



## **Introduction to the Practice Guideline for the Treatment of Patients with Panic Disorder**

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## **Purpose of This Document**

This document is an introduction to Magellan Health Services' (Magellan) adopted clinical practice guideline (CPG) for the treatment of patients with a panic disorder.

As with all CPGs, the adopted guideline and this Introduction are intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to this practice guideline should be noted in the member's treatment record, documenting the clinical reasoning used in making the exception. Magellan periodically requests clinical files from providers in order to monitor compliance with adopted guidelines. Clear documentation of the rationale for exceptions to the guideline's recommendations should be documented in the member's treatment record whenever there is evidence of deviation from the guideline.

Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval of specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

## **Adopted Guideline**

The guideline Magellan has adopted to augment providers' clinical decision-making with those members who have panic disorder is the **American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition*** and a companion synopsis of this publication, ***Treating Panic Disorder A Quick Reference Guide***. The APA incorporates developments in pharmacotherapy and other areas of psychiatric management of individuals with panic disorder. The APA guideline is a research-based document covering all areas of psychiatric management of patients with this disorder, from clinical features and epidemiology to treatment approach and planning.

## **Additional Recommendations Based on Recent Literature Review**

The APA guideline is based on a literature review through June 2007. Magellan conducted a further review of the clinical literature on assessment and treatment of panic disorder published through March 2011. Key relevant recommendations from this more recent literature review are summarized here. Magellan encourages providers to be familiar with this information, as well as the information in the guideline.

## **Disease Classification Issues**

Following an extensive appraisal of the empirical evidence, the diagnostic criteria for panic attacks (PA) and panic disorder (PD) were reviewed by the DSM V Anxiety, OC (Obsessive-Compulsive) Spectrum, Posttraumatic and Dissociative Disorder Work Group (Craske et al., 2010). This panel was commissioned by the APA as part of its formal revision to the Diagnostic and Statistical Manual (DSM) IV-TR currently in use. Their preliminary recommendations include the retention of all thirteen PA symptoms and the four or more symptoms cut off for full-blown vs. limited symptom PAs. A re-phrasing of "hot flushes" to "heat sensations" was proposed along with a re-ordering of

the symptom list. Regarding changes to diagnostic criteria for PD, the work group did not find any empirical evidence to support revisions or quantifications to the term “recurrent” as the descriptor to panic attacks nor did they find any evidence warranting alternative criteria or definitions across age groups. However, the group did suggest changes in light of the fact that many individuals with PD experience “expected/cued” PAs along with their “unexpected/uncued” PAs (Craske et al., 2010).

### **Predictors of Outcome and Comorbid Clinical Conditions**

A prospective analysis examining the demographic, clinical and attitudinal variables impacting improvement was conducted using primary care patients (n=232) meeting criteria for PD upon enrollment in a randomized controlled study comparing a collaborative care intervention to treatment as usual (Chavira et al., 2009). The analysis identified diagnostic and clinical severity variables at baseline that predicted both short- and long-term clinical improvement. A high level of anxiety sensitivity, a greater severity of panic-related symptoms, the presence of comorbid social phobia and posttraumatic stress disorder (PTSD), greater disability at baseline or impaired functioning in daily life were all related to a less-favorable outcome. Conversely, a low level of neuroticism (phobic avoidance), being Caucasian and having a college education was associated with a more favorable clinical outcome at long-term follow-up. Marital status, age and gender were not predictors of clinical improvement at either time point (Chavira et al., 2009).

The APA guideline indicates panic disorder patients with concurrent medical conditions may have difficulty in differentiating symptoms of a general medical condition from those related to the panic attacks. Medical conditions frequently comorbid with PD and specified in the guideline are: thyroid disease, cancer, chronic pain, cardiac disease, irritable bowel syndrome, migraine, mitral valve prolapse, vestibular disorder and allergic and respiratory disease. The guideline stresses that the relationship between the medical condition and PD determines the treatment approach – i.e., whether the medical condition or its treatment may be the primary cause of panic symptoms or may worsen them.

Since publication of the guideline, the more recent multi-center cross-sectional **H**eadache, **A**nxiety and **D**epressive disorders (HADAS) **S**tudy was conducted at secondary and tertiary headache centers in Italy using patients with migraine without aura (n=158), tension-type headache (n=110) and migraine plus tension-type headache (n=106). Study findings supported a statistically significant correlation between panic disorder and migraine without aura, which was stronger when migraine and tension-type headaches were both present (Beghi et al. 2010). The Women’s Health Initiative Observational Study (n=3,369) of community dwelling, generally healthy postmenopausal women aged 51-83 years, revealed that a six month history of full-blown panic attack was endorsed by 10 percent of postmenopausal women in this cohort. After adjusting for multiple potential confounders and known cardiovascular risk factors, this recent history of panic attack was independently associated with nearly a threefold increased risk of fatal or nonfatal myocardial infarction or stroke. Researchers implied that this subgroup of women require careful monitoring and cardiovascular risk reduction efforts (Smoller et al., 2007).

## Psychosocial Treatments

The APA guideline specifies that individual patient circumstances should dictate the initial choice of treatment in PD since empirical evidence shows that psychosocial, pharmacological and combined treatments are equally efficacious modalities. The guideline indicates that Cognitive Behavioral Therapy (CBT) for panic disorder is the psychosocial treatment that would be indicated most often because it is supported by multiple positive randomized controlled trials and can be recommended with substantial clinical confidence. The guideline describes CBT as a modality that targets maladaptive cognitions and behaviors that maintain PD (i.e., catastrophic misinterpretations of physical symptoms) and seeks to identify and change mistaken beliefs/learned associations about physical symptoms while strengthening non-anxious responses. A more recently published large meta-analysis evaluating 364 CBT studies for anxiety disorders (31 studies targeted PD) showed that significant treatment effect sizes have consistently been demonstrated over the last four decades and that these effects remain very high over this entire time period in placebo-controlled studies (Ost 2008).

The guideline's discussion of psychosocial therapy also indicates that Group CBT, Self-directed CBT and Exposure Therapy in the treatment of PD are supported by several controlled studies. Newly published studies include one randomized controlled trial (n=100) which compared 14-session standard, 14-session group and 7-session brief CBT in the treatment of patients diagnosed with moderate to severe panic disorder with agoraphobia taking either anxiolytic or antidepressant medication or a combination of both. Investigators reported several positive outcomes in that all three treatment conditions significantly reduced the intensity of symptoms, increased participants' quality of life, offered high effect sizes, superior maintenance of gains over time and lower rates of relapse compared to the wait-list controls (Marchand et al., 2009). Traditional spaced weekly group CBT in the treatment of patients with PD with or without agoraphobia (n=39) was compared to a new approach of massed 3-week CBT. The massed approach delivery, structured as CBT daily in 4-hour sessions in week one, two 2-hour sessions in week two and one 2-hour session in week three, was compared to the traditional approach of group CBT for 13 consecutive weekly 2-hour sessions. Both approaches showed equally large treatment effective sizes and patient satisfaction. Investigators suggested that the massed CBT schedule might be advantageous by leading to faster recovery and thereby reducing patient suffering (Spindler et al., 2009).

Three further studies were published on Internet or computer-based treatment (ICT) as a novel approach to self-directed CBT since publication of the guideline. A meta-analysis by Reger and Gahm reviewing 19 ICT studies, found that the clinical benefits of ICT were superior to wait-list or placebo conditions and that they were equal to traditional therapist-delivered treatment of anxiety disorders. Additionally, the investigators noted that while treatment effect sizes were very large in the panic disorder studies (i.e., mean ES of .93, CI=.49, 1.38), more well-designed and larger studies of this new approach are warranted (Reger et al., 2009). Another randomized controlled trial (n=113) which compared ICT of 10 self-help modules with therapist e-mail feedback against traditional group CBT over 10 weeks of treatment for PD patients (with and without agoraphobia) found them to be equally effective in reducing panic and agoraphobic symptoms (Bergstrom et al., 2010). The third ICT study (n=57) evaluated the frequency of therapist support/contact and its impact on clinical outcome for PD patients with and without agoraphobia. In this study design, frequent (i.e., three therapist e-mails per week) was compared to infrequent (one therapist e-mail per week) psychologist support. Investigators reported no difference in clinical outcomes between

treatment conditions along all measures – i.e., clinical severity ratings, panic-related cognitions, negative affect, psychological and physical quality of life domains, therapist alliance, treatment credibility and patient satisfaction (Klein et al., 2009).

There was one more recently published systematic review on Virtual Reality Exposure Therapy (VRET) in the treatment of anxiety disorders. The investigators noted that meta-analytic data are robust and can confirm the efficacy of VRET compared to traditional exposure therapy for the treatment of phobias (i.e., fear of flying and acrophobia). However, authors reported there was only one study in their analysis (Botella et al. 2007) that used strict methodological criteria showing equal effectiveness of CBT plus VRET against CBT plus exposure ‘in vivo’ in the treatment of panic disorder (Meyerbröker et al., 2010).

Since publication of the guideline, researchers in The Netherlands conducted an early intervention study on patients with either subthreshold or mild panic disorder in an effort to determine the value of preventative measures in this population (Meulenbeek et al., 2010). This multi-site randomized controlled trial (n=217) evaluated the eight session *Don't Panic* course against wait-list controls and gathered outcome data through the six month follow-up period. This psychoeducational program was designed to include the following: information on the psychological and physiological nature of anxiety and panic attacks, stress management/relaxation techniques, cognitive restructuring to challenge and correct dysfunctional cognitions about panic, interoceptive and ‘in vivo’ exposure to reduce fear of somatic sensations and agoraphobic avoidance. Findings showed that the early intervention group demonstrated clinically significant change in panic symptomatology severity for both subthreshold and mild PD patient groups that were maintained through follow-up (Meulenbeek et al., 2010).

Use of benzodiazepines in panic disorder as monotherapy or adjunctive to antidepressants is cautiously supported in the adopted guideline due to the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. In light of this issue, there have been attempts to provide patients undergoing benzodiazepine withdrawal with psychosocial therapy as an additive intervention to assist patients in successful drug discontinuation. The randomized controlled trial conducted by the research team of Otto et al., was designed to establish and compare the efficacy of three strategies for the discontinuation of benzodiazepine treatment (alprazolam or clonazepam) in PD patients – a conservative taper program, a taper program in conjunction with an individual, exposure-based CBT or a taper program in conjunction with individual muscle-relaxation therapy (Otto, McHugh et al., 2010). The CBT in this trial applied methods associated with reducing the fears of anxiety symptoms which often contribute to discontinuation difficulties or relapse – i.e., information, interoceptive exposure, somatic coping skills and cognitive restructuring. Study findings showed that patients who received CBT had significantly higher rates of discontinuation success than those who received relaxation training or taper alone with the additional benefit of preventing the return of panic symptoms (Otto, McHugh et al., 2010)

A meta-analysis of studies for PD without agoraphobia and Generalized Anxiety Disorder (GAD) directly comparing CBT with Relaxation Therapy (RT) showed that RT produced comparable results to CBT in the treatment of GAD. This was, however, not the case in PD without agoraphobia where CBT was superior to RT in the treatment of domains directly relevant to panic such as fear of anxiety, panic-related cognitions and resulted in superior outcomes – i.e., increased

percentage of treated patients who were panic-free and demonstration of significant clinical change (Siev et al., 2007). Another meta-analysis reviewed findings from 42 studies of either exposure therapy alone, cognitive therapy alone, relaxation and breathing training alone or any combination of these in the treatment of PD with and without agoraphobia. This review affirmed that exposure was the treatment of choice for reducing panic behaviors and that the inclusion of relaxation/breathing training techniques improved the effects of exposure (Sanchez-Meca et al., 2010).

Panic Control Treatment (PCT) is a CBT consisting of education, cognitive restructuring and behavioral exercises that was compared with a psycho-educational/supportive treatment on veterans (n=49) diagnosed with combat-related Posttraumatic Stress Disorder (PTSD) and comorbid panic attacks (Teng et al., 2008). In this randomized controlled trial, patients received either intervention for 10 treatment sessions and were monitored for clinical change at the end of treatment and at the 3- month follow-up. The investigative team reported findings that the PCT was superior to the active control therapy in reducing the frequency, severity and distress associated with panic disorder and that this new modality was able to effectively treat panic symptoms within the context of comorbid PTSD in the veteran population. The authors also discussed future research in this area using PCT to treat panic symptoms prior to treating PTSD or developing an integrated treatment approach (Teng et al., 2008).

## **Pharmacotherapeutic Interventions**

According to the APA guideline, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and benzodiazepines have comparable efficacy in the treatment of panic disorder. The guideline emphasizes that a number of patient-specific considerations are evaluated in the selection of an appropriate agent (i.e., prior treatment history, co-occurring medical/psychiatric conditions, potential drug interactions and specific pharmacological properties of the drug) but specifies the SSRIs and SNRIs as best initial choices for monotherapy due to their favorable side effect profile. In addition, the guideline notes that benzodiazepines may be best used adjunctively with antidepressants to treat residual anxiety or in cases where rapid symptom control is necessary. Other medications discussed in the guideline are the monoamine oxidase inhibitors (MAOIs) and anticonvulsants (i.e., gabapentin) that may be considered as monotherapy or adjunctive treatments for patients not responding to standard options or the second generation antipsychotics (SGAs) for judicious use in patients with severe, treatment-resistant panic disorder. Since publication of the guideline, two large meta-analyses have been published on the pharmacological treatment of anxiety disorders (Ravindran et al., 2010) and specifically on the efficacy of SSRIs in the treatment of panic disorder (Mochcovitch et al., 2010) where their findings continued to support the adopted guideline recommendations on pharmacotherapeutic interventions for PD treatment.

There have been four new clinical trials published on the efficacy of venlafaxine extended-release (ER) in the treatment of panic disorder. Pollack et al. conducted two related studies comparing venlafaxine ER 75mg/day or 150mg/day against the “gold standard” of paroxetine 40mg/day or placebo for 12 weeks in one study (Pollack et al., 2006) and then venlafaxine ER 75mg/day or 225mg/day against paroxetine 40mg/day or placebo for 12 weeks in another clinical trial conducted the following year (Pollack et al., 2007). Both trials demonstrated that venlafaxine ER and paroxetine were well tolerated and effective for short-term treatment of PD. Additionally, in the later trial, the venlafaxine ER 225 mg/day dosage showed greater efficacy as assessed by panic-free rates and

improvement in mean total Panic Disorder Severity Scale (PDSS) scores relative to paroxetine, suggesting the possibility of a dose-response relationship by the investigators (Pollack et al., 2006; Pollack et al., 2007).

Findings from a flexible-dose study of venlafaxine ER (75 to 225mg/day) compared to placebo showed that venlafaxine ER was not statistically different from placebo on the primary end point of full symptom panic attacks as measured by the Panic and Anticipatory Anxiety Scale (PAAS). In spite of this, investigators reported venlafaxine ER to be superior to placebo on several secondary efficacy measures of symptom/quality of life/functionality improvement (Liebowitz et al., 2009). An international study using 52 research sites in Australia, Canada, Denmark, France, Hungary, Italy, Poland and the United States participated in a randomized, double-blind, placebo-controlled study (n=169) following an open-label efficacy trial (n=291) of venlafaxine ER. Results showed that time to relapse was significantly longer with venlafaxine ER than placebo ( $p<.001$ ) and that all secondary measures of panic attack (i.e., treatment efficacy, quality of life and disability) were significantly better with venlafaxine ER than placebo ( $p<.005$ ). Researcher noted the promising findings while calling for continued research in the long-term treatment and prevention of PD using the SNRI class of drugs (Ferguson et al., 2007).

The adopted guideline indicates that use of SGAs may be considered in rare individual circumstances while highlighting concerns about their side effects of weight gain, poor glycemic control and metabolic syndrome. Noting the receptor blocking activity of risperidone at both the D2 receptor family and serotonin receptors, the research team of Prosser et al. discussed the drug's merit as an anxiolytic agent and its use at low doses in other conditions such as depression with comorbid anxiety, treatment-resistant anxiety in the elderly, GAD, PTSD and obsessive-compulsive disorder (OCD) (Prosser et al., 2009). This randomized, single-blind, clinical trial using 56 subjects with a history of panic attacks were treated with either risperidone (0.25 mg/day up to 16 mg/day) or paroxetine (30 mg/day up to 60 mg/day) for eight weeks. Results showed that all subjects demonstrated a reduction in both the frequency and severity of panic attacks and were equally well tolerated regardless of treatment received. There were no reported differences in the efficacy of paroxetine and low-dose risperidone in the treatment of panic attacks (Prosser et al., 2009).

Patients (n=36) that presented features of both social anxiety disorder and PD were treated with the MAOI, tranylcypromine, in a double-blind controlled comparison to measure the effects of 30 mg and 60 mg over a period of 12 weeks (Nardi et al., 2010). Investigators reported that while panic symptoms disappeared at a low dose (30 mg daily), tranylcypromine was only efficacious in comorbid cases with symptoms of both PD and social anxiety disorder at a higher dose (60 mg daily). Investigators noted that while patients treated with the high dose showed a significant reduction in the number of full or limited panic attacks and in the level of social anxiety symptoms, more research is needed in this subpopulation of patients on this drug and other possible agents (Nardi et al., 2010).

Caution and careful monitoring are indicated when elderly persons are taking benzodiazepines for PD wherein the guideline specifically warns about potential problems such as sedation, fatigue, ataxia, slurred speech, weakness, substance dependence and a greater risk of falls. In spite of these warnings, the more recently published longitudinal, prospective Harvard/Brown Anxiety Research (HARP) Project conducted over nine years on the use of benzodiazepines (BZ) and SSRIs in middle-aged (n=211) and older adults (n=51) with anxiety disorders yielded surprising and

somewhat disappointing findings (Benitez et al., 2007). Their principal results showed that the rates of BZ use were high among both the older (53 percent) and the younger age groups (37.4 percent) and did not significantly decrease over time even after controlling for the length of the episode. The trend showed an increase in SSRI/SSNI use over time in both groups where 18 percent of the older and 21 percent of the younger group were using SSRI/SNRIs at the beginning of the study and increasing to 35 percent and 42 percent, respectively. Overall, only 35 percent of the participants were using SSRI/SNRIs, signaling an underutilization of their appropriate usage, while more than half of the patients continued to use BZs (Benitez et al., 2007).

Another more recent study focusing solely on older adults demonstrated that both paroxetine (40 mg/day) and 14 individual weekly CBT sessions were equally effective in treating late-life panic disorder with and without agoraphobia. Investigators indicated that while life-time prevalence of PD is lower in the elderly population than in other age groups, it remains as high as 2 percent with agoraphobic avoidance not seeming to decline with age as does the overall severity of PD symptoms (Hendriks et al., 2009).

### **Combined Treatments**

The APA guideline emphasizes there are insufficient data to routinely recommend a combination of treatments over monotherapy and stresses that the evidence does not demonstrate the superiority of either psychosocial or pharmacological interventions. The guideline indicates that combined treatment may be considered if the patient has failed to respond to standard monotherapies, prefers immediate amelioration of symptoms or would like to reduce the need for continuing medications.

Since publication of the guideline, two more recent meta-analyses reported more favorable outcomes with combined treatment. The review by Furukawa et al., analyzed 21 trials with 1,709 patients and found that in the acute phase of treatment, combined therapy was superior to antidepressant pharmacotherapy or psychotherapy (cognitive or behavioral) but produced more dropouts due to side effects. After the acute phase, the superiority of combined treatment over either monotherapy persisted as long as the drug was continued (Furukawa et al., 2009). Similarly, a meta-analysis of 24 studies, where 16 studies focused specifically on PD, Bandelow et al. reported that only in PD did the combination of pharmacological and psychological (CBT) therapy show superiority to either treatment alone (Bandelow et al., 2007). However, these investigators noted that the relatively small number of available studies and inability to precisely classify drug classes or CBT methods still prevented reliable conclusions (Bandelow et al., 2007).

Another clinical trial conducted in The Netherlands on patients with PD (n=150) found that combined (SSRI + CBT) treatment was superior to monotherapy but the difference between SSRI-only and the combined treatment was modest (van Apeldoorn et al., 2008). Investigators concluded that the additive value of a CBT package to SSRI-only was limited when evaluated after nine months of treatment and argued the need to compare longer-term outcomes especially after the SSRIs are tapered off (van Apeldoorn et al., 2008). This same Dutch team continued the study in order to confirm treatment results through a 1-year follow-up. Their overall results showed no significant differences in clinical outcomes between treatment modalities or loss of treatment gains and therefore concluded no modality to be clearly superior. Client satisfaction was high for all groups but there were significant differences between SSRI+CBT and the CBT-only groups. Investigators

speculated that the delayed onset of treatment effects associated with CBT might be considered a drawback of the CBT-only approach (van Apelboorn et al., 2008).

Other more recently published studies examined the efficacy of psychotherapy combined with drugs other than SSRI antidepressants in the treatment of PD. One meta-analysis consisted of two trials (n=166) comparing a behavioral intervention (exposure) alone or in combination with a benzodiazepine over 16 weeks and one trial (n=77) comparing CBT alone or in combination with and a benzodiazepine or alone over 12 weeks (Watanabe et al., 2009). The investigators concluded that due to the paucity of high quality data, they were unable to assess the efficacy of psychotherapy alone or in combination as intended. Based on these limited data however, authors did present results indicating that combined therapy did not seem to lead to a significant difference from psychotherapy alone during and at the end of the intervention. Further, their data from the 6 to 12-month naturalistic follow-up indicated that combined treatment might even be inferior to psychotherapy alone (Watanabe et al., 2009).

A novel strategy for combining CBT and pharmacotherapy was tested in a small pilot study (n=31) with D-cycloserine (DCS), a partial agonist of the N-methyl-D-aspartate (NMDA) receptor, where investigators theorized its use as an agent capable of enhancing extinction learning (Otto et al., 2009). Researchers have touted DCS as the “clearest example of a medication that increases neuroplasticity diffusely in the brain to enhance the efficacy of a behavioral therapy that produces neuroadaptations in particular circuits” causing interference with the re-consolidation of fear memories (Krystal et al., 2009, p. 691). These preliminary findings showed large effect sizes for the additive benefit of DCS augmentation of CBT for panic disorder in symptom severity and clinical change status along with no significant adverse effects with DCS administration (Otto, Tolin et al., 2010).

## **Somatic Therapies**

The APA guideline does not address neurostimulation therapies for the treatment of PD although there has been some interest in researching the effects of slow Repetitive Transcranial Magnetic Stimulation (rTMS) administered to the right prefrontal cortex to ameliorate symptoms of anxiety disorders (Zwanger et al. 2002). A small open study of six patients with comorbid Major Depressive Disorder (MDD) and PD were treated daily with active 1-Hz-rTMS to the right dorsolateral prefrontal cortex (DLPFC) for two weeks which resulted in significant clinical improvement and reduction of ipsilateral motor cortex excitability (Montovani et al., 2007). Another clinical trial by Prasko et al. examined the effects of rTMS on PD as an add-on therapy to SSRIs. Findings from this clinical trial showed that low frequency (1 Hz, 30-minutes, 110 percent of motor threshold) rTMS administered over the right DLPFC during 10 sessions did not differ from sham rTMS in facilitating the effect of SSRI therapy in these patients (Prasko et al., 2007).

## Obtaining Copies of the APA Guideline

Copies of the *Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition* may be obtained through the APA at <http://psych.org/>, by calling (800) 368-5777, or by U.S. mail at:

American Psychiatric Publishing, Inc.  
1000 Wilson Blvd., Suite 1825  
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## Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We consider your suggestions and recommendations in our ongoing review of the guidelines. Submit your comments to:

Clinical Operations Coordinator  
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