Introduction to Magellan's Adopted Clinical Practice Guideline for the Treatment of Patients with Panic Disorder

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Purpose of This Document

This document is an introduction and update to Magellan Healthcare's adopted clinical practice guideline (CPG) for the treatment of patients with panic disorder. Magellan has adopted the American Psychiatric Association's (APA) 2009 *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,* to serve as an evidence-based framework for practitioners' clinical decision-making with adult patients who have panic disorder. These documents incorporate developments in pharmacotherapy and most areas of psychiatric management of patients with panic disorder. A research-based resource, the guideline covers the psychiatric management of patients with this disorder, from clinical features and epidemiology to numerous aspects of treatment approach and planning.

An extensive literature review suggests that the APA guideline is among the most comprehensive evidence-based clinical practice guidelines (CPGs) for this disorder, and in general, APA guidelines are widely used. Since this guideline is broadly accepted by managed behavioral healthcare organizations (MBHOs), this adoption will minimize the burden on practitioners serving multiple MBHOs.

As with all CPGs, the adopted guideline and Magellan's introduction augments, but does not replace, sound clinical judgment. As a matter of good practice, clearly note clinically sound exceptions to this practice guideline in the member's treatment record, documenting the clinical reasoning used when making an exception. Magellan periodically requests clinical files from providers in order to monitor compliance with adopted guidelines.

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 issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

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 April 2015. Key relevant recommendations from this more recent literature review are summarized

below. Magellan encourages providers to be familiar with this information, as well as the information in the guideline.

Executive Summary

(Discussion of changes/new information in this updated guideline.)

Predictors of Outcome and Comorbid Clinical Conditions

A recent study examined whether an intolerance of uncertainty (IU) moderated the association between startle potentiation and panic disorder during safety conditions and a threat-of-shock task. Adult participants (n= 74 with diagnoses of panic disorder, and n= 98 without panic disorder) were seated in a booth, electrically shielded and sound-attenuated, where they received electric shocks (annoying but not painful) under three "threat conditions:" no shock, shock possible during a cue or shock possible at any time. Participants were aware of the current "threat condition" displayed on a computer monitor. Startle probes were presented during interstimulus intervals (ISIs), as well as during the cue. Response to startle probes during the ISI was an indicator of safety responding since the ISI condition was between threat conditions and participants knew they were safe from shock during this period. Results showed that participants with panic disorder reported greater IU compared with those without panic disorder. Other results from this study showed that "at high levels of IU, PD was associated with greater startle potentiation during safety. At low levels of IU, PD was not associated with startle potentiation during safety" (Gorka et al., 2014, p 734). Researchers noted that patients with panic disorder who have high levels of IU interpret ambiguous information as threatening, failing to inhibit aversive responding in the presence of safety information. They suggested that this subgroup of individuals benefits from exposure-based interventions directly addressing safety and inhibitory learning, and intolerance of uncertainty training (Gorka et al., 2014).

Another recent study examined the role of three cognitive factors, i.e., anxiety sensitivity, catastrophic misinterpretations of benign bodily sensations, and coping self-efficacy, in predicting the severity of panic disorder. Prior to receiving psychological treatment, adults with panic disorder (n=168) completed measures of the cognitive factors. Indicators of panic disorder severity were assessed by the *Anxiety Disorders Diagnostic Interview;* catastrophic misinterpretation of bodily sensations was assessed by the *Panic Catastrophic Misinterpretations Scale;* panic self-efficacy was measured through the *Panic Self-efficacy Scale;* and anxiety sensitivity was assessed using the *Anxiety Sensitivity Index*. Analysis of the data suggested that both anxiety sensitivity and panic self-efficacy uniquely predict panic disorder severity through cognitive-behavior therapy treatment and that "catastrophic misinterpretation and panic self-efficacy may be mechanisms of change of cognitive-behavior therapy for PD" (Sandin et al., 2015, p. 38). Researchers noted that this study demonstrates that the three factors independently predict PD severity (p. 38) and that their data suggests a comprehensive tripartite cognitive model of panic integrating the three main cognitive factors. They further suggested that cognitive behavior therapy should specifically target increasing the levels of panic self-efficacy while reducing both the increased levels of anxiety sensitivity and catastrophic misinterpretations (Sandin et al., 2015).

Psychosocial Treatments

A systematic review and meta-analysis investigated the efficacy of guided internet delivered psychological treatments (ICBT) compared with face-to-face CBT in 13 studies, of which three specifically targeted panic disorder (Andersson et al., 2014). Examples of ICBT programs include therapist guidance over encrypted e-mail, text exchange between therapist and client and real time

chat-based Internet treatments. Results showed that ICBT and face-to-face CBT are equally effective in panic disorder as well as in other conditions such as social anxiety disorder and depressive symptoms, suggesting that a face-face therapist may not be crucial in generating large treatment effects. Authors concluded, "smart phone applications and ICBT will blend in with face-to-face treatment in the near future" and concluded that ICBT is effective and is a potential alternative and complement to face-to-face therapy (Andersson et al., 2014, p. 293).

In a recent study, researchers examined the effects of safety behavior use, e.g., mental distracting, checking vital signs, during everyday life and during exposure-based treatment for panic disorder and agoraphobia using data from a multi-centered randomized controlled trial by Gloster et al., "Mechanisms of Action in Cognitive Behavioral Therapy" (Helbig-Lang et al., 2014). In this trial, participants with both panic disorder and agoraphobia (n=268) were randomized to 12 sessions of exposure-based CBT carried out weekly. One group (T+) received therapist-guided exposure, while the other group (T-) entered exposure situations without therapist guidance. In analysis of the associations between safety behavior at baseline, measured by the Texas Safety Maneuver Scale (TSMS), and symptom change, researchers found that the more safety behavior at baseline, the higher the improvement in symptoms. They suggested that patients relying on safety behaviors prior to therapy benefitted from the treatment protocol encouraging patients to omit all safety behavior during treatment. Patients entering the exposure situations without therapist guidance reported higher safety behavior use during the exercise and less improvement in symptoms. Researchers concluded that these results confirm the importance of assessing safety behaviors in patients with panic disorder and agoraphobia and that further research on safety behaviors in daily life and during treatment may improve understanding of mechanisms of change in cognitive behavioral therapy for panic disorder and agoraphobia (Helbig-Lang et al., 2014).

Researchers have conducted recent studies to learn more about how CBT reduces panic symptoms. In a randomized, controlled, multicenter trial, Kircher et al. compared the brain activity of persons (n=42) with panic disorder and agoraphobia before and after 12 twice-weekly sessions of CBT (both therapist guided and non-therapist guided) using functional magnetic resonance imaging (fMRI). Their investigation focused on how CBT influences the neural correlates of fear conditioning in panic disorder/agoraphobia. The CBT fMRI results were compared to the fMRI results from healthy control subjects (n=42). Researchers found that, after CBT, patients showed significant reduction of inferior frontal gyrus (IFG) activity compared to control subjects along with reduction in agoraphobic symptoms. Additionally, they demonstrated increased connectivity between the IFG and "fear network" regions (amygdalae, insulae, anterior cingulated cortex) with CBT inducing a lower level of activity of the fear network. The study demonstrated the left IFG involvement in both the pathology and psychotherapy of panic disorder and the link between the cerebral correlates of cognitive (IFG) and fear during symptom improvement. Researchers suggested further research to support the development of more targeted treatments for panic disorder (Kircher et al., 2012).

Another recent longitudinal study including patients (n=49) with panic disorder and agoraphobia, who were receiving twelve CBT sessions twice weekly that focused on behavioral exposure, investigated the potential of fMRI data for CBT response prediction. Researchers concluded that their proof-of-concept study including functional magnetic resonance imaging demonstrated an accuracy of 82 percent with 92 percent sensitivity showing that predicting treatment response to CBT based on whole brain fMRI data is possible and has the potential to bring personalized medicine within reach (Hahn et al., 2015).

A recent randomized controlled switching trial tested the efficacy of an acceptance and commitment therapy (ACT) intervention for adult patients (n=43) with treatment-resistant

primary panic disorder and/or agoraphobia (Gloster et al., 2015). Researchers noted that ACT focuses on helping patients observe their symptoms rather than trying to eliminate them, thus discontinuing a longstanding and unsuccessful struggle with symptoms. Patients with one or more previous courses of psychological and/or pharmacological treatment were randomized to either immediate, brief treatment of eight sessions (90 – 120 minutes) of ACT administered twice weekly over four weeks or a four-week waiting list (where patients received treatment after a four-week period), and patients were followed up for six months. ACT included the following: "acceptance, present moment awareness, defusion, self-as-context (observer perspective), value clarification, and committed action" (Gloster et al., 2015, p. 102). Outcomes, measured with the Panic and Agoraphobia Scale (PAS, the Clinical Global Impression (CGI), and the Mobility Inventory (MI) showed that the ACT group improved significantly in terms of the symptoms of panic disorder and agoraphobia compared to the waitlist group.

Pharmacotherapeutic Interventions

A recent review of literature examined pharmacological interventions, alone or in combination with psychotherapy, for the treatment of panic disorder (Freire et al., 2014). Authors noted that the World Federation of Societies of Biological Psychiatry (WFSBP) considered the following antidepressants as highest recommended grade in the treatment of panic disorder: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, clomipramine and imipramine. This level of evidence was based on at least two double blind, parallel group, randomized controlled trials showing that the medication was found to be superior to placebo. This level also required that the antidepressants show equivalent or superior efficacy compared with established comparator treatment in randomized controlled trials. Also noted by the authors, the National Institute for Health and Clinical Excellence (NICE) guidelines indicated the best treatment options for panic disorder included pharmacological interventions with antidepressants (SSRIs as first choice), CBT and self-help. The guidelines indicated that antipsychotic medications should not be prescribed for patients with panic disorder and that benzodiazepines should be avoided in the treatment of panic disorder due to "less good outcome in long term" (Freire, p. 1062). The NICE guidelines did not acknowledge evidence of venlafaxine's effectiveness in more recent high quality studies. Authors noted that recent studies have demonstrated that benzodiazepines are safer and more effective than previously reported. Caution should be exercised in prescribing benzodiazepines for long-term use or in patients with current or recent history of substance use disorders. They may be prescribed for short-term, intermittent, acute care. Memon et al. noted that benzodiazepines can be effective in treating residual anxiety symptoms for patients who require rapid symptom control, but the benefit of more rapid response must be assessed against potential complication of benzodiazepine therapy (Medscape, 2015).

Freire et al. discussed recent studies comparing two antidepressants where both drugs were effective showing similar efficacies: sertraline vs paroxetine, sertraline vs imipramine, fluoxetine vs clomipramine, fluoxetine vs mirtazapine, paroxetin vs citalopram, paroxetin vs venlafaxine, citalopram vs escitalopram (Freire et al., 2014). Studies reported tricyclic antidepressants showed faster improvement but more side effects than SSRIs. In their conclusions, they noted that research has provided evidence of the effectiveness of SSRIs, SNRIs, TCAs and benzodiazepines, and that new compounds, i.e., inositol, duloxetine, mirtazapine, milnacipran and nefazodone may be effective in treating panic disorder. Based on their research, authors suggested that the efficacy of reboxetine and anticonvulsants is controversial, also noting that atypical antipsychotics should not be first choice treatments due to unfavorable side-effect profile.

In its revision of the drug label for citalopram, the FDA advised that citalopram use be avoided in patients with congenital long QT syndrome, but in recognition that some patients with this condition may benefit from a low dose of citalopram, it changed the labeling for this condition from "contraindicated" to "not recommended." The FDA stated citalopram is not recommended for use at doses greater than 40 mg per day, and that the maximum recommended dose for patients older than 60 years of age is 20 mg per day. According to the FDA, citalopram should be discontinued in patients who have persistent QTc measurements greater than 500 ms (FDA, 2012).

Nardi et al. conducted another long-term extension of an earlier study comparing the efficacy and safety of treatment with paroxetine and clonazepam in patients with panic disorder. Results were presented at the 2015 European Psychiatric Association. Adult participants (n=105) entered the long term study during which they received three years of treatment with either clonazepam, paroxetine, or combination of both, followed by a slow tapering of drugs during two-four months. Participants were followed for a period of more than six years. This study found that almost all the patients relapsed during the six-year follow-up period with rates of 41 percent, 77 percent and 94 percent for years one, three and six, respectively. Researchers concluded that "clonazepam and paroxetine were highly effective and well tolerated during acute and chronic treatment and after relapse" and also noted that "clonazepam was consistently better tolerated than paroxetine during all periods." Due to the high relapse rate even after three years, Nardi suggested stopping drugs earlier (Medscape, 2015).

Combined Treatments

In a randomized double blind clinical trial, patients (n=39) with panic disorder with or without agoraphobia were treated with 11 sessions of brief exposure-based CBT augmented with 50 mg d-cycloserine (DCS) or pill placebo (Siegmund et al, 2011). One hour before CBT, patients received the study drug or placebo. Outcome measures included the Panic Disorder Severity Scale (PDSS) and Clinicians' Global Impressions of Severity. There was no statistical difference between DCS and placebo groups in symptom reduction although both groups profited from therapy. More severely ill patients in the DCS group showed greater accelerated symptom reduction than the placebo group. Researchers suggested that DCS augmented CBT for severely ill patients with panic disorder deserves further investigation (Siegmund et al., 2011).

A recent study investigated the feasibility of combining ICBT with supervised and unsupervised physical exercise as treatment for panic disorder (Hovland et al., 2015). After a screening for risk factors related to heart disease, adult patients diagnosed with panic disorder (n=4) were introduced to the therapist, the Internet portal for ICBT, the exercise facility, and an exercise diary. The intervention included guided ICBT combined with 12 weeks of physical exercise, with each week including one supervised and two unsupervised sessions. The therapist both provided the physical exercise therapy and supervised the CBT, which included the following: psycho-education and setting goals for treatment, exposure and behavioral experiments, and plans for relapse prevention. Seventy-five percent of the participants completed all of the physical exercise and half completed all of the ICBT. Participants reported positive change and impact of the combined treatment and no negative impact. Researchers suggested the combination of physical exercise and ICBT is beneficial, and concluded that it is feasible for patients with panic disorder to complete the combined treatment (Hovland et al., 2015).

A recent randomized, double blind controlled study compared the effect of aerobic exercise compared to physical activity with low impact to improve the effect of CBT in patients with panic disorder. Adult patients (n=58), with or without agoraphobia, were randomized to an eight-week

protocol of aerobic exercise or to exercises with very low intensity while receiving group CBT treatment. CBT included interoceptive exposure twice weekly over a one-month period plus one booster session one month later. Examples of interoceptive exposure were one minute running on the spot to increase heart rate and spinning to evoke dizziness, triggering strong symptoms. The therapist encouraged the patients to practice these exercises at home. Patients in the aerobic exercise group performed endurance training on a treadmill over a period of eight weeks (three times a week for thirty minutes each time) while those in the low intensity exercise group performed movements requiring little strain, e.g., stretching the legs for the same amount of time. The exercise program and the group CBT started the same week. Results found no significant difference in number of dropouts or in compliance. When comparing Hamilton Anxiety Rating Scale scores before and after psychotherapy, the two groups did not differ significantly. Results showed "a significant time x group interaction for the primary outcome measure, the Ham-A, revealing further improvement of anxiety over time with a medium-sized effect in the endurance training group, but not in the light exercise group" and was significant at the seven-month follow-up (Gaudlitz, et al., p. 225). Researchers noted this study showed improvements in symptoms of anxiety due to combination CBT and aerobic exercise, not only holding stable, but also increasing over the long run. They concluded that aerobic exercise be considered as a supporting therapy for persons with or without agoraphobia as it can further improve the effects of CBT (Gaudlitz et al., 2015).

Somatic Therapies

A recent systematic review assessed the efficacy and safety of rTMS for panic disorder in persons between 18 and 65 years, either as a monotherapy or augmentation strategy. Included in the review were two randomized controlled trials comparing rTMS with sham. One of the trials reported a superior effect of rTMS compared with sham rTMS in reducing panic symptoms in the participants (n=25), but this trial also showed a high risk of attrition bias (16 percent dropout rate). The other trial reported a reduction in panic symptoms in all participants (n=15) with no significant difference between rTMS and sham rTMS. Researchers concluded that they were unable t o draw any conclusions about the efficacy of rTMS for panic disorder and that further trials with large sample sizes and adequate methodology are needed (Li et al., 2014).

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-5 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).

In the recently published DSM-5, panic disorder and agoraphobia are no longer linked as in DSM-IV (American Psychiatric Association 2013). Panic disorder and agoraphobia are now separate disorders each with its own set of distinct diagnostic criteria. Coding with two diagnoses will be required when panic disorder and agoraphobia are co-occurring. DSM-5 criteria for panic disorder require that at least one of the panic attacks has been followed by at least one month of one or both of the following: 1) worry or persistent concern about additional panic attacks or the consequences of additional attacks, e.g., "going crazy," loss of control or having a heart attack; and 2) significant behavioral change related to panic attacks, e.g., avoidance of unfamiliar situations. According to the DSM-5, panic disorder is not diagnosed when panic attacks are a direct physiological consequence of another medical condition, e.g., hyperparathyroidism. Additionally, the disorder is not diagnosed when panic attacks are a direct physiological consequence of a substance, e.g., cocaine, alcohol or when they occur as a symptom of other anxiety disorders (American Psychiatric Association, 2013).

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 panic disorder 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).

A later study, using a cluster analysis on a small sample of adults (n-36) with a diagnosis of panic disorder, evaluated whether patterns of change during treatment predict future panic symptoms (Steinman et al., 2012). Treatment sessions included 12-weeks of CBT to help participants learn to tolerate bodily sensation fears. Results showed three patterns of change: "initial unstable drop cluster" (symptoms of panic disorder dropped initially but were followed by instability in continuing the gain); "oscillating cluster" (symptoms dropped initially, returned and then dropped again); and "sudden gain" (sudden drop in symptoms initially followed by decline in symptoms). In all three of the change patterns, the total change in panic symptom severity was similar at the end of the 12-week sessions. Researchers found that the level of panic symptom severity in the sudden gain cluster increased from the end of treatment to the six-month follow-up while the severity of symptoms continued to decrease in the oscillating cluster. The highest level of panic symptom severity at six-month follow-up was in the initial unstable drop cluster. Researchers concluded that clusters are predictors of panic symptom severity after termination of treatment and suggested further study to characterize complex change patterns (Steinman et al., 2012).

A recent study examined whether an intolerance of uncertainty (IU) moderated the association between startle potentiation and panic disorder during safety conditions and a threat-of-shock task. Adult participants (n= 74 with diagnoses of panic disorder and n= 98 without panic disorder) were seated in a booth, electrically shielded and sound-attenuated, where they received electric shocks (annoying but not painful) under three "threat conditions:" no shock, shock possible during a cue or shock possible at any time. Participants were aware of the current "threat condition" displayed on a

computer monitor. Startle probes were presented during interstimulus intervals (ISIs), as well as during the cue. Response to startle probes during the ISI was an indicator of safety responding since the ISI condition was between threat conditions and participants knew they were safe from shock during this period. Results showed that participants with panic disorder reported greater IU compared with those without panic disorder. Other results from this study showed that "at high levels of IU, PD was associated with greater startle potentiation during safety. At low levels of IU, PD was not associated with startle potentiation during safety" (Gorka et al., 2014, p. 734). Researchers noted that patients with panic disorder who have high levels of IU may interpret ambiguous information as threatening, failing to inhibit aversive responding in the presence of safety information. They suggested that this subgroup of individuals benefits from exposure-based interventions directly addressing safety and inhibitory learning, and intolerance of uncertainty training (Gorka et al., 2014).

Another recent study examined the role of three cognitive factors, i.e., anxiety sensitivity, catastrophic misinterpretations of benign bodily sensations, and panic self-efficacy, in predicting the severity of panic disorder. Prior to receiving psychological treatment, adults with panic disorder (n=168) completed measures of the cognitive factors. Indicators of panic disorder severity were assessed by the *Anxiety Disorders Diagnostic Interview;* catastrophic misinterpretation of bodily sensations was assessed by the *Panic Catastrophic Misinterpretations Scale;* panic self-efficacy was measured through the *Panic Self-efficacy Scale;* and anxiety sensitivity was assessed using the *Anxiety Sensitivity Index*. Analysis of the data suggested that both anxiety sensitivity and panic self-efficacy uniquely predict the severity panic disorder through cognitive-behavior therapy treatment and that "catastrophic misinterpretation and panic self-efficacy may be mechanisms of change of cognitive-behavior therapy for PD" (Sandin et al., 2015, p. 38). Researchers noted that this study demonstrates that the three factors independently predict PD severity (p. 38) and that their data suggests a comprehensive tripartite cognitive model of panic integrating the three main cognitive factors. They further suggested that cognitive behavior therapy should specifically target increasing the levels of panic self-efficacy while reducing both the increased levels of anxiety sensitivity and catastrophic misinterpretations (Sandin et al., 2015).

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, e.g., whether the medical condition or its treatment may be the primary cause of panic symptoms or may worsen them.

Exploring the basis for the co-occurrence of panic disorder in Parkinson's Disease, researchers examined the familial aggregation of panic disorder in patients with Parkinson's Disease (Pontone et al., 2011). Twenty probands and 115 relatives of patients with both Parkinson's Disease and panic disorder, and 17 control probands and 108 relatives of patients with Parkinson's Disease and no active psychiatric illness were interviewed by phone to determine panic status. Researchers found that the prevalence and odds of panic disorder and panic-like disorder are greater for relatives of probands with Parkinson's Disease and panic disorder than for relatives of probands with Parkinson's Disease and no active psychiatric illness. Suggesting that panic disorder and "panic like" disturbances may be genetically based, they recommended consideration of routine screening for panic phenomena in patients with Parkinson's Disease (Pontone et al., 2011).

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).

As noted earlier, panic disorder and agoraphobia, often co-occurring, are two separate diagnoses in the new DSM-5. A recent study suggested that the development of agoraphobia may be associated with the symptoms and location of a patient's first panic attack (Hara et al., 2012). In this study patients with panic disorder (n=830) were classified into five groups according to the locations, i.e., home, school/office, driving a car, in a public transportation vehicle or outside of home, where they had their first panic attack. Results of the study showed that patients who had their first panic attack while driving a car or while riding in public transportation had a higher incidence of co-morbid agoraphobia than the other groups; the group having their first panic attack at home had a higher frequency of fear of dying compared to the out-of-home group. Researchers suggested that the location of the first panic attack may be linked to the development of agoraphobia and may affect treatment (Hara et al., 2012).

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 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 support, i.e., three therapist e-mails per week, was compared to infrequent support (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).

A later systematic review and meta-analysis investigated the efficacy of guided internet delivered psychological treatments (ICBT) compared with face-to-face CBT in 13 studies, of which three specifically targeted panic disorder (Andersson et al., 2014). Results showed that ICBT and face-to-face CBT are equally effective in panic disorder as well as in other conditions such as social anxiety disorder and depressive symptoms. Authors concluded that "smart phone applications and ICBT will blend in with face-to-face treatment in the near future" and concluded that ICBT is effective and is a potential alternative and complement to face-to-face therapy (Andersson et al., 2014, p. 293).

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). The Netherlands Institute of Mental Health and Addiction has sponsored/initiated a clinical trial, "Don't Panic Online: A Randomised Trial to the Effects of an Internet Based Self-help Course for Reducing Panic Symptoms." This study is based on *Don't Panic* and will evaluate an Internet based self-help intervention for sub-clinical and mild PD compared to a waiting list control group (Ballegooijen et al., 2011).

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 three-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).

In an exploratory study comparing two ways to deliver cognitive behavioral bibliotherapy for panic disorder, researchers cited several studies suggesting the efficacy of bibliotherapy, with or without therapist contact during treatment (Carlbring et al., 2011). Bibliotherapy entails guiding the patient through the course of treatment by the use of a self-help book/manual containing written instructional materials. In this study, researchers tested whether there was a difference in effectiveness among patients with primary diagnosis of PD (n=28) randomized to one of two groups: patients who were assigned a full book with 10 chapters all at once and patients who were gradually provided chapters based on progress (10 paced chapters). The results of the study showed that pacing did not have any clinically relevant effects on the outcome of guided self-help for PD at post-treatment and at two-year follow-up. Researchers concluded that all instructional materials can be provided at once when the treatment is guided by a therapist without the need of pacing (Carlbring et al., 2011).

A quasi-experimental study evaluated the efficacy of two brief CBT interventions in patients with PD presenting to the emergency department with non-cardiac chest pain (Lessard et al., 2011). Researchers presented the following rationale for their study: 1) CBT is first-line treatment for PD according to APA guideline; 2) brief or self-help CBT has been found to be as effective as longer CBT formats; 3) CBT has been shown to be effective treatment for non-cardiac chest pain patients in medical settings; 4) untreated PD may become chronic and 5) patients with PD have the highest rate of emergency department utilization compared to other mental disorders. Patients with PD (n=58) who were discharged from the emergency department with a diagnosis of non-cardiac chest pain were assigned to one of three conditions: one session CBT intervention lasting two hours; seven sessions biweekly CBT lasting a total of seven hours; or usual care control condition involving being informed by the physician that the chest pain was non-cardiac and the possibility of referral for further treatment. Results of this study demonstrated that the two brief CBT interventions were more efficacious than a usual-care control condition on severity of panic disorder at three- and six-month follow-up, and the seven-session intervention was no more efficacious than the one-session CBT intervention. Researchers highlighted the importance of implementing brief psychological interventions in the ED and/or primary care setting for the treatment of panic disorder (Lessard et al., 2011).

A narrative review of published studies examined the efficacy of cognitive-behavioral treatment of panic disorder in brief session interventions (Otto et al., 2012). Based on their review, authors suggested there is potential for providing ultra-brief CBT in a bite-sized or ultra-brief format, allowing non-CBT clinicians to integrate CBT into their practice by beginning with only 10 minutes of CBT during five sessions. They suggested that further research is necessary to determine whether this ultra-brief "foot in the door" technique has advantages over the 12-15 session approach (Otto et al., 2012).

The APA guideline discusses the use of CBT for patients with panic disorder and co-occurring mood disorders, citing studies suggesting that co-occurring major depressive disorder does not adversely affect the response to CBT for panic disorder. In a later evaluation study including patients with panic disorder with and without comorbid axis-one disorder, researchers found that inpatient CBT was equally effective in both groups at discharge as well as at 20 months follow-up (Rathgeb-Fuetsch et al., 2011). They concluded that psychiatric comorbidity should not be an exclusion criterion for inpatient CBT in patients with severe panic disorder.

In a study to determine whether manualized, therapist guided exposure outside the therapy room is associated with more pervasive and long-lasting effects than therapist prescribed CBT, patients with PD and agoraphobia (n=369) were randomized to two manual-based variants of CBT implemented over six weeks or to a wait-list control group over six weeks including 12 sessions (Gloster et al., 2011). CBT variants were identical except for implementation of exposure in situ; in one group, patients completed a therapist-guided exposure before assigned two exposures to complete independently, whereas in the second group, patients received instructions to independently complete all three exposures. Both treatment groups improved significantly more than the control group on outcome measures. Results of this study showed that both the therapist prescribed CBT and the therapist guided CBT led to continued improvement following the end of the six-week period. However, the therapist guided CBT treatment was more effective in overall functioning, decreased panic attacks in the follow-up period and agoraphobic avoidance than therapist prescribed CBT. Researchers suggested that therapist guided CBT mediates an increase in physical engagement in feared situations and promotes additional therapeutic improvement beyond the effects of a CBT treatment in which exposure is only prescribed by the therapist, rather than guided (Gloster et al., 2011).

In a recent study, researchers examined the effects of safety behavior use, e.g., mental distracting, checking vital signs, during everyday life and during exposure-based treatment for panic disorder and agoraphobia using data from the above multi-centered randomized controlled trial by Gloster et al., "Mechanisms of Action in Cognitive Behavioral Therapy" (Helbig-Lang et al., 2014). In this trial, participants with both panic disorder and agoraphobia (n=268) were randomized to 12 sessions of exposure-based CBT carried out weekly. One group (T+) received therapist-guided exposure, while the other group (T-) entered exposure situations without therapist guidance. In analysis of the associations between safety behavior at baseline, measured by the Texas Safety Maneuver Scale (TSMS), and symptom change, researchers found that the more safety behavior at baseline, the higher the improvement in symptoms. They suggested that patients relying on safety behaviors prior to therapy benefitted from the treatment protocol encouraging patients to abandon all safety behavior during treatment. Patients entering the exposure situations without therapist guidance reported higher safety behavior use during the exercise and less improvement in symptoms. Researchers concluded that these results confirm the importance of assessing safety behaviors in patients with panic disorder and agoraphobia and that further research on safety behaviors in daily life and during treatment may improve understanding of mechanisms of change in cognitive behavioral therapy for panic disorder and agoraphobia (Helbig-Lang et al., 2014).

Researchers have conducted recent studies to learn more about how CBT reduces panic symptoms. In a randomized, controlled, multicenter trial, Kircher et al. compared the brain activity of persons (n=42) with panic disorder and agoraphobia before and after 12 twice-weekly sessions of CBT (both therapist guided and non-therapist guided) using functional magnetic resonance imaging (fMRI). Their investigation focused on how CBT influences the neural correlates of fear conditioning in panic disorder/agoraphobia. The CBT fMRI results were compared to the fMRI results from healthy control subjects (n=42). Researchers found that, after CBT, patients showed significant reduction of inferior frontal gyrus (IFG) activity compared to control subjects along with reduction in agoraphobic symptoms. Additionally, they demonstrated increased connectivity between the IFG and "fear network" regions (amygdalae, insulae, anterior cingulated cortex) with CBT inducing a lower level of activity of the fear network. The study demonstrated involvement of the left IFG in both the pathology and psychotherapy of panic disorder and the link between the cerebral correlates of cognitive IFG and fear during symptom improvement. Researchers suggested further research to support the development of more targeted treatments for panic disorder (Kircher et al., 2012).

A more recent longitudinal study including patients (n=49) with panic disorder and agoraphobia, who were receiving twelve CBT sessions twice weekly that focused on behavioral exposure, investigated the potential of fMRI data for CBT response prediction. Researchers concluded that their proof-of-concept study including functional magnetic resonance imaging demonstrated an accuracy of 82 percent with 92 percent sensitivity showing that predicting treatment response to CBT based on whole brain fMRI data is possible and has the potential to bring personalized medicine within reach (Hahn et al., 2015).

A recent randomized controlled switching trial tested the efficacy of an acceptance and commitment therapy (ACT) intervention for adult patients (n=43) with treatment-resistant primary panic disorder and/or agoraphobia (Gloster et al., 2015). Researchers noted that ACT focuses on helping patients observe their symptoms rather than trying to eliminate them, thus abandoning a longstanding and unsuccessful struggle with symptoms. Patients with one or more previous courses of psychological and/or pharmacological treatment were randomized to either immediate treatment of eight sessions (90 – 120 minutes) administered twice weekly over four weeks or a four-week waiting list, and patients were followed up for six months. ACT included the following: "acceptance, present moment awareness, defusion, self-as-context (observer perspective), value clarification, and committed action" (Gloster et al., 2015, p. 102). Outcomes showed that the ACT group improved significantly in terms of the symptoms of panic disorder and agoraphobia compared to the waitlist group.

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.

A recent review of literature examined pharmacological interventions, alone or in combination with psychotherapy, for the treatment of panic disorder (Freire et al., 2014). Authors noted that the World Federation of Societies of Biological Psychiatry (WFSBP) considered the following antidepressants as highest recommended grade in the treatment of panic disorder: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, clomipramine and imipramine. This level of evidence was based on at least two double blind, parallel group, randomized controlled trials showing that the medication was found to be superior to placebo. This level also required that the antidepressants show equivalent or superior efficacy compared with

established comparator treatment in randomized controlled trials. The National Institute for Health and Clinical Excellence (NICE) guidelines indicated the best treatment options for panic disorder included pharmacological interventions with antidepressants (SSRIs as first choice), CBT and self-help. The guidelines indicated that antipsychotic medications should not be prescribed for patients with panic disorder and that benzodiazepines should be avoided in the treatment of panic disorder due to "less good outcome in long term." The NICE guidelines did not acknowledge evidence of venlafaxine's effectiveness in more recent high quality studies. Authors also noted that recent studies have demonstrated that benzodiazepines are safer and more effective than previously reported. Caution should be exercised in prescribing benzodiazepines for long-term use or in patients with current or recent history of substance use disorders. They may be prescribed for short-term, intermittent, acute care. Memon et al. noted that benzodiazepines can be effective in treating residual anxiety symptoms for patients who require rapid symptom control, but the benefit of more rapid response must be assessed against potential complication of benzodiazepine therapy (Medscape, 2015).

Freire et al. discussed recent studies comparing two antidepressants where both drugs were effective showing similar efficacies: sertraline vs paroxetine, sertraline vs imipramine, fluoxetine vs clomipramine, fluoxetine vs mirtazapine, paroxetin vs citalopram, paroxetin vs venlafaxine, citalopram vs escitalopram (Freire et al., 2014). Studies reported tricyclic antidepressants showed faster improvement but more side effects than SSRIs. In their conclusions, they noted that research has provided evidence of the effectiveness of SSRIs, SNRIs, TCAs, and benzodiazepines, and that new compounds, i.e., inositol, duloxetine, mirtazapine, milnacipran and nefazodone may be effective in treating panic disorder. Based on their research, authors suggested that the efficacy of reboxetine and anticonvulsants is controversial, also noting that atypical antipsychotics should not be first choice treatments due to unfavorable side-effect profile.

In its revision of the drug label for citalopram, the FDA advised that citalopram use be avoided in patients with congenital long QT syndrome, but in recognition that some patients with this condition may benefit from a low dose of citalopram, it changed the labeling for this condition from "contraindicated" to "not recommended." The FDA stated citalopram is not recommended for use at doses greater than 40 mg per day, and that the maximum recommended dose for patients older than 60 years of age is 20 mg per day. According to the FDA, citalopram should be discontinued in patients who have persistent QTc measurements greater than 500 ms (FDA, 2012).

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).

A more recent meta-analysis, noting that SSRIs and venlafaxine are currently considered as first-line pharmacological treatments for PD, compared the short-term efficacy and tolerability of newer antidepressants (Andrisano et al., 2013). The meta-analysis, focusing on patients (n=5236) with PD who were treated with citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine, included 50 studies. Results of the study showed that most of the antidepressants investigated were significantly more efficacious than placebo in reducing panic symptoms and anxiety levels. Antidepressants found to be superior to placebo in reducing panic symptoms included citalopram, sertraline, paroxetine, fluoxetine and venlafaxine. In reducing anxiety levels, except for reboxetine and sertraline, all antidepressants were more efficacious than placebo. Paroxetine had the smallest effect and mirtazapine had the largest effect in reducing anxiety symptoms. Reboxetine was the only antidepressant found to be ineffective in treating both panic symptoms and anxiety levels, and the only drugs found to be ineffective in alleviating panic symptoms were mirtazapine and fluvoxamine. Researchers acknowledged that this study was the first to provide information that ranks antidepressants' efficacy for PD symptoms and anxiety. They cautioned that there is a need for more rigorous and double-blind comparison trials to provide reliable data comparing drugs in terms of efficacy and tolerability for the treatment of PD. Researchers stressed that results of their analyses cannot be generalized to periods longer than 12 weeks as their analyses focused only on the acute-phase treatment of PD (Andrisano et al., 2013).

The efficacy and safety of treatment with paroxetine and clonazepam in patients with panic disorder were evaluated in a randomized, open-label, eight-week trial (Nardi et al., 2011). Patients (n=120) were initially randomized to one of two treatment groups: clonazepam 0.5 to 2 mg/d or paroxetine 10 to 40 mg/d. According to the patient's symptoms, dose adjustments were allowed during the eight-week treatment period. By the end of the second treatment week, doses increased to 2 mg/d clonazepam and 40 mg/d paroxetine. Results of the study showed dramatic decrease in the number of weekly panic attacks in both treatment groups which persisted over the eight-week treatment period. Patients treated with paroxetine had significantly more adverse events than those treated with clonazepam, but most adverse events in each group were of mild severity. Researchers concluded that this study confirmed the efficacy and tolerability of both clonazepam and paroxetine in the acute treatment of PD, with clonazepam-treated patients showing greater clinical improvements, faster onset of action, and a more favorable adverse event profile. They acknowledged that this study does not address important problems linked to long-term use of these drugs, e.g., weight gain, sexual dysfunction in SSRIs and abuse or misuse, physical dependence, and withdrawal and rebound symptoms in benzodiazepines (Nardi et al., 2011). In a long-term extension of the study (34 months following the initial eight-weeks), patients with a good outcome during acute treatment continued monotherapy with clonazepam or paroxetine (Nardi et al., 2012). Patients with partial treatment success during acute treatment were switched to combination therapy (paroxetine and clonazepam) and were excluded from statistical comparisons. Researchers concluded that the efficacy of clonazepam and paroxetine in the treatment of PD was maintained during the long term study with clonazepam showing a significant advantage over paroxetine with regard to the frequency/nature of adverse events (Nardi et al., 2012).

Nardi et al. conducted another long-term extension of the above study with results presented at the 2015 European Psychiatric Association. Adult participants (n=105) entered the long term study during which they received three years of treatment with either clonazepam, paroxetine or combination of both, followed by a slow tapering of drugs during two-four months. Participants were followed for a period of more than six years. This study found that almost all the patients relapsed during the six-year follow-up period with rates of 41 percent, 77 percent, and 94 percent for years one, three, and six, respectively. Researchers concluded that "clonazepam and paroxetine were highly effective and well tolerated during acute and chronic treatment and after relapse" and also noted that "clonazepam was consistently better tolerated than paroxetine during all periods." Due to the high relapse rate even after three years, Nardi suggested stopping drugs earlier (Medscape, 2015).

Another study examined the efficacy of 24-week prospective, naturalistic, open-labeled escitalopram treatment in patients with panic disorder (Choi et al., 2012). Patients with PD (n=119) were treated with escitalopram at 5 mg or 10 mg per day initially, increasing up to 20 mg per day. The use of alprazolam or clonazepam was allowed during the first four weeks, but it was tapered off after 12 weeks. Remission was attained by the end of the study in 73.1 percent of patients treated with excitalopram. The response rate increased until the end of the study (from 45.4 percent at week four to 80.6 percent at week 24. Researchers suggest that based on their study, escitalopram treatment should be maintained for more than six months in PD patients, supporting the APA practice guideline which recommend continuing SSRI pharmacotherapy for at least one year for the treatment of PD (Choi et al., 2012).

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 attaches 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).

In a recent review of non-antidepressant pharmacologic long-term treatments of panic disorder, 38 studies were reviewed, including open-label studies, case-reports and review articles as very few randomized-controlled studies were available (Chady et al., 2013). In their review, authors cited several studies of anticonvulsants for the treatment of PD suggesting that valproate seems to show efficacy in treating PD. In a review of GABAergic agents, they found studies reporting the success of gabapentin in the treatment of PD. Both case reports and a double-blind and placebo controlled trial with gabapentin showed significant improvement in patients with severe symptoms of panic disorder. Studies including the use of atypical antipsychotics, e.g., olanzapine and ziprasidone, as augmentation therapy in treatment resistant panic disorder showed reduction of anxiety symptoms. Other agents reviewed included benzodiapepines, i.e., alprazolam and clonazepam, which have been shown to be effective in treating acute panic disorder. However, authors cautioned that significant memory impairment and dependence problems may limit their use. Authors concluded that there is insufficient data to argue a solid alternative to antidepressants in the treatment of panic disorder (Chady et al., 2013).

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 one-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). In a later study, patients (n=169) with panic disorder with or without agoraphobia were randomized to CBT, SSRI or CBT+SSRI (Van Apeldoorn et al., 2013). During a full year of treatment, including three months of medication taper, patients who completed treatment (n=83) kept records of the frequency of panic attacks. Results showed a significant decline in frequency of panic attacks for each treatment modality. Treatment with both SSRI and CBT+SSRI showed a significantly increased rate of improvements as compared to CBT and these gains were maintained after the medication taper. CBT+SSRI treatment was associated with a more rapid improvement in the frequency of panic symptoms as compared to patient receiving CBT or SSRI as monotherapy. Researchers concluded that for patients without agoraphobia, SSRI monotherapy will suffice, but for patients with moderate or severe agoraphobia, CBT+SSRI is the recommended treatment (van Apeldoorn et al., 2013).

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 six to12-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). In a later randomized double blind clinical trial, patients (n=39) with panic disorder and

agoraphobia were treated with 11 sessions of CBT augmented with DCS or placebo (Siegmund et al., 2011). There was no statistical difference between DCS and placebo groups in symptom reduction although both groups profited from therapy. More severely ill patients in the DCS group showed greater accelerated symptom reduction than the placebo group. Researchers suggested that DCS augmented CBT for severely ill patients with panic disorder deserves further investigation (Siegmund et al., 2011).

A randomized, double-blind, placebo-controlled, parallel-group study examined the efficacy of another glutamatergic compound, Org 25935 (4 mg or 12 mg), as augmentation to cognitive-behavioral therapy for panic disorder (Nations et al., 2012). Patients with or without agoraphobia (n=46) were randomized to receive Org 25935 or placebo prior to beginning CBT sessions three, four and five. Results showed no benefit for Org 25935 over placebo in decreasing the severity of panic symptoms. No safety issues were shown at either the 4-mg dose level of the 12-mg dose level (Nations et al., 2012).

A recent study investigated the feasibility of combining ICBT with supervised and unsupervised physical exercise as treatment for panic disorder (Hovland et al., 2015). After a screening for risk factors related to heart disease, adult patients diagnosed with panic disorder (n=4) were introduced to the therapist, the Internet portal for ICBT, the exercise facility and an exercise diary. The intervention included guided ICBT combined with 12 weeks of physical exercise, with each week including one supervised and two unsupervised sessions. The therapist both provided the physical exercise therapy and supervised the CBT, which included the following: psycho-education and setting goals for treatment, exposure and behavioural experiments, and plans for relapse prevention. Seventy-five percent of the participants completed all of the physical exercise and half completed all of the ICBT. Participants reported positive change and impact of the combined treatment and no negative impact. Researchers suggested the combination of physical exercise and ICBT is beneficial, and concluded that it is feasible for patients with panic disorder to complete the combined treatment (Hovland et al., 2015).

A recent randomized, double blind controlled study compared the effect of aerobic exercise or physical activity with low impact to improve the effect of CBT in patients with panic disorder. Adult patients (n=58), with or without agoraphobia, were randomized to an eight-week protocol of aerobic exercise or to exercises with very low intensity while receiving group CBT treatment. CBT included interoceptive exposure twice weekly over a one-month period plus one booster session one-month later. Examples of interoceptive exposure were one minute running on the spot to increase heart rate and spinning to evoke dizziness, triggering strong symptoms. The therapist encouraged the patients to practice these exercises at home. Patients in the aerobic exercise group performed endurance training on a treadmill over a period of eight weeks (three times a week for thirty minutes each time) while those in the low intensity exercise group performed movements requiring little strain, e.g., stretching the legs for the same amount of time. The exercise program and the group CBT started the same week. Results found no significant difference in number of dropouts or in compliance. When comparing Hamilton Anxiety Rating Scale scores before and after psychotherapy, the two groups did not differ significantly. Results showed “a significant time x group interaction for the primary outcome measure, the Ham-A, revealing further improvement of anxiety over time with a medium-sized effect in the endurance training group, but not in the light exercise group” and was significant at the seven-month follow-up (Gaudlitz, et al., p. 225). Researchers noted this study showed improvements in symptoms of anxiety due to combination CBT and aerobic exercise, not only holding stable, but also increasing over the long run. They concluded that aerobic exercise should be considered as a supporting therapy for persons with or without agoraphobia as it can further improve the effects of CBT (Gaudlitz et al., 2015).

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).

A recent systematic review assessed the efficacy and safety of rTMS for panic disorder in persons between 18 and 65 year of age, either as a monotherapy or augmentation strategy. Included in the review were two randomized controlled trials comparing rTMS with sham. One of the trials reported a superior effect of rTMS compared with sham rTMS in reducing panic symptoms in the participants (n=25), but this trial also showed a high risk of attrition bias (16 percent dropout rate). The other trial reported a reduction in panic symptoms in all participants (n=15) with no significant difference between rTMS and sham rTMS. Researcher concluded that they were unable t o draw any conclusions about the efficacy of rTMS for panic disorder and that further trials with large sample sizes and adequate methodology are needed (Li et al., 2014).

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://psychiatryonline.org/guidelines , by calling (800) 368-5777, or by U.S. mail at:

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