Management of panic disorder with or without agoraphobia in adults

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INTRODUCTION

Panic disorder is characterized by recurrent, unexpected panic attacks along with one month of either worry about future attacks or the consequences of attacks (eg, medical concerns), or a significant change in behavior due to the attacks (eg, phobic avoidance or repetitive seeking of medical evaluations). Agoraphobia is diagnosed as a separate disorder in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Panic disorder is a relatively common disorder, most often with an adult onset and chronic course [1-4]. It can lead to impairments in functioning, poor quality of life, and high health care costs [5,6]. The disorder can be effectively treated with cognitive-behavioral therapy, medication, or a combination of the two modalities [7]. Other psychotherapies may also have efficacy although this has been less well established.

This topic and the accompanying algorithms describe our approach to selecting among treatments for panic disorder and the subsequent pharmacologic management of panic disorder (algorithm 1 and algorithm 2). The epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of panic disorder and psychotherapy for panic disorder are reviewed separately. Topics related to the epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of agoraphobia are also reviewed separately. (See "Psychotherapy for panic disorder with or without agoraphobia in adults" and "Panic disorder in

adults: Epidemiology, clinical manifestations, and diagnosis" and "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

INITIAL MANAGEMENT DECISIONS

An algorithm describes our initial management decisions for panic disorder (algorithm 1).

Determining need for treatment — Once a diagnosis of panic disorder is made, our next step is to determine, based on clinical assessment of severity of illness, extent of distress or impairment, and patient preference, whether treatment of the disorder is needed. The main objectives of treatment are to minimize attack frequency, anticipatory anxiety, and phobic avoidance, thereby improving functioning. Individuals with mild panic disorder whose symptoms do not interfere significantly with functioning may reasonably elect to forgo treatment initially. We follow up with these individuals every three to six months as necessary, to determine if symptoms are worsening or impeding function. These are indications that treatment may be advisable. For example, individuals with limited to no phobic avoidance and no health concerns, and whose day-to-day functioning is not being compromised by frequent panic attacks may reasonably elect to forgo treatment. These individuals may respond to education and reassurance with reduced anxiety about panic and come to have less frequent attacks and gradual disappearance of symptoms [8]. (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Assessment'.)

Choosing between psychotherapy and medication — We make the selection between antidepressant medication and cognitive-behavioral therapy (CBT) on the basis of patient preference and treatment availability. There is no evidence of robust differences in effectiveness between these modalities in panic disorder [9-11]. We typically prefer combined treatment for individuals who stand to benefit and who are willing to do both. This is particularly true in individuals with suicidality, comorbid psychiatric disorder or in those with severe initial distress or problematic functional impairment. (See 'Suicidality or co-occurring mental disorders' below and 'Adjunctive treatment for marked distress or early side effects' below.)

In our clinical experience, some patients have strong preferences between medication and psychotherapy, including hesitancy for undergoing CBT, time necessary for CBT, and medication side effects. Individuals for whom CBT works best are generally highly motivated and value a problem-solving approach, while the absence of this motivation and belief may make CBT a less optimal choice. There is wide variation across the United States and internationally in the availability of therapists trained to provide CBT for anxiety disorders [9,12].

In a meta-analysis of 16 studies including 966 individuals with panic disorder, treatment with psychological therapies (eg, CBT, behavior therapy, supportive therapy, or psychoeducation) had similar effects on short-term response and short-term remission as selective serotonin reuptake inhibitors (SSRIs; relative risk 0.97, 95% CI, 0.5-1.9 and relative risk 0.85, 95% CI 0.6-1.2, respectively), tricyclic antidepressants (relative risk 0.75, 95% CI 0.5-1.1 and relative risk 0.82, 95% CI 0.6-1.1, respectively), other antidepressants (relative risk 0.96, 95% CI 0.7-1.4 and relative risk 0.9, 95% CI 0.5-1.7, respectively) and benzodiazepines (relative risk 1.58, 95% CI 0.7-3.6 and relative risk 1.08, 95% CI 0.7-1.7 respectively) [11]. Dropout rates for each treatment were similar.

In another clinical trial, 312 individuals with panic disorder were randomized to receive either imipramine only, CBT only, placebo, or imipramine plus CBT [10]. After three months of treatment, patients treated with imipramine only and CBT only were equally more likely to respond compared with the placebo treated group (45.8 and 48.7 versus 21.7 percent [9,10]). After medication discontinuation, longer-term outcome was better for the group that had received CBT in some but not all analyses. A second trial in 150 individuals with panic disorder compared one of five of the more commonly used SSRIs with CBT, and the combination after 9 months of treatment, at 12 months after treatment discontinuation, and 6 and 12 months later, and found all three groups equivalent [13].

While some experts continue to believe that longer-term outcome may be superior when including CBT, evidence from the above meta-analysis and two available studies does not definitively support this [13].

INITIATING TREATMENT

CBT as preferred psychotherapy — We suggest treatment with cognitive-behavioral therapy (CBT) rather than other psychotherapies for individuals with panic disorder who are treated with psychotherapy. CBT is an effective treatment for panic disorder [14] and is supported by a greater number of randomized clinical trials with more participants compared with other psychotherapies tested on panic disorder [15,16]. (See "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'Response to CBT'.)

Treatment with CBT is broadly generalizable and may not require doctoral level expertise. Two large effectiveness studies found that CBT delivered by novice therapists (after training) to primary care patients with panic disorder led to better outcomes on measures of symptom severity, and rates of response and remission, compared with treatment as usual (usual care via primary care) [17,18].

Further discussion of CBT, remote CBT (eg, internet-delivered, videoconferencing CBT, and bibliotherapy-delivered CBT) including predictors of outcome, as well as other forms of psychotherapy in the treatment of panic disorder can be found elsewhere. (See "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'Response to CBT' and "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'Remote CBT and internet-delivered exposure therapy' and "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'Other psychotherapies'.)

SSRIs as preferred initial pharmacotherapy — For individuals who prefer pharmacotherapy, we typically suggest treatment with a selective serotonin reuptake inhibitor (SSRI). Others such as serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and benzodiazepines have demonstrated efficacy in panic disorder, but we generally reserve them for patients with suboptimal response to SSRIs (see 'Management of suboptimal response' below). There are few head-to-head clinical trials comparing these drugs in panic disorder, but these trials and trials comparing these drugs with placebo suggest that they all have comparable efficacy.

Our preference for SSRIs over other antidepressants is based on their relatively benign side effect profile and safety in overdose. Among medications for panic disorder, SSRIs have been the most widely tested in clinical trials and shown to be efficacious compared with placebo [19].

- **Choosing an SSRI** – There is no evidence for superior efficacy in panic disorder for any particular SSRI versus any other [20]. Our selection of a particular medication is guided by differences in side effect profile, propensity for medication interactions, half-life, and availability of less expensive, generic preparations. Adverse effects of SSRIs and other antidepressants can be found elsewhere and on the table (table 1). (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

- **Dose and titration of SSRIs in panic disorder** – We begin treatment with SSRIs at lower doses than for depression, as individuals with panic disorder are unusually sensitive to overstimulation effects of antidepressants [21] (see 'Adjunctive treatment for marked distress or early side effects' below). We then gradually increase to the therapeutic dose. Therapeutic doses of SSRIs are approximately the same for panic disorder as for the treatment of depression. Time to onset of clinically meaningful action for an SSRI varies by patient, but averages approximately four weeks. Starting and usual total daily doses for antidepressants used in the treatment of unipolar depression are listed in the associated table (table 2).

As examples, when initiating treatment with sertraline, our starting dose would be 25 mg (ie, half the starting dose for unipolar depression). We monitor for three to seven days after initial dose, and if tolerated, we titrate by 25 to 50 mg to the lower end of the therapeutic range (ie, 50 to 75 mg). We monitor at this dose for up to four weeks. If clinical improvement is not seen, we increase the dose by 50 mg at weekly intervals to the higher end of the therapeutic range (ie, 200 mg per day). We initiate escitalopram at 5 mg or fluoxetine at the even lower dose of 5 mg because it is more activating than other SSRIs. We titrate the dose upwards in a similar manner to what we do for sertraline.

We consider a therapeutic trial of an SSRI for panic disorder to be six weeks at the maximally tolerated dose within the therapeutic range (table 2).

In a meta-analysis of trials in patients with anxiety disorders, including panic disorder, increasing doses of SSRI within the therapeutic range were associated with greater symptom improvement [22].

- **Therapeutic effects and efficacy of SSRIs** – Therapeutic effects, particularly effects on anticipatory anxiety and phobic avoidance can increase over the first 6 to 12 months in many individuals [23,24]. Virtually every clinical trial of SSRIs for panic disorder that measured phobic avoidance has found a reduction in agoraphobic symptoms. Additionally, a reduction in the core components of the disorder (eg, frequency of attacks, severity of anticipatory anxiety) has been shown in trials. A number of trials have shown that panic attacks improve before anticipatory anxiety and phobic avoidance, however, other studies suggest this sequence of response is not always the case [25].

  A meta-analysis of 12 trials of treatment for panic disorder found SSRIs to be efficacious compared with placebo, with a medium effect size [19]. Randomized trials have shown fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram to be effective for panic disorder compared with placebo.

  As an example, 168 patients with panic disorder with or without agoraphobia were randomly assigned to receive sertraline or placebo in a 10-week trial. Patients receiving sertraline experienced a greater mean reduction in the number of panic attacks per week compared with patients receiving placebo (88 versus 53 percent) [26].

- **Adverse effects** – Common side effects of SSRIs are headaches, irritability, gastrointestinal distress (nausea or diarrhea), insomnia and sexual dysfunction. An increased risk of suicidality is seen in all patients under age 25 who are prescribed SSRIs and this risk is likely to be similar in individuals with panic disorder and depression though no data are available to confirm this conclusion. A syndrome of neurologic,

gastrointestinal, and psychiatric symptoms can occur if an SSRI is discontinued too quickly. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects' and "Discontinuing antidepressant medications in adults".)

Considerations for specific populations

Suicidality or co-occurring mental disorders — We prefer first-line treatment with the combination of an SSRI antidepressant and CBT for patients treated for panic disorder who have suicidality or a comorbid disorder (eg, depression, posttraumatic stress disorder, anxiety disorder) [27]. (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Comorbidities'.)

Some patients with panic disorder and severe depression may be too symptomatic to fully engage and participate in CBT. In these cases we begin with medication management until symptoms permit further work in CBT.

Adjunctive treatment for marked distress or early side effects — Prior to considering further medication for these individuals, we review the history of symptoms to rule out the possibility of an undiagnosed atypical bipolar disorder with the serotonin reuptake inhibitor precipitating a “mixed-state” switch. (See "Bipolar disorder in adults: Clinical features", section on 'Mixed features'.)

For individuals with marked distress (eg, unable to wait for medication for panic disorder to be effective) or in those with initial worsening of symptoms upon SSRI initiation, we typically use either an increase in sessions to provide support until the medication can take effect [28], or adjunctive pharmacotherapy. This choice is one of shared decision making and is based on patient preference and level of distress. Our preference for a specific adjunctive agent is based on whether the individual has a substance use disorder (SUD; either active or by history).

- **For individuals without an SUD** – Our preference is to use a long-acting benzodiazepine such as clonazepam as adjunctive treatment for individuals without an SUD who are experiencing marked distress or early side effects with initial SSRI treatment. Onset of the antipanic effects of benzodiazepines is very rapid, beginning within the first week of treatment [29,30]. This may be a distinct advantage in severely symptomatic and functionally impaired patients who require rapid relief to avoid further clinical deterioration.

  We continue treatment for 10 to 12 weeks at which point significant antipanic efficacy attributable to the serotonin reuptake inhibitor should have been reached. We taper

clonazepam by 0.25 mg per week until 0.5 mg is reached and then by 0.125 mg per week. Many patients appear to have difficulty stopping benzodiazepines and tolerating the effects of discontinuation (eg, hyperarousal, rebound worsening of anxiety, insomnia, tremor and seizures). There is no rush to complete the taper and a slow gradual approach will minimize any withdrawal symptoms. Dose and titration of benzodiazepines are discussed below. (See 'Benzodiazepines for those without an SUD' below.)

- **For individuals with an SUD (active or by history)** – For these individuals, our preference is to augment antidepressant treatment with gabapentin. Pregabalin is another option; however, concerns about misuse and its designation as a controlled substance limit its utility. In individuals with insomnia, we occasionally use mirtazapine. We typically treat with these medications for 10 to 12 weeks at which time maximal antidepressant effect should have been reached. We then slowly taper off of the medication over up to four weeks. Dosing of gabapentin, pregabalin and mirtazapine are discussed elsewhere. (See 'Active or past SUD' below.)

DURATION OF TREATMENT

We continue medications that are effective for panic disorder for at least one year after symptom control has been attained. We base decisions about discontinuation of medications on prior history of relapse and the presence of risk factors for relapse (eg, severity of the initial syndrome, the presence of psychiatric comorbidity [depression, agoraphobia, or personality disorder], presence of ongoing psychosocial or medical stressors, and the presence of residual symptoms of panic disorder, especially phobic avoidance which may be less evident to the clinician unless specifically probed once anxious distress resolves). We often continue treatment beyond one year and up to two years in individuals with more severe panic disorder [20].

While there are no studies that systematically address the optimal duration of treatment, available evidence suggests that effective pharmacotherapy for panic disorder should be continued for this period of time.

- Studies have found that symptoms continue to improve over the first six months of treatment with a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or tricyclic antidepressant (TCA); many studies suggest that improvement continues between months 6 and 12 [23,31,32].

- In a meta-analysis of six randomized discontinuation trials, 796 patients were treated for panic disorder with an antidepressant (ie, SSRI, SNRI, or TCA) versus placebo. Treatment

with an antidepressant was associated with a lower likelihood of relapse (defined as an increase in the Clinical Global Impressions Scale or increase in panic frequency) as compared with individuals treated with placebo during the first year of treatment (odds ratio 0.35, 95% CI 0.23-0.51) [33]. Relapse rates following antidepressant discontinuation were approximately 25 to 50 percent [23,34,35].

- Although relapse rates following discontinuation of benzodiazepine treatment for panic disorder have been reported to be as high as 70 percent, these results are difficult to validate because symptoms that follow discontinuation can reflect either transient withdrawal symptoms or re-emergence of panic anxiety [36].

Clinical trials and our experience generally show that in individuals with robust response to cognitive-behavioral therapy, there is little decrease in gains at 6 to 12 months [37,38], although relapse can occur [39]. Booster sessions have been shown to enhance long-term outcomes [40,41]. Further discussion on psychotherapy for panic disorder is found elsewhere. (See "Psychotherapy for panic disorder with or without agoraphobia in adults".)

MANAGEMENT OF SUBOPTIMAL RESPONSE

For suboptimal response (poor or partial response) to either pharmacologic or psychological treatment, after confirming adequate exposure and engagement in treatment (for those in cognitive-behavioral therapy [CBT]) or adherence to medications, we typically suggest augmentation with the opposite treatment. (See 'For those agreeing to combined treatment' below.)

Psychodynamic psychotherapy for those with "adult separation anxiety" — In some clinical scenarios, we use psychodynamic psychotherapy as a next step rather than pharmacologic management (eg, when the panic attacks appear to be related to threatened attachment to a key figure, often because of conflicts around emerging autonomy in young adults). This “adult separation anxiety” conflict is a common focus of the brief psychodynamic psychotherapy for panic that has previously been shown to be effective [42]. Discussion of psychodynamic psychotherapy and other psychotherapies for panic disorder can be found elsewhere. (See "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'Psychodynamic therapy'.)

For those agreeing to combined treatment

- **Medication for suboptimal response to CBT** – For individuals with suboptimal response to CBT (eg, poor response or partial response) our first step is to confirm that adequate

exposure during CBT treatment has been attempted, since treatment failure in CBT may be associated with inadequately delivered exposure. Exposure may represent the most crucial element for optimal outcome and appears to be associated with superior outcomes [43,44]. (See "Psychotherapy for panic disorder with or without agoraphobia in adults", section on 'CBT techniques'.)

For those with symptoms despite adequate exposure and full engagement in treatment (eg, present for all sessions, completed all homework assignments), our preference is to augment CBT with a selective serotonin reuptake inhibitor (SSRI) [45,46].

- **Adjunctive CBT for suboptimal response to medication** – Among patients who do not respond fully to an initial or subsequent medication, we favor augmenting the medication with CBT rather than other medications.

  Our preference for the combined modality is based on clinical experience. However, limited data have also suggested that the combination of CBT and antidepressant treatment provides a small advantage over either CBT alone or antidepressants alone for panic disorder/agoraphobia [47-51].

- In a meta-analysis of 21 trials with 1709 patients, combined treatment was superior to antidepressant pharmacotherapy (relative risk 1.24, 95% CI 1.02-1.52) or psychotherapy (relative risk 1.17, 95% CI 1.05-1.31) [50].

- A randomized effectiveness trial in the primary care setting found that the addition of even one component of CBT to medications for panic disorder/agoraphobia resulted in clinically meaningful improvement following treatment and 12 months later [49].

- Another trial in 232 patients with mixed anxiety disorders (107 with panic disorder) who experienced no response or a partial response to medication (mostly SSRIs) were randomized to receive either ongoing care with medication versus addition of CBT to the medication [51]. Treatment with CBT was associated with greater response at six months (adjusted odds ratio 3.78, 95% CI 2.0-7.0) and 12 months (adjusted odds ratio 2.49, 95% CI 1.4-4.6) compared with those receiving usual medication continuation. Additionally, treatment with combined treatment was associated with higher rates of remission versus treatment as usual at 6, 12, and 18 months.

Subsequent pharmacologic management — Many patients initially treated with medication will continue with medication treatment rather than switch to CBT (eg, due to patient preference or access to CBT). An algorithm describes our subsequent pharmacologic management of panic disorder (algorithm 2).

Poor response to initial medication — After titrating up the initial SSRI, we maintain patients on the maximally tolerated dose for at least six weeks before determining their response to treatment. For those with a poor response (eg, minimal to no response), our preference is to change to another SSRI. There is no systematic research evidence to inform this selection but in our clinical experience, an inadequate response to one SSRI does not predict failure of a second SSRI in panic disorder. If response to a second SSRI is poor we typically try a serotonin-norepinephrine reuptake inhibitor (SNRI) such as venlafaxine as the next option.

We prefer to taper off the first medication by 25 percent each week while titrating up the second medication at the same time. Typically, this can be done over four weeks.

- **SNRI** – Venlafaxine ER, an SNRI, has been found to be effective in the treatment of patients with panic disorder [52,53]. Venlafaxine reduces all three core components of panic disorder (attack frequency, anticipatory anxiety, and phobic avoidance).

  - **Dose and titration** – We start venlafaxine ER at 37.5 mg once daily in the morning. We increase to 75 mg per day after one week and then 150 mg after two more weeks, if tolerated. We monitor for six weeks and if clinical response is inadequate, we raise the dose to 225 mg daily. Venlafaxine ER has a linear dose response curve in depression studies; in one study of individuals with panic disorder, the higher dose of venlafaxine appeared to be more effective [52]. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

    We do not recommend using the immediate-release version of venlafaxine in treatment of panic disorder due to its much greater side effect burden and the difficulty individuals with panic disorder have tolerating internal bodily sensation and somatic side effects.

  - **Monitoring blood pressure** – We monitor blood pressure at regular intervals (ie, every visit) in all individuals treated with venlafaxine. We exercise extreme vigilance in treating and monitoring effects of medication on blood pressure in older adults. In individuals who have increases in blood pressure to >90 diastolic, we refer to an internist to assist in evaluating the risks and benefits of continuation (and possibly treating the hypertension) versus tapering off of venlafaxine.

    A small subset of patients (estimated to be 10 to 15 percent) may develop hypertension at doses of 225 mg of venlafaxine or above. In older patients, the risk of hypertension with lower doses (mean 190 mg) was seen in one study to be relatively high (24 percent) in previously nonhypertensive patients and even greater in those with pre-existing hypertension (54 percent) [54].

- **Other adverse effects** – Common side effects include nausea, dry mouth, constipation, anorexia, sweating, somnolence, and sexual dysfunction. Adverse effects including neurologic, gastrointestinal, and psychiatric symptoms can be seen if an SNRI is withdrawn too quickly [55]. SNRIs may have a higher risk of both discontinuation related side effects as well as lethal overdose compared with SSRIs [56,57].

- **Efficacy of SNRIs** – There is no evidence that the small and subtle advantages of SNRIs over SSRIs observed in depression studies [58] apply to panic disorder. One trial showed treatment venlafaxine or paroxetine led to similar magnitude of benefit as compared with placebo.

  For example, in a trial, 664 nondepressed adults with panic disorder were randomly assigned to treatment with venlafaxine ER (75 or 150 mg/day), paroxetine 40 mg/day, or placebo [52]. After 12 weeks, patients receiving venlafaxine ER 75 mg, venlafaxine ER 150 mg or paroxetine were more likely to be free of full symptom panic attacks compared with patients on placebo (54 versus 60 versus 61 versus 35 percent, respectively).

  We do not typically use other SNRIs (eg, duloxetine, milnacipran, levomilnacipran) as there no randomized trials and very few open label studies of their efficacy in panic disorder.

Partial response to initial medication — For individuals who have a partial response to an SSRI at the maximally tolerated dose, we suggest augmentation. Our choice of augmenting agent is based on whether there is a comorbid substance use disorder (SUD; active or by history).

Benzodiazepines for those without an SUD — We typically use the long-acting benzodiazepine, clonazepam, as augmentation for individuals without a history of an SUD who have had a partial response to initial pharmacologic agent. (See 'Adjunctive treatment for marked distress or early side effects' above.)

- **Preference for long-acting benzodiazepine (clonazepam)** – Clonazepam's longer half-life allows dosing once to twice daily, versus three to four times daily required for commonly used alprazolam. For individuals who have difficulty tolerating clonazepam due to sedation, use of the more slowly absorbed lorazepam is a consideration.

  Alprazolam XR, an extended-release formulation of alprazolam, demonstrated to be effective in a controlled trial [59], requires twice daily dosing according to most clinical experts [20]. Our preference for clonazepam over alprazolam is due to its longer half-life

and slower absorption which may help to avoid interdose anxiety often seen with alprazolam as well as rapid onset of effect, either of which may reinforce pill-taking to alleviate anxiety and can lead to enhanced potential for misuse, and reduced self-efficacy (ie, patients' confidence that they can manage their anxiety on their own). Clonazepam has less intensive symptoms on discontinuation than alprazolam [60].

Doses and comparative potency of benzodiazepines used to treat anxiety are found on the table (table 3).

- **Initiating and titrating clonazepam in panic disorder** – When adding clonazepam, we begin with a dose of 0.25 to 0.5 mg at bedtime and increasing by 0.25 to 0.5 mg every three days to 3 mg until symptomatic distress is improved. Increases in dosing are guided by therapeutic effects and side effects of medications. Most individuals will respond to a dose of 1 to 2 mg/day, although some older patients or those with reduced body weight may respond to a lower dose and a small proportion of individuals might need more. We only consider higher doses after a careful search for other factors maintaining panic (eg, medical illness or psychosocial stress), and after ruling out the possibility of escalating tolerance associated with a personal or familial history of substance use disorder [61]. Our clinical experience suggests that the majority of patients with continued anxiety on 3 mg of clonazepam would be unlikely to improve at higher doses.

  We prescribe divided doses if there is breakthrough anxiety. However, this is less preferred. Patients requesting to take multiple doses during the day instead of just at bedtime and in the morning may be using the medication as a safety signal to reduce avoidance of daytime activities. Ongoing avoidance of activities is a less desirable outcome as it interferes with the gradual desensitization to situations and the growing confidence that comes with successful navigation of these situations.

- **Risk of misuse and dependence** – The principal disadvantage of benzodiazepines is the risk of misuse and dependence. The risk of misuse of benzodiazepines is largely confined to individuals with an SUD history though a family history of SUD may be a risk factor for some individuals [61]. We occasionally treat individuals with a past history of substance dependence (eg, not an active SUD) with benzodiazepines; however, we see these individuals more frequently (eg, twice monthly), use long-acting benzodiazepines with slower onset of action (eg, clonazepam) and limit the number of doses given. There have been recent concerns that chronic use of benzodiazepines may be associated with an increased risk of dementia compared with never users of benzodiazepines. However, studies show mixed findings and further research is needed [62-64]. (See "Prescription

drug misuse: Epidemiology, prevention, identification, and management", section on 'Sedatives-hypnotics'.)

Other adverse effects include sedation, fatigue psychomotor impairment, and reduced memory and concentration. Benzodiazepines are usually well-tolerated, particularly compared with other medications for panic disorder [65]. Side effects can usually be limited by careful dose adjustment. Patients should be cautioned against operating motor vehicles or heavy machinery during initiation or dose increases.

Treatment lasting months or more is likely to lead to physiological dependence and consequent withdrawal symptoms if discontinued too quickly.

- **Efficacy of benzodiazepines in panic disorder** – Numerous randomized trials have found alprazolam (in standard and sustained-release formulations), clonazepam, lorazepam, and diazepam to be efficacious for panic disorder [20]. There are no clinical trials testing the utility of adjunctive benzodiazepine treatment in partial serotonin reuptake inhibitor responders. Much of the information is derived from the efficacy as monotherapy in the treatment of panic disorder. However, this strategy is widely employed by clinicians treating this population as a second step, and has been proven in a randomized clinical trial to be effective when treating partially responsive social anxiety disorder, a disorder related to panic disorder [66].

  In a meta-analysis of 24 randomized clinical trials, most with poor methodologic quality, benzodiazepines, compared with placebo, produced greater response and remission and improved social functioning [67]. Calculated effect sizes for benzodiazepine efficacy in two other metanalyses [9] were similar to those seen for SSRIs or TCAs [9,68]. All agents in this class appear to be equally effective with non-placebo-controlled trials showing comparability among alprazolam, clonazepam, lorazepam, and diazepam [65]. Only alprazolam and clonazepam are approved by the US Food and Drug Administration for the treatment of panic disorder.

- **Benzodiazepines and CBT** – Initiating a benzodiazepine once CBT has begun is not recommended, nor are increasing the dose of an existing benzodiazepine, or using “as needed” dosing. Findings from methodologically limited studies of the combination of behavioral interventions for agoraphobia with high potency benzodiazepines suggest a detrimental effect on CBT outcome in some patients [69,70].

  Several studies suggest that chronic use of benzodiazepines for panic disorder/agoraphobia may have detrimental effects on short- and long-term outcomes from CBT including more attrition, less improvement, and greater likelihood of relapse [70-

72]. "As needed" dosing of benzodiazepines was associated with poorer outcomes than routine daily dosing or no use of benzodiazepines, in one small uncontrolled study [73]. In patients already on benzodiazepines, once CBT treatment has reduced panic anxiety symptoms, CBT can be used to facilitate taper and discontinuation of the benzodiazepine [74].

Active or past SUD — For individuals with panic disorder and a partial response to treatment, who have a co-occurring substance use disorder (SUD; active or by history) we favor treatment with gabapentin. Mirtazapine and pregabalin are alternative choices for some. (See 'Treatment resistance' below and 'Adjunctive treatment for marked distress or early side effects' above.)

None of the medications have been well studied in panic disorder; limited data and our clinical experience support their use:

- **Gabapentin** – We typically begin gabapentin at 200 mg three times daily and increase each week by 600 to 900 mg in divided doses to a maximum daily dose of 600 to 900 mg three times daily. The onset of action for gabapentin is within hours. Although there are reports of some misuse potential of this class of agents, it has much lower risks of misuse, development of physiologic dependence, or a prominent discontinuation syndrome compared with benzodiazepines. Our clinical experience and post-hoc analysis of clinical trial data have suggested that gabapentin may have anxiolytic effects in more severe forms of the disorder, but this remains to be determined [75].

- **Pregabalin** – Pregabalin is an alternative choice to gabapentin. Although no data have compared its abuse potential with gabapentin, its placement on a controlled schedule in the United States suggests more concern. We typically begin pregabalin at 50 mg per day and increase by 75 mg in divided doses to a total daily dose of 300 mg in divided doses.

- **Mirtazapine** – We occasionally use mirtazapine as an augmenting agent for individuals with a history of an SUD and partial response to initial treatment. This is particularly true in individuals with insomnia. Our preference is based on our clinical experience, case reports [76,77], and two uncontrolled studies [78,79].

We typically start mirtazapine at 15 mg once daily at bedtime. If there is no response we increase to 30 mg/night after one week with maximum dose of 45 mg/night if needed. Side effects include sedation, appetite increase, and weight gain. These effects are maximum at lower doses and decrease with dose increases.

TREATMENT RESISTANCE

In individuals who have not responded to treatment to this point, we review the patient history closely to make sure alternative diagnosis have not been overlooked.

Our preference is to treat individuals who have poor to no response to two or three separate serotonin reuptake inhibitors (selective serotonin reuptake inhibitors [SSRIs] or serotonin-norepinephrine reuptake inhibitors [SNRIs]) and benzodiazepines or nonbenzodiazepine alternatives (eg, gabapentin, pregabalin, mirtazapine) with a tricyclic antidepressant (TCA). If the tricyclic antidepressant is ineffective our next choice is a monoamine oxidase inhibitor (MAOI).

- **TCAs** – Among TCAs, although most all studies utilized imipramine, our preference is to begin with nortriptyline, based on its lower propensity to induce postural hypotension and lower rate of anticholinergic side effects as compared with other TCAs.

  We typically start at 25 mg per day and increase in 25 mg increments each week to a total of 50 to 100 mg. If there is no response after four weeks we raise the dose to 150 mg/day. Blood levels are available but have only been validated for efficacy for major depression (therapeutic window of 50 to 150 mg). These could be used to check for adherence and to aim for the lower end of the therapeutic window to minimize side effects. Doses and titration of TCAs in the treatment of depression are discussed elsewhere and can be found on the associated table (table 2).

  Sixteen randomized trials (11 for imipramine and 5 for clomipramine) have found TCAs to be superior to placebo in reducing the frequency of panic attacks. However, their effects on anticipatory anxiety and phobic avoidance has been found to be more variable and, in some cases, less robust compared with other antidepressants [80]. Smaller trials have suggested that other agents in this class are also effective. Most studies of TCAs do not show drug-placebo differences until week four with maximal difference in responses by the end of the trial (weeks 8 to 12) [81]. Continued improvement has been observed with open label treatment through six months [31].

  While similar to the serotonergic antidepressants in efficacy, TCAs have a greater side effect burden than SSRIs and greater morbidity and mortality in overdose. Additionally, individuals with panic disorder are often highly sensitive to somatic symptoms, and less able to tolerate tricyclic antidepressant side effects. Side effects may produce physical sensations that exacerbate panic disorder worries. Other side effects include anticholinergic effects, sweating, sleep disturbance, orthostatic hypotension, fatigue and weakness, weight gain, modest blood pressure increases, and sexual dysfunction.

Further discussion about initiating TCAs, titration, monitoring of cardiac effects and other side effects can be found elsewhere. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Side effects'.)

- **MAOIs** – The MAOIs appear to have efficacy against panic disorder; however, relative to serotonin reuptake inhibitors and TCAs, there have been fewer and generally smaller clinical trials comparing these with placebo [82]. MAOIs are infrequently used due to dietary restrictions and side effects. In our experience, they are unusually effective in rare cases of panic disorder that have failed multiple other treatments both pharmacologic and psychotherapeutic.

  Due to the risk of serotonin syndrome, we do not prescribe MAOIs concurrently with an SSRI or SNRI. Additionally we follow the discontinuation of the serotonergic drug with a washout period based on the drug's half-life prior to initiating MAOI.

  Phenelzine is the preferred MAOI, based on its more frequent use in studies. We start phenelzine at 15 mg daily for three days, then 15 mg twice a day for seven days, then 15 mg three times a day for 10 days, and then 30 mg twice a day thereafter. Dose increments should be based on tolerability and longer periods of time may be required to get used to the medication. A dose of 60 mg is likely the minimally effective dose for panic disorder based on older studies of anxious depression.

- **Other medications with limited data supporting their use**

  - **Anticonvulsants** – Carbamazepine [83] and tiagabine [84] have not been shown to be effective as monotherapy in the treatment of panic disorder.

  - **Atypical antidepressants or buspirone** – Randomized trials have generally not supported the efficacy of trazadone, bupropion, nefazodone, or buspirone in the treatment of panic disorder [20,65]. There are no randomized trials testing the efficacy of vilazodone or vortioxetine in the treatment of panic disorder.

  - **Adrenergic blockers** – Trials have found monotherapy with beta-blockers or clonidine, an alpha-2 noradrenergic agonist, to be no more effective than placebo for panic disorder [85,86].

  - **Antipsychotics** – A small clinical trial of patients with panic disorder who did not respond fully to SSRIs compared second-generation antipsychotic augmentation with placebo, found no difference between groups [87]. These findings combined with

substantial concern about metabolic side effects of these agents, suggests that they should not be used as augmentation much less monotherapy for the disorder.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anxiety and anxiety disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- **Initial management decisions** – An algorithm describes our initial management decisions for panic disorder (algorithm 1).
  - **Determine the need for treatment** – Once a diagnosis of panic disorder is made, our next step is to determine, based on clinical assessment of severity of illness, extent of distress or impairment, and patient preference, whether treatment of the disorder is needed. (See 'Determining need for treatment' above.)
  - **Choosing initial treatment modality** – We choose between pharmacotherapy and psychotherapy on the basis of patient preference and treatment availability. However, for individuals with suicidality or comorbid psychiatric disorders (eg, depression, anxiety) we suggest combined treatment rather than either alone (**Grade 2C**). (See 'Choosing between psychotherapy and medication' above and 'Suicidality or co-occurring mental disorders' above.)
- **Initiating treatment**
  - **Cognitive-behavioral therapy (CBT) as preferred psychotherapy** – For individuals who are treated with psychotherapy, we suggest treatment with CBT rather than other psychotherapies (**Grade 2C**). (See 'CBT as preferred psychotherapy' above.)
  - **Selective serotonin reuptake inhibitors (SSRIs) as preferred initial pharmacotherapy** – For individuals who are treated with pharmacotherapy, we suggest first-line treatment with an SSRI rather than other agents (**Grade 2C**).

    In cases of marked distress or dysfunction, when immediate intervention is necessary, we suggest short-term treatment with either a benzodiazepine or gabapentin in

addition to the SSRI (**Grade 2C**). (See 'SSRIs as preferred initial pharmacotherapy' above and 'Adjunctive treatment for marked distress or early side effects' above.)

- **Duration of treatment** – We continue medications that have been effective for a period of at least one year after symptom control has been attained. For individuals with a response to psychotherapy, clinical trials and our experience show that gains are typically maintained for 6 to 12 months. (See 'Duration of treatment' above.)

- **Management of suboptimal response** – For suboptimal response to either treatment, after confirming adequate exposure and engagement treatment (for initial management with CBT) and full adherence to medications, we prefer augmentation with the other treatment modality. (See 'For those agreeing to combined treatment' above.)

  - **For individuals preferring medication** – For patients who prefer medication management and who do not respond adequately to initial medication, our choice of treatment is based on the level of response to the initial agent (see 'Subsequent pharmacologic management' above). An algorithm describes our subsequent pharmacologic management of panic disorder (algorithm 2).

    - For poor response to SSRI treatment, our preference is to change to another SSRI. We typically use a serotonin-norepinephrine reuptake inhibitor (SNRI) after two unsuccessful SSRI trials. (See 'Subsequent pharmacologic management' above.)

    - For poor response to two SSRIs and an SNRI we prefer sequential trials of a benzodiazepine (for those without a substance use disorder [SUD]) or gabapentin (for those with an SUD), mirtazapine, nortriptyline or the monoamine oxidase inhibitor, phenelzine. (See 'Poor response to initial medication' above and 'Treatment resistance' above.)

    - For partial response to SSRI or SNRI treatment we prefer augmentation trials with a benzodiazepine (for those without an SUD) or gabapentin (for those with an SUD), mirtazapine, or nortriptyline. (See 'Partial response to initial medication' above and 'Treatment resistance' above.)

- **Treatment resistance** – For individuals with ongoing limited response to the above agents we review the patient history to make sure alternative diagnosis have not been overlooked. Limited data support the efficacy of anticonvulsants, other antidepressants (ie, bupropion, nefazodone, trazadone), buspirone, antipsychotics, or adrenergic antagonists. (See 'Treatment resistance' above.)

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