# GENERALIZED ANXIETY DISORDER, PANIC DISORDER, AND SOCIAL ANXIETY DISORDER

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# Introduction



- Anxiety disorders are among the most frequent mental disorders encountered by clinicians.
- All anxiety disorders share features of fear and anxiety that differ from developmentally normative fear or anxiety by:
  - being excessive, persistent, and resulting in behavioral disturbances.

# EPIDEMIOLOGY AND ETIOLOGY



## Prevalence

- The lifetime prevalence of anxiety disorders collectively is 28.8% with specific phobia (12.5%) and social anxiety disorder (SAD) (12.1%) being the most common.
- More prevalent among women than men(2:1).
- Prevalence rates increase from the younger age group (18–29 years) to older age groups (30–44 and 45–59 years).

# EPIDEMIOLOGY AND ETIOLOGY



## Course of Illness

- PD and GAD have a median age of onset of 24 and 31 years, respectively, whereas SAD develops earlier (median age 13 years.
- Are chronic, and symptoms tend to wax and wane, with fewer than one-third of patients experiencing spontaneous symptom remission.
- The risk for relapse and recurrence of symptoms is also high.

# EPIDEMIOLOGY AND ETIOLOGY



- **Comorbidity** :
- >90% of individuals with an anxiety disorder have a lifetime history of one or more other psychiatric disorders.
- Depression is the most common comorbidity, followed by alcohol and substance use disorders, as well as other co-occurring anxiety disorders, especially GAD and PD.
- Comorbid psychiatric illness is associated with lower rates of remission and higher rates of relapse.

# EPIDEMIOLOGY AND ETIOLOGY



- **Etiology**
- Genetics may create a vulnerable phenotype for an anxiety disorder, and
- An individual's life stressors and means of coping with the stress may play a role in precipitation and continued expression of the anxiety disorder.

# Pathophysiology



## *Noradrenergic model:*

- Autonomic nervous system of anxious pts is hypersensitive & overreacts to various stimuli.
- The **locus ceruleus** may have a role in **regulating anxiety**, as it activates NE release & stimulates the SNS or PSNS.
- **Chronic noradrenergic over activity** down regulates α2-adrenoreceptors in pts with GAD & PTSD.

- **GABA receptor model**

  GABA is the major inhibitory neurotransmitter in the CNS.

  - ✓ Anxiety symptoms are linked underactivity of GABA systems or down regulated central BZ receptors.

- **5-HT model**

  - ✓ Over activity of the stimulatory 5-HT pathways
  - **In GAD**: enhanced central serotonergic response.

# Clinical Presentation and Diagnosis of GAD



- **Symptoms**

- Excessive anxiety or worry involving multiple events or activities occurring more days than not for at least 6 months.
- Difficulty controlling worry.
- Anxiety and worry associated with at least three of the following: Restlessness, Easily fatigued, Poor concentration or mind going blank, Irritability, Muscle tension, Insomnia or unsatisfying sleep
- The anxiety or worry causes significant distress or functional impairment and is NOT attributable to another substance, medical, or psychiatric condition

## Medical Conditions That Can Cause Anxiety

**Psychiatric Disorders**
Mood disorders, hypochondriasis, personality disorders, alcohol or substance abuse, alcohol or substance withdrawal, other anxiety disorders

**Neurologic Disorders**
CVA, seizure disorders, dementia, stroke, migraine, encephalitis, vestibular dysfunction

**Cardiovascular Disorders**
Angina, arrhythmias, congestive heart failure, mitral valve prolapse, myocardial infarction

**Endocrine and Metabolic Disorders**
Hypothyroidism or hyperthyroidism, hypoglycemia, Cushing disease, Addison disease, pheochromocytoma, hyperadrenocorticism, hyponatremia, hyperkalemia, vitamin $B_{12}$ deficiency

**Respiratory Disorders**
Asthma, COPD, pulmonary embolism, pneumonia, hyperventilation

**Other**
Carcinoid syndrome, anemias, SLE

## Medications Associated with Anxiety Symptoms

| Category | Examples |
|---|---|
| Anticonvulsants | Carbamazepine, ethosuximide |
| Antidepressants | Bupropion, SSRIs, SNRIs, TCAs |
| Antihypertensives | Felodipine |
| Antimicrobials | Cephalosporins, ofloxacin, isoniazid |
| Antiparkinson drugs | Levodopa |
| Bronchodilators | Albuterol, isoproterenol, theophylline |
| Corticosteroids | Prednisone, methylprednisolone |
| Decongestants | Pseudoephedrine, phenylephrine |
| Herbals | Ma huang, St. John's wort, ginseng, guarana, belladonna |
| NSAIDs | Ibuprofen, indomethacin |
| Stimulants | Amphetamines, caffeine, cocaine, methylphenidate |
| Thyroid hormones | Levothyroxine |
| Toxicity | Anticholinergics, antihistamines, digoxin |
| Withdrawal of CNS depressants (abrupt) | Alcohol, barbiturates, benzodiazepines |

# TREATMENT: GENERALIZED ANXIETY DISORDER



- Patients with GAD may be managed with psychotherapy, pharmacotherapy, or both.
- Treatment should be individualized based on symptom severity, comorbid illnesses, medical status, age, and patient preference.
- Patients with severe symptoms resulting in functional impairment should receive antianxiety medication.

# Nonpharmacologic Therapy



- Patients should be instructed to avoid stimulating agents and regular exercise is also recommended.
- CBT is the most effective psychological therapy for GAD patients, treatment gains with CBT may be maintained for up to 1 year.
- Computerized CBT offered over the Internet is effective.
- The effect sizes of trials with CBT are comparable to those of pharmacologic therapies.
- A recent trial in children with GAD suggests the combination of CBT and medication is superior to either treatment alone

# Pharmacologic Therapy



- Antidepressants, benzodiazepines, pregabalin, buspirone, hydroxyzine, and the second-generation antipsychotics (SGAs) have controlled clinical trial data supporting their use in GAD.
- Antidepressants are the drugs of choice for chronic GAD because of a tolerable side-effect profile; no risk for dependency; and efficacy in common comorbid conditions, including depression, panic, obsessive compulsive disorder (OCD), and SAD.

# Pharmacologic Therapy



- Benzodiazepines remain the most effective and commonly used treatment for short-term management of anxiety when immediate relief of symptoms is desired.
- They are also recommended for intermittent or adjunctive use during GAD exacerbation or for sleep disturbance during the initiation of antidepressant treatment.

# Pharmacologic Therapy



- Buspirone and pregabalin are alternative agents for patients with GAD without depression.
- Hydroxyzine is usually adjunctive and is less desirable for long-term treatment because of side effects, eg, sedation and anticholinergic effects.
- Patients with GAD should be treated to symptom remission.
- **Recent guidelines recommend continuing treatment for 1 year.**

# Antidepressants



- Antidepressants reduce the psychic symptoms of anxiety with a modest effect on autonomic or somatic symptoms (eg, tremor, rapid heart rate, and/or sweating).
- All antidepressants evaluated provide a similar degree of anxiety reduction.
- The onset of antianxiety effect is delayed 2 to 4 weeks.
- SSRIs or SNRIs are usually preferred over TCAs.

# SNRIs



- Venlafaxine and duloxetine are approved by FDA for the treatment of GAD.
- Venlafaxine is effective at doses 75 to 225 mg/day and maintains response with extended treatment.
- It is also effective for GAD in children and adolescents. Duloxetine is similarly effective and tolerated as venlafaxine.
- For patients with concurrent pain syndromes, duloxetine has been found to improve anxiety, pain, and functional impairment more than placebo.

# SSRIs



- The SSRIs paroxetine, escitalopram, and sertraline have been shown to be significantly more effective than placebo in reducing anxiety symptoms in adults with GAD.
- Citalopram is efficacious in the treatment of GAD in the elderly.
- The SSRIs, sertraline, fluoxetine, and fluvoxamine have demonstrated benefits in children and adolescents with GAD and are the preferred pharmacologic treatment in this population.

# Tricyclic Antidepressants



- Imipramine treatment of GAD results in a higher rate of remission of anxiety symptoms than treatment with trazodone or diazepam.
- TCA use is limited by bothersome adverse effects .
- TCAs have a narrow therapeutic index and are lethal in overdose because of atrioventricular block.

# Novel Antidepressants



- Mirtazapine is an effective antidepressant but has not been extensively evaluated in anxiety disorders.
- Bupropion has not been studied or used extensively in anxiety disorders owing to its stimulating effects.
- Vilazodone, a SSRI, and 5-HT 1A receptor partial agonist has not been evaluated in anxiety disorders.

**Antidepressants Used in the Treatment of Generalized Anxiety Disorder**

| Medication Class | Recommended Starting Dose (mg/day) | Usual Therapeutic Dosage Range (mg/day) | Hepatic Insufficiency | Renal Insufficiency |
|---|---|---|---|---|
| **SSRIs** | | | | |
| Citalopram[a] (Celexa) | 20 | 20–40 | Maximum, 20 mg/day | |
| Escitalopram[b] (Lexapro) | 10 | 10–20 | Maximum, 10 mg/day | |
| Fluoxetine (Prozac) | 20 | 20–80 | Titrate with caution | |
| Fluvoxamine (Luvox) | 50 | 100–300 | Titrate with caution | |
| Paroxetine (Paxil) | 20 | 20–50 | Titrate with caution | |
| Paroxetine CR (Paxil CR) | 25 | 25–62.5 | Maximum, 50 mg/day | Maximum, 50 mg/day |
| Sertraline (Zoloft) | 50–100 | 50–200 | Reduce dose | |
| **SNRIs** | | | | |
| Venlafaxine XR[b] (Effexor XR) | 75 | 75–225 | Reduce dose by 50% | Reduce dose 25%–50% |
| Desvenlafaxine (Pristiq) | 50 | 50–100 | Maximum, 100 mg/day | Maximun, 50 mg/day; CrCl < 30 mL/min (0.50 mL/s), dose once every other day |
| Duloxetine[c] (Cymbalta) | 30 | 60–120 | Use not recommended | CrCl < 30 mL/min (0.50 mL/s) Use not recommended[b] |
| **TCAs** | | | | |
| Imipramine (Tofranil) | 50–75 | 75–200 | Titrate with caution | |

[a]Maximum daily dose of citalopram is 20 mg/day when used in the elderly or when given concomitantly with CYP2C19 inhibitors.

[b]Food and Drug Administration approved for use in generalized anxiety disorder.

[c]Duloxetine use is not recommended in severe renal impairment (creatinine clearance < 30 mL/min [< 0.50 mL/s])

SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

# Benzodiazepines



- Are recommended for acute treatment of GAD when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or to improve sleep.
- More effective for somatic symptoms than psychic symptoms and major disadvantages are lack of effectiveness for depression; risk for dependency and abuse; and potential interdose rebound anxiety.
- They should be avoided in older adults and patients with current or past chemical dependency

# Benzodiazepines



- The most common side effects of include CNS depressive effects (eg, drowsiness, sedation, psychomotor impairment, and ataxia) and cognitive effects (eg, poor recall and anterograde amnesia).
- Anterograde amnesia is more likely with high-potency benzodiazepines such as alprazolam.
- Discontinuation of BZDs may be associated with withdrawal, rebound anxiety, and a high rate of relapse.

# Benzodiazepines



- Patients should be tapered from benzodiazepine therapy to avoid withdrawal symptoms.
- Patients on benzodiazepine therapy for 2 to 6 months should be tapered over 2 to 8 weeks, but patients receiving 12 months of treatment should be tapered over 2 to 4 months.
- Reduce the dose by 25% every 5 to 7 days until reaching half the original dose and then decreasing by 10% to 12% per week until discontinued.

**Comparison of the Benzodiazepines**

| Drug Name (Brand Name)<br>*Active Metabolites* | Time to Peak Concentration (hours) | Half-Life Range (hours) | Approved Dosage Range (mg/day) | Dose Equivalent (mg) |
|---|---|---|---|---|
| Alprazolam[a,b] (Xanax) | 1–2 | 12–15 | 1–4 (GAD)<br>1–10 (PD) | 0.5 |
| Chlordiazepoxide[a] (Librium) | 1–4 | 5–30 | 25–100 | 10 |
| *Desmethylchlordiazepoxide* | | 18 | | |
| *Demoxepam* | | 14–95 | | |
| *Desmethyldiazepam* | | 40–120 | | |
| *Oxazepam* | | 5–15 | | |
| Clonazepam[b] (Klonopin) | 1–4 | 18–50 | 1–4 | 0.25 |
| Clorazepate[a] (Tranzene) | 1–2 | | 7.5–60 | 7.5 |
| *Desmethyldiazepam* | | 40–120 | | |
| *Oxazepam* | | 5–15 | | |
| Diazepam[a] (Valium) | 0.5–2 | 20–80 | 2–40 | 5 |
| *Desmethyldiazepam* | | 40–120[c] | | |
| *Temazepam* | | 8–15 | | |
| *Oxazepam* | | 5–15 | | |
| Lorazepam[a] (Ativan) | 2–4 | 10–20 | 0.5–10 | 0.75–1 |
| Oxazepam[a] (Serax) | 2–4 | 5–15 | 30–120 | 15 |

[a]Food and Drug Administration (FDA) approved for use in generalized anxiety disorder.

[b]FDA approved for use in panic disorder.

[c]CYP2C19 genetic polymorphisms resulting in little or no enzyme activity are present in 15% to 20% of Asians and 3% to 5% of blacks and whites, resulting in reduced clearance of desmethyldiazepam.[34]

# Pregabalin



- Pregabalin is a calcium channel modulator
- Pregabalin was effective for both somatic and psychic symptoms of anxiety with onset of effect similar to that of alprazolam.
- Compared with venlafaxine and placebo, pregabalin was safe, well tolerated, and efficacious in GAD, and results were seen 1 week sooner than with venlafaxine.

# Pregabalin



- Pregabalin is a controlled substance owing to a propensity to cause euphoria.
- It should be used cautiously in patients with a current or past history of substance abuse.
- It is not beneficial for depression or other anxiety disorders.

# Alternative Agents



- Hydroxyzine, buspirone, and SGAs are alternative agents.
- Hydroxyzine may be effective for acute reduction of somatic symptoms of anxiety but not for psychic features of anxiety, depression, or other common comorbid anxiety disorders.

# Treatment Algorithm for GAD



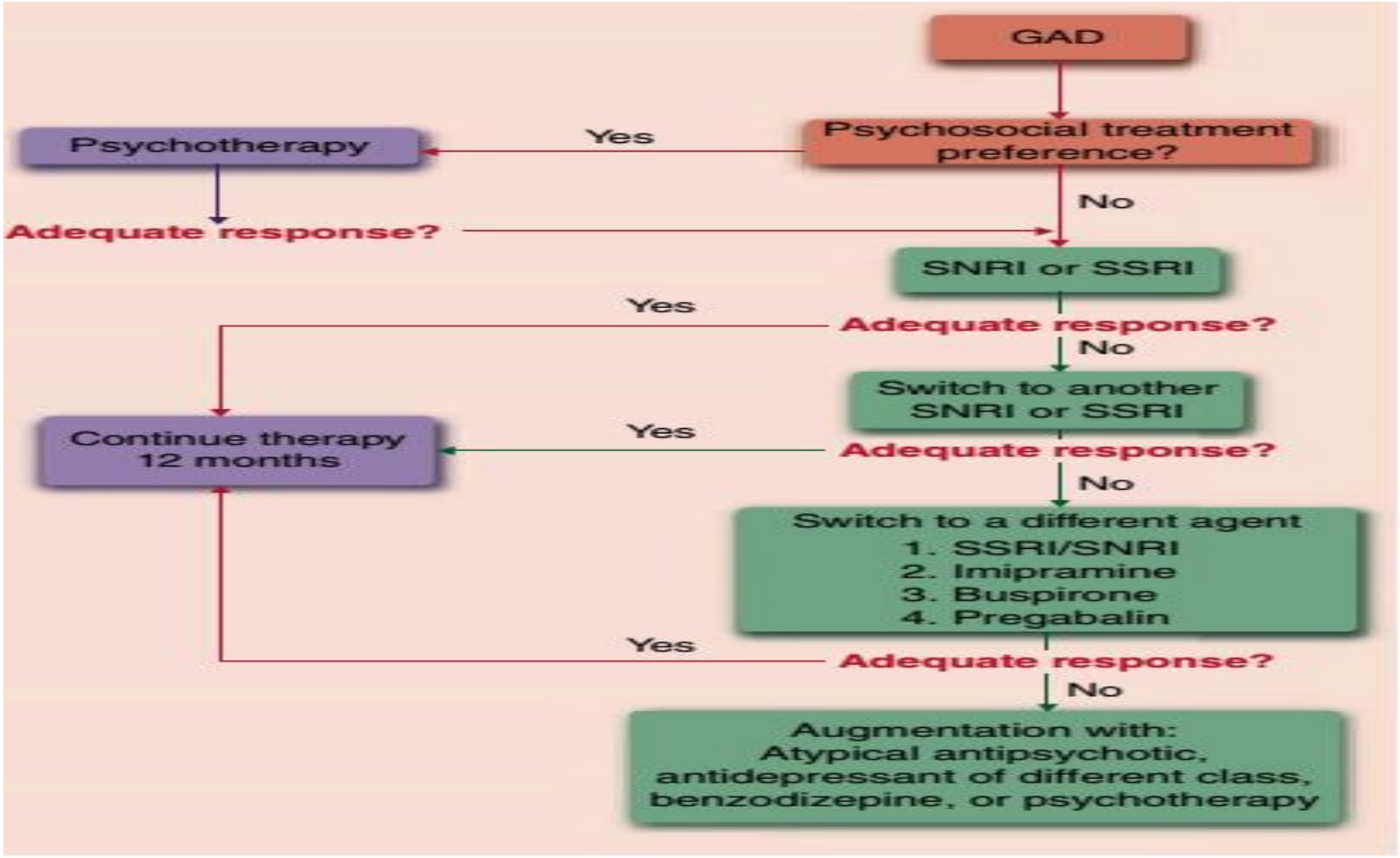



**FIGURE 40–2.** Treatment algorithm for generalized anxiety

# Outcome Evaluation



- Assess patients for improvement of anxiety symptoms and return to baseline functioning.
- With effective treatment, patients should have no or minimal symptoms of anxiety or depression.
- Monitor for suicidal ideation and behaviors for children, adolescents, and young adults initiated on antidepressants.
- Increase the dose in patients exhibiting a partial response after 2 to 4 weeks on an antidepressant or 2 weeks on a benzodiazepine.

# Clinical Presentation and Diagnosis of PD

## General

Typically presents in late adolescence or early adulthood. Onset in older adults raises suspicion of a relationship to medical disorders or substance use. Laboratory evaluation must be driven by history and physical examination.

## Symptoms[2]

Recurrent, unexpected panic attacks. A panic attack is an abrupt surge of intense fear or discomfort peaking within minutes, and with four or more of the following symptoms:

- Palpitations or rapid heart rate
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy or lightheaded
- Chills or hot flushes
- Paresthesias
- Derealization or depersonalization
- Fear of dying
- Fear of losing control or "going crazy"

At least one of the attacks has been followed by 1 month or more of one or both:

- Persistent concern or worry about additional attacks
- Significant maladaptive change in behavior related to the attacks (eg, avoidance)

# TREATMENT: PANIC DISORDER



- **Desired Outcomes**
- The main objectives of treatment are:
  - To reduce the severity and frequency of panic attacks,
  - Reduce anticipatory anxiety and agoraphobic behavior, and
  - Minimize symptoms of depression or other comorbid disorders.
- The long-term goal is to achieve and sustain remission and restore overall functioning.

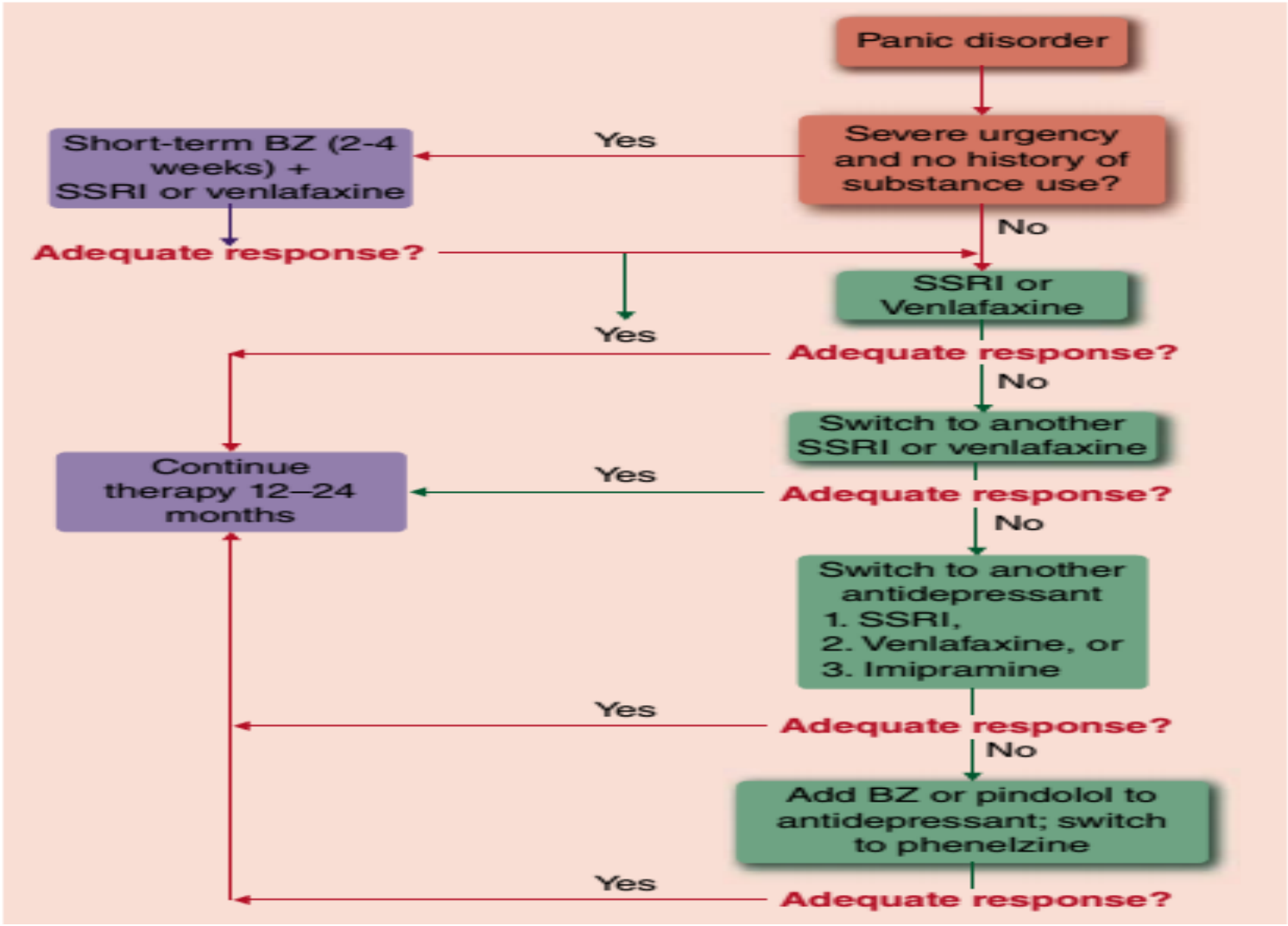
# General Approach to Treatment



- RX options include medication, psychotherapy, or a combination of both.
- Patients with panic symptoms without agoraphobia may respond to pharmacotherapy alone.
- Agoraphobic symptoms generally take longer to respond than panic symptoms.
- The acute phase of PD treatment lasts about 12 weeks.
- RX should be continued to prevent relapse for an additional 12-18 months before attempting discontinuation.

# Treatment Algorithm





# Nonpharmacologic Therapy



- Avoid stimulant agents that may precipitate a panic attack and Exposure therapy is useful for patients with phobic avoidance.
- CBT is considered a first-line treatment of PD, with efficacy similar to that of pharmacotherapy.
- Some studies suggest lower risk of relapse after CBT versus drug therapy.
- In a trial of PD with or without agoraphobia, SSRI plus CBT was more effective than either therapy alone after 9 months of treatment

# Pharmacologic Therapy



- SSRIs have become the treatment of choice.
- Benzodiazepines often are used concomitantly with antidepressants, especially early in treatment, or as monotherapy to acutely reduce panic symptoms.
- Benzodiazepines are not preferred for long-term treatment but may be used when patients fail several antidepressant trials.

# Antidepressants



- Antidepressants typically require 4 weeks for onset of antipanic effect, with optimal response at 6 to 12 weeks.
- Reduction of anticipatory anxiety and phobic avoidance generally follows improvement in panic symptoms.
- PD patients are more likely to experience stimulant-like side effects of antidepressants than patients with MDD.
- So, should be initiated at lower doses in PD than in depressed patients. But, target doses are similar.

# Tricyclic Antidepressants



- Treatment with imipramine, leaves 45% to 70% of patients panic free.
- Desipramine and clomipramine are also effective.
- However, TCAs are considered second or third-line pharmacotherapy because of poorer tolerability and toxicity on overdose.

# Selective Serotonin Reuptake Inhibitors



- SSRIs are the drugs of choice for patients with PD.
- All SSRIs have demonstrated effectiveness in controlled trials, with 60% to 80% of patients achieving a panic-free state.
- With similar efficacy reported and no trials comparing different SSRIs.

**Antidepressants Used in the Treatment of Panic Disorder**[18,23,42]

| Medication Class | Recommended Starting Dose (mg/day) | Usual Therapeutic Dosage Range (mg/day) | Advantages | Disadvantages |
|---|---|---|---|---|
| **SSRIs/SNRIs** | | | **SSRIs (in general)** | **SSRIs (in general)** |
| Citalopram | 10 | 20–40 | Antidepressant activity; antianxiety activity; single daily dosing (all but fluvoxamine); low toxicity; available in generic | Activation; delayed onset of action; may precipitate mania; sexual side effects; GI side effects |
| Escitalopram | 5–10 | 10–20 | | |
| Fluoxetine[a] | 5–10 | 20–60 | | |
| Fluvoxamine | 25 | 100–300 | | |
| Paroxetine[a] | 10 | 20–60 | | |
| Sertraline[a] | 25 | 50–200 | | |
| Venlafaxine XR[a] | 37.5 | 75–225 | | |
| **TCAs** | | | **TCAs (in general)** | **TCAs (in general)** |
| Clomipramine | 25 mg (twice a day) | 75–250 | Established efficacy; available in generic | Activation; sedation; anticholinergic effects; cardiovascular effects; delayed onset of action; may precipitate mania; sexual side effects; toxic in overdose; weight gain |
| Imipramine[a] | 10–25 | 75–250 | | |
| **MAOI** | | | | |
| Phenelzine | 15 | 45–90 | Antidepressant effects; available in generic | Dietary restrictions; drug interactions; weight gain; orthostasis; may precipitate mania |

[a] Food and Drug Administration approved for use in panic disorder.

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

# Benzodiazepines



- BDZs are effective antipanic agents with significant effects on anticipatory anxiety and phobic behaviors.
- Alprazolam, the BDZ most studied, is associated with significant panic reduction after 1 week of therapy (eg, 55%–75% panic free).
- BDZs achieve outcomes similar to antidepressants over extended treatment, but benzodiazepine-treated patients are more likely to relapse when the drugs are discontinued.

# Benzodiazepines



- The dose of benzodiazepine required for improvement generally is higher than that used in other anxiety disorders and this may explain why high-potency agents such as alprazolam and clonazepam generally are preferred.
- Lorazepam and diazepam, when given in equivalent doses, produce similar treatment benefits.
- Doses should be titrated to response

# Other Antidepressants



- There is insufficient evidence to support the use of bupropion, trazodone, nefazodone, or mirtazapine for treatment of PD.

# Outcome Evaluation



- Assess patients for symptom improvement frequently (eg, weekly) during the first 4 weeks of therapy.
- **Alter the therapy of patients** who do not achieve a significant reduction in panic symptoms after 6 to 8 weeks on an adequate dose of antidepressant or 3 weeks on a benzodiazepine.
- When significant response to drug therapy is achieved, continue treatment for at least 1 year.
- Evaluate for symptom relapse and adverse effects.

# Clinical Presentation and Diagnosis of SAD

## General

Individuals have marked fear or anxiety about one or more social situations where they are exposed to possible scrutiny or negative evaluation (eg, common social interactions, conversation, eating, drinking or performing). SAD differs from specific phobia, in which the fear and anxiety are limited to a particular object or situation (eg, insects, heights, public transportation). In children, the anxiety must be present in peer settings, not just in interactions with adults.

## Symptoms[2]

- The individual fears acting in a way or showing anxiety that will be negatively evaluated (ie, humiliating or embarrassing or lead to rejection or offend others)
- Social situations almost always provoke fear or anxiety and are avoided or endured with intense fear or anxiety. Children may express fear or anxiety by crying, tantrums, freezing, clinging or failing to speak in social situations.

*The fear or anxiety is*

- out of proportion to the actual threat posed by the social situation;
- persistent, typically lasting for 6 months or more;
- causes clinically significant distress or impairment in social, occupational, or other area of functioning;
- not attributable to physiological effects of a substance or another medical condition; and
- not better explained by the symptoms of another mental disorder (eg, panic disorder, body dysmorphic disorder, or autism spectrum disorder)

# General Approach to Treatment



- Patients with SAD may be managed with pharmacotherapy or psychotherapy.
- Children with SAD should be offered psychotherapy first.
- Pharmacotherapy often is the first choice of treatment owing to relative greater access and reduced cost compared with psychotherapy.
- Many patients will not achieve a full response.

# Nonpharmacologic Therapy



- Patient education on disease course, and Rx options is essential.
- CBT targets negative thinking patterns associated with social anxiety.
- CBT is effective for reducing anxiety and phobic avoidance and leads to a greater likelihood of maintaining response after treatment discontinuation than does pharmacotherapy

# Pharmacologic Therapy



- Several pharmacologic agents have demonstrated effectiveness in SAD.
- SSRIs are considered the drugs of choice based on their tolerability and efficacy for SAD and comorbid depression if present.
- The onset of response for antidepressants may be as long as 8 to 12 weeks.
- Patients responding to medication should be continued on treatment for at least 1 year.

# SSRIs and Venlafaxine



- The efficacy of paroxetine, sertraline, escitalopram, fluvoxamine, and venlafaxine was established in large controlled trials.
- Limited data support the effectiveness of citalopram and fluoxetine in SAD
- SSRIs and SNRIs improve social anxiety and phobic avoidance and reduce overall disability.
- The initial dose of SSRI is similar to that used in depression.
- Patients should be titrated as tolerated to response.
- Many patients require maximum recommended daily doses

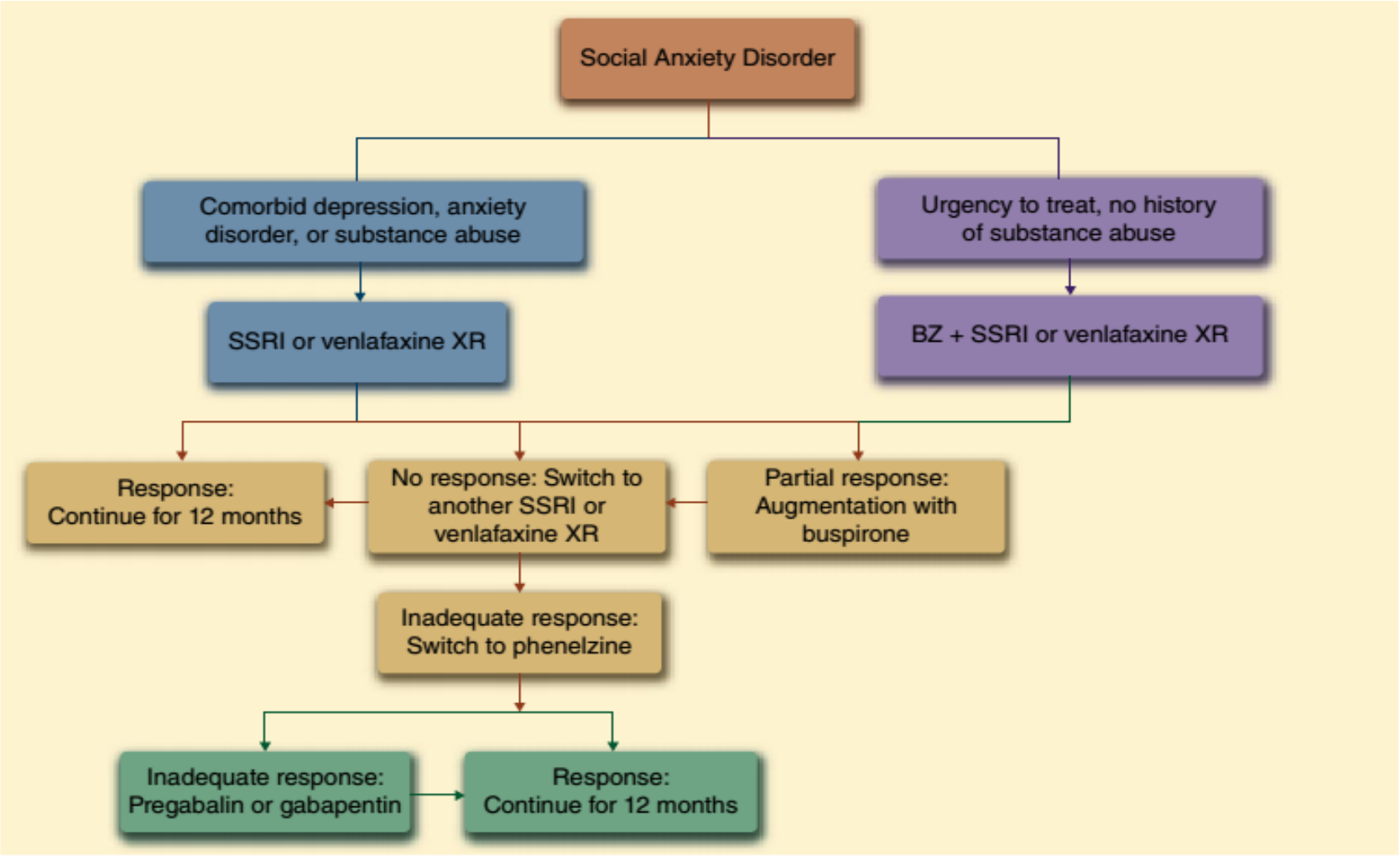
# Alternative Agents



- Benzodiazepines, clonazepan
- Anticonvulsants, gabapentin, pregabalin
- **β-Blockers** β-blockers decrease the physiologic symptoms of anxiety and are useful for reducing performance anxiety.
- Propranolol or atenolol should be administered 1 hour before a performance situation.

# Treatment Algorithm for SAD





# Outcome Evaluation



- Many patients will experience significant improvement in symptoms but may not achieve full remission.
- Monitor patients weekly during acute treatment (eg, initiation and titration of pharmacotherapy) and monthly once stabilized.
- Counsel patients on appropriate expectations of pharmacotherapy in SAD, including gradual onset of effect and the need for extended treatment of at least 6 months following response.