorder	SSRIs Venlafaxine XR	Alprazolam Clomipramine Clonazepam Imipramine	Phenelzine
Social anxiety disorder	Escitalopram Fluvoxamine Paroxetine Sertraline Venlafaxine XR	Citalopram Clonazepam	Buspirone Gabapentin Mirtazapine Phenelzine Pregabalin

Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder			
Generic	Trade Name	Starting Dose	Dosage Range (mg/day)*a*
Antidepressants			
Duloxetine	Cymbalta	30 or 60 mg per day	60–120
Escitalopram.	Lexapro	10 mg per day	10–20
Imipramine.	Tofranil	50 mg per day	75–200
Paroxetine	Paxil	20 mg per day.	20–50
Venlafaxine.	Effexor XR	37.5 or 75 mg per day	75–225
Azapirones			
Buspirone.	BuSpar	7.5 mg twice per day	15–60
Diphenylmethane			
Hydroxyzine	Vistaril, Atarax	25 or 50 mg four times daily	200–400
Anticonvulsant			
Pregabalin	Lyrica	50 mg three times daily	150–600


Panic Disorder
Severe urgency?
Yes
BZ (A)
Adequate Response?
No
SSRI (A) or venlafaxine (A)
Adequate Response?
Yes
No
Switch to another SSRI or venlafaxine (C)
Adequate Response?
Yes
Continue therapy for 6 months (A)
No
Switch to another antidepressant (C)
1. another SSRI
2. venlafaxine
3. imipramine
Adequate Response?
Yes
No
Add BZ or pindolol to antidepressant (D)
Adequate Response?
Yes


Generalized Social Anxiety Disorder
SSRI or venlafaxine XR (A) for 12 weeks (A)
Response: continue for 12 months (A)
No response: switch to another SSRI or venlafaxine XR (C)
Partial response: consider augmentation with buspirone (C) or clonazepam (D)
Inadequate response: switch to phenelzine (A)
Nonresponse: consider gabapentin or pregabalin (A)
Response: continue for 12 months (A)


PTSD
SSRI (A)
No response: change to another SSRI or venlafaxine extended-release (A)
Response: continue for 12 months (D)
No response: change to TCA or mirtazapine (A)
Response: continue for 12 months (D)

Abuse, Dependence, Withdrawal, and Tolerance:

- Those with a history of drug abuse are at the greatest risk for becoming BZ abusers.

- BZ dependence is defined by the appearance of a predictable withdrawal syndrome (i.e., anxiety, insomnia, agitation, muscle tension, irritability, nausea, malaise, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) upon abrupt discontinuation.

Benzodiazepine Discontinuation

After BZs are abruptly discontinued, three events can occur:

1- Rebound symptoms are an immediate, but transient, return of original symptoms with an increased intensity compared with baseline.

2- Recurrence or relapse is the return of original symptoms at the same intensity as before treatment.

3- Withdrawal is the emergence of new symptoms and a worsening of preexisting symptoms.

The onset of withdrawal symptoms is within 24 to 48 hours after discontinuation of short elimination half-life BZs and 3 to 8 days after discontinuation of long elimination half-life drugs.

Discontinuation strategies include the following:

- A 25% per week reduction in dosage until 50% of the dose is reached, then dosage reduction by one-eighth every 4 to 7 days.

- If therapy exceeds 8 weeks, a taper over 2 to 3 weeks is recommended, but if duration of treatment is 6 months, a taper over 4 to 8 weeks should ensue.

- Longer durations of treatment may require a 2- to 4-month taper.
- A BZ with along elimination half-life (t1/2) (e.g., **diazepam, clonazepam**) may be substituted for a drug with a short t1/2 (e.g., **lorazepam, oxazepam, alprazolam**).

- The substituted drug should be given for several weeks before gradual tapering begins.

- Adjunctive use of **imipramine, valproic acid,** or **buspirone** can help to reduce withdrawal symptoms during the BZ taper.

Dosing and Administration:

- Initial doses should be low, and dosage adjustments can be made weekly.

- Treatment of acute anxiety generally should not exceed 4 weeks. BZs can be given as needed, and if several acute courses are necessary, a BZ-free period of 2 to 4 weeks should be implemented between courses.

- Persistent symptoms should be managed with antidepressants.

- BZs with a long half life may be dosed once daily at bedtime and may provide nighttime hypnotic and anxiolytic effects the next day.