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A Risk-Benefit Assessment of Pharmacological Treatments for Panic Disorder

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Summary

Panic disorder, a psychiatric disorder characterised by frequent panic attacks, is the most common anxiety disorder, affecting 2 to 6% of the general population. No one line of treatment has been found to be superior, making a risk-benefit assessment of the treatments available useful for treating patients. Choice of treatment depends on a number of issues, including the adverse effect profile, efficacy and the presence of concomitant syndromes.

Tricyclic antidepressants (TCAs) are beneficial in the treatment of panic disorder. They have a proven efficacy, are affordable and are conveniently administered. Adverse effects, including jitteriness syndrome, bodyweight gain, anticholinergic effects and orthostatic hypotension are commonly associated with TCAs, but can be managed successfully.

Selective serotonin (5-hydroxytryptamine; 5HT) reuptake inhibitors are also potential first line agents and are well tolerated and effective, with a favourable adverse effects profile. There is little risk in overdose or of anticholinergic effects. Adverse effects include sedation, dyspepsia and headache early in treatment, and sexual dysfunction and increased anxiety, but these can be effectively managed with proper dosage escalation and management.

Benzodiazepines are an effective treatment, providing short-term relief of panic-related symptoms. Patients respond to treatment quickly, providing rapid relief of symptoms. Adverse effects include ataxia and drowsiness, and cognitive and psycho-motor impairment. There are reservations over their first-line use because of concerns regarding abuse and dependence.

Monoamine oxidase inhibitors, because of their adverse effects profile, poten-

tial drug interactions, dietary restrictions, gradual onset of effect and overdose risk, are not considered to be first-line agents. They are effective however, and should be considered for patients with refractory disease.

Valproic acid (valproate sodium), while not intensively studied, shows potential for use in panic disorder. More studies are needed in this area before the available data can be confirmed. As a supplement to drug therapy, cognitive behavioural therapy is effective. It is well tolerated, and may be beneficial in certain clinical situations. Its main drawback is the time commitment and effort needed to be made by the patient.

Panic disorder is a major psychiatric disorder characterised by recurrent and unpredictable panic attacks involving a feeling of terrifying fear and extreme discomfort often accompanied by a sense of impending doom. Panic attacks involve a variety of physiological symptoms such as shortness of breath, a smothering sensation, dizziness, sweating, faintness, tachycardia, depersonalisation, numbness, chills, chest pain, choking, nausea and a fear of dying or going crazy. Panic disorder (with and without phobic avoidance) is the most common anxiety disorder, with an estimated lifetime prevalence of 2 to 6% in the general population.[1]

Effective pharmacological treatments for panic disorder have been available since the early 1960s. Current therapeutic options include tricyclic antidepressants (TCAs), selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), benzodiazepines, monoamine oxidase inhibitors (MAOIs) and valproic acid (valproate sodium). Overall, no single agent has demonstrated superior efficacy in the treatment of panic disorder. Selection of an appropriate agent for a particular patient involves consideration of the various risks and benefits of the different treatment options. Thus, a risk-benefit analysis of the available treatments is warranted in order to form rational therapeutic strategies when treating patients with panic disorder.

1. Tricyclic Antidepressants

A role for TCAs in the treatment of panic attacks was first suggested by Klein[2,3] when he observed that imipramine improved anxiety associated with panic attacks. Subsequent double-blind, placebo-controlled studies have shown imipramine to be superior to placebo and equal to alprazolam in reducing panic symptoms.[4-6] Several studies have also demonstrated efficacy of clomipramine in the treatment of panic disorder,[7-9] and 1 study suggested that clomipramine may be superior to imipramine in treating panic symptoms.[10]

Evidence of a dose response relationship for imipramine in the treatment of panic disorder is inconclusive. Two studies[10,11] suggest that optimal response occurs at plasma concentrations between 125 to 150 μg/ml. However, 2 other studies[12,13] showed no relationship between imipramine or desipramine plasma concentrations and therapeutic response. Patients may require lower dosages during maintenance treatment than during acute treatment. Mavissakalian and Perel[14] showed that patients receiving maintenance therapy at half the dose required for acute treatment remained in remission for 12 months. Studies show that the disorder tends to relapse after treatment with TCAs is discontinued;[15] however, the relapse rate is decreased if the dosage is tapered after an 18 month maintenance phase rather than after a 6 month acute treatment phase.[16]

In addition to their proven efficacy in panic disorder, TCAs offer several benefits in the treatment of this condition. Their long half-life allows once daily administration and generic preparations are available which make them affordable for most patients. As many as 60% of patients with panic disorder have comorbid major depression.[17] Nevertheless, there has been 1 study[18] showing that, in patients with panic disorder and comorbid major depression of mild to moderate severity, alprazolam and imipramine were equally effective in

treating both panic and depressive symptoms. One study[19] found that patients treated with imipramine reported less sedation than patients receiving maintenance therapy with alprazolam.

Adverse effects are fairly common with TCAs. In a study of the long term treatment of panic disorder with imipramine, 84% of patients were found to have experienced adverse effects.[20] In 34% of patients, adverse effects were present but not distressing, 23% found adverse effects distressing but tolerable, 10% were very distressed, and 17% found adverse effects intolerable. 20 to 30% of patients with panic disorder experience an amphetamine-like reaction to TCAs.[21] In fact, this adverse effect is the most common reason for early discontinuation of TCA treatment of panic disorder.[20] Symptoms of this so-called 'jitteriness syndrome' include: tachycardia, activation, restlessness, insomnia, tremulousness and apparent intensification of anxiety symptoms in some patients.[22] The symptoms often last between 2 to 3 weeks.[21]

Another difficulty associated with TCAs in the treatment of panic disorder is that once treatment has been started it may take 4 to 6 weeks for the treatment to be effective.[23] Also, it is also important to screen patients for a history of manic or hypomanic symptoms, since all antidepressants may precipitate mania in patients with concomitant bipolar disorder.

Bodyweight gain is the most common reason for discontinuation of TCAs during the maintenance phase of treatment.[20] In 1 naturalistic follow-up study of patients treated with imipramine for 1 to 4 years, women gained an average of 9kg and men gained an average of 12kg.[20] In this study, patients tended to gain more bodyweight the longer they were treated. Nevertheless, 1 double-blind, placebo-controlled study specifically examining bodyweight gain and appetite changes in the treatment of panic disorder, found no bodyweight gain in patients taking imipramine, diazepam or placebo.[24]

Anticholinergic adverse effects, including dry mouth, blurred vision and constipation, are commonly associated with TCAs.[20] Orthostatic hypotension caused by α-adrenoceptor blockade is also common,[20] and can be of particular concern in the elderly and in patients with pre-existing heart disease. Conversely, there is evidence that TCAs can precipitate systemic hypertension in patients with panic disorder. One study[25] compared patients with panic disorder and patients with depression treated with imipramine. Six of 114 patients with panic disorder developed systemic hypertension while none of the patients with depression developed changes in blood pressure. The authors of the study speculated that patients with panic disorder may have cardiovascular disregulation that increases their risk for antidepressant-induced hypertension.

Both men and women can experience impairment in sexual functioning with TCA use.[26] Another disadvantage of using the TCAs is that they are dangerous in overdose. Also, abrupt discontinuation of TCAs can cause a syndrome of cholinergic rebound consisting of upset stomach, nausea, vomiting and abdominal cramping.[26]

There are several strategies for managing TCA adverse effects. Because patients with panic disorder often experience overstimulation and 'jitteriness' during the first 2 to 3 weeks of TCA treatment, it is important to begin therapy with low dosages. Treatment can be initiated with an imipramine dosage of 10 mg/day and the dosage can be increased by 10mg every 2 to 4 days.[27] If this initial dose is tolerated, the dosage can be increased more quickly, e.g. 25mg every few days. If the patient experiences jitteriness, despite a low starting dose, benzodiazepines or β-blockers can be added during the first few weeks of treatment.[21] Jitteriness may also be reduced by giving dividing doses.[10] Because treatment response may not occur until 4 to 6 weeks into treatment, it is important not to abandon a trial too early because of a lack of response.[23] After an initial therapeutic response is achieved, some patients experience a reduction in both adverse effects and therapeutic effect.[23] A dosage increase usually recaptures the therapeutic response but may also be associated with a re-

emergence or increase in adverse effects. Even during the maintenance phase, dosage adjustment may help manage adverse effects. In the long term study conducted by Noyes et al.[20] of imipramine treatment of panic disorder, 25 of 33 patients experiencing adverse effects successfully reduced their dosage while maintaining clinical benefit. One can limit anticholinergic adverse effects by choosing a TCA, such as nortriptyline or desipramine, which is less likely than amitriptyline or imipramine to cause these adverse effects.

In summary, TCAs are clearly beneficial in the treatment of panic disorder. In addition, these agents are affordable and can be conveniently administered. The main limitations of their use in the treatment of panic disorder include their gradual onset of action, the constellation of adverse effects, and their potential risks in overdose. The TCAs provide a reasonable approach in the treatment of panic disorder, as long as the treating physician screens patients properly for complicating psychiatric and medical illness and manages adverse effects appropriately.

2. Selective Serotonin Reuptake Inhibitors

To date, the SSRIs have been less extensively studied than TCAs in the treatment of panic disorder, but the studies available indicate that they are well tolerated and effective. Although noradrenergic function has been central to theories of the pathophysiology of panic disorder, the effectiveness of SSRIs in panic has caused researchers to consider that panic disorder may in part be related to an inability to regulate perturbations in CNS serotonin neurotransmission.[28] Fluvoxamine and paroxetine have been shown to be effective in panic disorder in double-blind, placebo-controlled trials.[22,29-31] Fluvoxamine was also shown to be superior to placebo in controlling yohimbine-induced panic attacks.[32] Open studies have suggested that fluoxetine is effective in treating panic disorder.[33,34]

SSRIs are generally well tolerated, are relatively safe in overdose, and do not produce anticholinergic adverse effects in most patients. In addition, they have not been shown to cause postural hypotension or systemic hypertension.

In treatment trials, patients have experienced sedation, dyspepsia and headache early in treatment.[30] These adverse effects usually diminish as treatment continues.[30] Sexual dysfunction has been reported in patients treated with SSRIs for depression.[24] Yohimbine or the dopaminergic agonist amantadine have been used as adjunctive agents to treat sexual dysfunction associated with the use of SSRIs.[35] Another disadvantage of SSRIs is the fact that abrupt withdrawal can cause a discontinuation syndrome consisting of dizziness, inco-ordination, headache, nausea and irritability.[36] These symptoms appear to peak at day 5 after discontinuation. Like all antidepressants, SSRIs have the potential to induce mania in patients with bipolar disorder. As with the TCAs, therapeutic response to the SSRIs may not occur for 3 to 6 weeks.[37]

The major problem observed with the SSRIs has been increased anxiety during the initiation of treatment. Patients experience, in the main, a feeling of jitteriness, but also restlessness, agitation and insomnia if treatment with an SSRI is started too aggressively.[35] This can lead to noncompliance or discontinuation of the treatment regimen. This adverse effect can be managed by beginning treatment with low dosages and gradually increasing the dosage to a therapeutic level over several weeks. Daily dosages of 5 to 10mg fluoxetine, 25 to 50mg sertraline, 10mg paroxetine and 25mg fluvoxamine are appropriate initiation dosages.[35] For patients who cannot even tolerate these dosages the dosage can be further decreased. Fluoxetine can be started at 2 to 5 mg/day by using elixir or by having patients dissolve the contents of the capsule in water, apple juice or cranberry juice.[27] Fluoxetine is stable in solution for several weeks.[27] The dosage can be increased by 2mg every 2 to 3 days. Although some patients may require dosages higher than 20 mg/day, some patients will respond to lower dosages.[25]

In summary, even though SSRIs have been less well studied in panic disorder than TCAs, their favourable adverse effect profile makes them viable first-line agents. In addition, these agents present little risk of physical complications or danger in overdose. To optimise therapy, proper dose escalation and adverse effect management should be followed.

3. Benzodiazepines

Benzodiazepines are commonly prescribed medications. Benzodiazepines are effective in the treatment of panic disorder. They have been extensively studied in the short term relief of panic-related symptoms with some investigation of their long term efficacy.[38] No evidence has been presented that shows that any one benzodiazepine is more effective than another, when adequate an dosage is used.[39] However, choosing the correct benzodiazepine depends primarily on the pharmacokinetic properties and tolerability of the medication.

The prototypic benzodiazepine in the treatment of panic disorder, alprazolam, has been extensively studied in short term, double-blind, placebo-controlled studies in patients with panic disorder.[38,40] Moreover, alprazolam is currently the only benzodiazepine approved by the US Food and Drug Administration for the treatment of panic disorder. This medication is approved for use in dosages of up to 10 mg/day. The usual starting adult dosage of alprazolam is between 0.25mg and 0.5mg, administered 4 times daily. A maintenance dosage of 2 to 6 mg/day has generally been reported to be the most efficacious. However, dosages closer to 6 mg/day have been found to be more effective by some investigators,[40] whereas other investigators found that dosages closer to 6 mg/day produced higher rates of treatment discontinuation due to adverse effects.[33] Dosages of >6 mg/day in patients with nonresponsive panic disorder are usually inadvisable if a family history of chemical dependence is present.[41] The need for higher dosages may indicate a rapidly increasing tolerance to the medication.[27] Also, the short half-life of alprazolam increases the likelihood of interdose recurrence of symptoms.[42] Alprazolam is effective in the short term treatment of panic symptoms; however, its long term efficacy requires further study in controlled trials.

Clonazepam is a high-potency benzodiazepine with anticonvulsant activity. Comparison studies indicate that clonazepam is approximately twice as potent as alprazolam on a mg per mg basis.[33,41,43-45] Clonazepam can usually be administered on a 4 or 2 times a day schedule. Studies suggest that clonazepam is an effective treatment for anxiety-related disorders.[41,42,46-52] In addition, the long half-life of clonazepam minimises the risk of interdose rebound anxiety which may be seen with alprazolam.

The major therapeutic benefit of benzodiazepines is that most patients respond to treatment rapidly. A response can be seen as quickly as 1 to 2 hours after initial dose. This initial response provides temporary relief of symptoms with the greater improvement occurring between 1 and 2 weeks of treatment. Increasing efficacy has been reported 4 to 6 weeks into treatment with benzodiazepines.[42] If a particular benzodiazepine is not effective, the patient may respond to an alternative benzodiazepine. The benzodiazepine used first usually depends on clinical circumstances. For example, the short half-life of alprazolam may pose problems if the patient misses doses or has recurrence of interdose symptoms. It is very important to investigate all the symptoms of the patients before the most beneficial benzodiazepine is chosen.

The most common adverse effects associated with alprazolam and clonazepam are transient ataxia and drowsiness.[38] It has been suggested that treatment emergent depression is associated with benzodiazepines, but this relationship has been poorly studied.[22,42] On the other hand, panic, anxiety and phobias have been associated as prodromes to depression and are frequently comorbid with major depression.[53-55] Thus, the relationship between benzodiazepine use and treatment emer-

gent depression maybe more coincidental than causal.

Another problematic factor associated with benzodiazepine treatment is cognitive and psychomotor impairment[56] which may be associated with the finding that patients who had received long term treatment with benzodiazepines showed greater ventricle-to-brain ratios on brain computed tomography scans compared with healthy controls.[57] There is a need for more research because this study did not control for psychiatric illness. In the later study, healthy controls showed cognitive and psychomotor impairments when they received high dosages of benzodiazepines.[57] Interestingly, there has been no evidence of these deficits in individuals with panic disorder taking long term benzodiazepine treatment.[57] It has been reported that acute cognitive effects occur less frequently in panic disorder patients than in healthy controls.[58] No long term study, i.e for 6 months or more, of the cognitive and psychomotor effects of benzodiazepine effects on panic disorder patients have been performed.[59] Further research needs to be completed examining the cognitive and psychomotor impairments associated with use of benzodiazepines.

All benzodiazepines produce some degree of physiological dependence, and therefore withdrawal symptoms are seen when they are abruptly discontinued.[42] Clonazepam has greater receptor affinity and therefore has been shown to be twice as potent at the benzodiazepine receptor when compared with alprazolam.[33,41,43-45] It has been hypothesised that the higher potency of clonazepam coupled with its long half-life allows easier tapering of the dosage of this agent. These pharmacological factors could mean that clonazepam is associated with less symptoms of withdrawal than are associated with other benzodiazepines when they are tapered.

The major risk of benzodiazepine therapy is the abuse potential associated with their long term use. Benzodiazepines are subject to control under the US Federal Controlled Substances Act of 1970. The risk of abuse is greatest in individuals with a personal history of substance abuse or dependence.[27] The risk of abuse may also be associated with individuals having a positive family history of substance use disorders. Patients who have first-degree relatives with substance use disorders, as defined by DSM IV,[60] are also vulnerable to benzodiazepine abuse.[61] Thus, the use of benzodiazepines in individuals with a personal history of substance abuse should be avoided unless all other treatment strategies are unsuccessful. Cautious use of benzodiazepines is important when family history is positive. Furthermore, a detailed personal history is pertinent to the treatment strategy of benzodiazepines in panic disorder patients.

A common problem is how to prevent long term use of benzodiazepines. There are no controlled studies evaluating safety and effectiveness of long term (i.e. >6 months) benzodiazepine use.[39] Furthermore, when discontinuing benzodiazepines, re-emergence of previously treated panic symptoms may be difficult to distinguish from withdrawal symptoms. However, recent evidence suggests that gradual tapering of benzodiazepine dosage minimises withdrawal symptoms, as well as the recurrence of panic symptoms. For example, a study has shown that as many as 35% of patients may experience withdrawal symptoms following rapid discontinuation of a benzodiazepine.[62] In contrast, slow tapering of medication, over 12 to 16 weeks, results in a decrease in clinically significant withdrawal symptoms, from 35% to 6%.[63] In addition, Woods et al.[64] have reported that adding an antidepressant prior to tapering maintenance benzodiazepine treatment proved helpful in decreasing the likelihood of panic disorder symptom recurrence. In this study,[64] if benzodiazepine dosages were rapidly tapered and antidepressant treatment initiated, the re-emergence of panic and anxiety symptoms was very similar to abruptly stopping the benzodiazepine treatment without starting antidepressant treatment.[64] Thus, a slow taper in dosage over at least 6 to 10 weeks appears to be the most useful strategy for patients requiring discontinuation of benzodiazepines.

Benzodiazepines are not typically prescribed as first-line antipanic drugs because of concerns regarding abuse and dependence.[27] The majority of patients are prescribed benzodiazepines for short term anxiolytic or hypnotic effects. A smaller number of patients are prescribed benzodiazepines for long term treatment of panic disorder. If rapid relief of panic-related symptoms is desired, as in acute situations, benzodiazepines are considered the preferential agents. Benzodiazepines can be used in combination with antidepressants to provide acute relief until the antidepressant takes full effect, after which the benzodiazepine can be tapered. SSRIs and TCAs are usually first-line panic disorder treatments, but when these treatments fail, the use of a benzodiazepine has benefits which outweigh the associated risks. Adverse effects of the first-line antipanic medications (SSRIs and TCAs) provide a need for alternative medications. Moreover, 25 to 35% of patients with panic disorder do not respond to SSRI and TCA treatment because of overstimulation or nonresponse.[27]

In summary, careful use of benzodiazepines with and without antidepressants has been shown to be a well tolerated and effective alternative to TCAs and SSRIs in the treatment of panic disorder.

4. Monoamine Oxidase Inhibitors

MAOIs have demonstrated efficacy in the treatment of panic disorder.[65-67] It has been suggested that these agents may be more effective in individuals with treatment resistant symptoms.[27] In addition, they may be more effective than TCAs for relief of phobic anxiety.[68] Of the MAOIs, phenelzine has been studied the most thoroughly in panic disorder, and large placebo-controlled studies have confirmed its efficacy in this condition.[17,69-71] Phenelzine and the other MAOIs have a favourable risk-benefit ratio that should be considered by all clinicians. Benefits of MAOIs include established efficacy, single or twice daily administration, antidepressant action and the availability of inexpensive generic preparations.

Common adverse effects of MAOIs include bodyweight gain, insomnia, orthostatic hypotension, oedema and sexual dysfunction.[72] The most treatment-limiting adverse effect is night-time insomnia with day-time lethargy.[73] Administration of doses early in the day, with the latest dose given by mid-afternoon often minimises this adverse effect. Alternatively, administering the medication at bedtime, occasionally and paradoxically minimises insomnia.

The MAOIs are also associated with potentially lethal reactions when the agents are taken with certain other medications and certain foods.[72] Concurrent administration of MAOIs and TCAs, pethidine (meperidine), SSRIs and trazodone can cause the serotonin syndrome which produces confusion, restlessness, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea and fever.[72] Also, concomitant administration of MAOIs and sympathomimetics (e.g. amphetamines, pseudoephedrine, phenylephrine and levodopa) or a tyramine-containing food (e.g. sauerkraut, aged cheese, beer, red wines) can cause a hypertensive crisis which is manifested by hypertension, severe headache, stiff neck, nausea and vomiting.[72] Because of these potential reactions, the use of MAOIs is limited by concomitant drug administration and strict mandatory dietary restrictions. MAOIs may be underused in the US because of these concerns, but the vast majority of patients with panic disorder are careful about adhering to dietary restrictions.[66] Clinicians are now looking towards the safer and better tolerated MAOIs known as reversible monoamine oxidase inhibitors of monoamine oxidase A (RIMAs). The RIMA brofaromine has shown antipanic effects in open and controlled studies.[34] However, RIMAs are currently not available in the US.

Other disadvantages of using the MAOIs include a gradual onset of action, requiring several weeks to see therapeutic benefits, and the potential risks when these agents are taken in overdose.

In summary, MAOIs are considered second or third line agents for the treatment of panic disorder because of their adverse effect profile, need for dietary restrictions, potential drug interactions, gradual onset of effect and risk in overdose. MAOIs

have been shown to be effective for the treatment of panic disorders and despite the adverse effect profile, these agents should be considered as a treatment option for the refractory variant of the disorder.

5. Valproic Acid (Valproate Sodium)

The antimanic and anticonvulsant agent valproic acid has been studied in the treatment of panic disorder based on several lines of evidence. First, valproic acid increases brain γ-aminobutyric acid (GABA) activity.[74] Studies in animals and humans have demonstrated that at least 1 class of drugs, the benzodiazepines, which enhance central GABAergic activity, exert anxiolytic effects.[75] Second, in preclinical studies, valproic acid has been found to exert anxiolytic effects comparable to those produced by benzodiazepines.[76] Third, fear and panic-like reactions can be triggered by electrical stimulation of limbic and temporal-lobe structures in humans[77] and auras resembling panic attacks have been described by some patients with complex partial-seizure disorders arising from these same brain regions.[78] Thus, the anticonvulsant activity of valproic acid in these brain regions was also thought to potentially serve as the mechanism for possible antipanic activity.[53]

To date, 3 case reports (Roy-Byrne,[79] McElroy et al.,[80] Roberts et al.[81]), 3 open trials (Primeau et al.,[82] Keck et al.,[83,84] Woodman and Noyes[85]) and 1 small placebo-controlled study (Lum et al.[86]) have suggested that valproic acid may be effective in the treatment of panic disorder. In the first open series reported, Primeau et al.[82] treated 10 patients with valproic acid (titrated to a maximum dosage of 2250 ng/day) for 7 weeks after a 1-week placebo washout. Significant improvement was found at the end of the 7-week treatment period compared with baseline on the Clinical Global Impression (CGI) Scale,[87] the Hamilton Anxiety Rating Scale (HARS)[88] and the panic factor of the Symptom Checklist-90.[89] Six of the 10 patients were at least moderately improved as measured by changes in the CGI scale and the panic factor of the SCL-90.

In the second open series, Keck et al.[83] treated 16 patients with valproic acid (17 mg/kg/day) for 28 days who also underwent lactate infusion before and after treatment. Of the 14 patients completing the 28-day trial, 10 (71%) displayed a >50% reduction in the weekly frequency of panic attacks as recorded by diary and 6 (43%) experienced complete remission. HARS scores also dropped significantly from a baseline mean of 30.8 ± 9.4 to 12.6 ± 7 after 4 weeks of treatment. Furthermore, valproic acid blocked reinduction of panic symptoms on lactate rechallenge in 10 (83%) of 12 patients who had initially experienced panic attacks with lactate provocation. Interestingly, Balon et al.[90] have reported that intravenous infusion of lactate produced a decrease in circulating plasma GABA levels which are thought to reflect changes in central GABA metabolism. Thus, it is possible that valproic acid may prevent lactate induction of panic attacks by its GABAergic activity.

In the third open series, Woodman and Noyes[85] administered valproic acid for a 6 week trial in 12 patients with panic disorder. Response was rated using the CGI scale, HARS, a panic diary and the Brief Symptom Inventory (BSI).[91] Panic disorder in all 12 patients was moderately to markedly improved by the end of the 6 week trial. Interestingly, 11 (92%) of the 12 patients continued to take valproic acid as long term maintenance therapy and continued to obtain a sustained response.

The results of these open trials should be considered with several caveats. The favourable response rates may have been subject to rater or patient bias and also to placebo response.[84] The results of the only placebo-controlled, double-blind, crossover study are therefore of particular interest. In this study, Lum and colleagues[86] reported statistically significant improvement in measures of duration and intensity of panic attacks, CGI scale and HARS scores in 12 patients during valproic acid treatment. However, the effect of valproic acid on the frequency of panic attacks was not described.

In the studies outlined above, valproic acid response was not associated with the presence, when

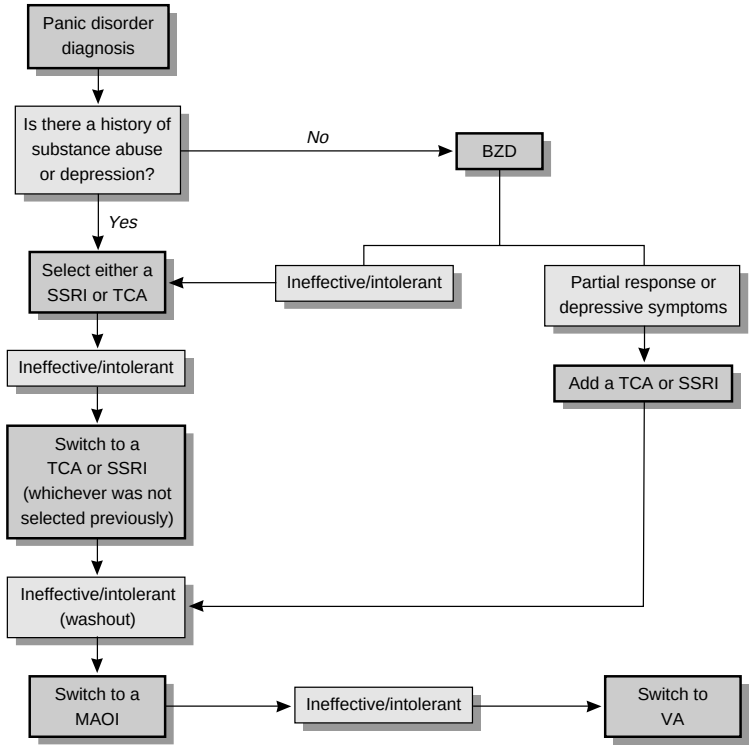

Fig. 1. A systematic approach to the treatment of panic disorder. *Abbreviations:* BZD = benzodiazepine; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor; TCA = tricyclic antidepressant; VA = valproic acid (valproate sodium).

assessed, of EEG abnormalities. Overall, the drug was well tolerated with reported adverse effects arising in <25% of patients. Valproic acid has a favourable adverse effect profile and has no abuse liability or dependence. Its onset of action in panic disorder appears to be within 1 to 2 weeks and thus may be intermediate between the more rapid onset of benzodiazepines and the more gradual onset associated with the TCAs and SSRIs.

In summary, this small group of studies should be regarded as preliminary support for the use of valproic acid in panic disorder. Further placebo-controlled, parallel-designed studies with larger sample sizes are needed to confirm these data.

6. Psychotherapy

There is growing evidence demonstrating the effectiveness of cognitive behavioural therapy (CBT) in the treatment of panic disorder. The main components of CBT include informational intervention, somatic management skills, including breathing and relaxation skills, cognitive restructuring, interoceptive exposure and situational exposure.

CBT has many advantages. CBT is found to be well tolerated with a low discontinuation rate of 6%.[46] Also, a meta-analysis[46] has revealed a greater retention of treatment effect with the combination of CBT and pharmacotherapy as compared with pharmacotherapy alone. CBT may also be beneficial in certain clinical situations. For example, the combination of benzodiazepines during early CBT may provide more rapid relief than CBT alone. This combination has also been shown to be helpful when patients are being withdrawn from benzodiazepine treatment.[46]

The main drawback of CBT is the time commitment and effort needed on the part of the patient. Also many barriers exist limiting the use of CBT. Some of the barriers include lack of funding, limited long term studies, and lack of practitioner's knowledge about adjunctive treatments.[92]

While drug therapy remains an important element of effective treatment of panic disorder for the majority of patients, CBT has become an important tool in this condition by augmenting the efficacy of pharmacological treatment.

7. Conclusion

Panic disorder is a terrifying, debilitating condition. It is the most common anxiety disorder occurring with a lifetime prevalence of 2 to 6% in the general population. Effective treatment approaches to panic disorder include the use of TCAs, SSRIs, benzodiazepines, MAOIs and valproic acid. Choice of treatment should be determined by a variety of issues including adverse effects, time course of efficacy, suicide potential, concerns about withdrawal reactions and the presence of concomitant syndromes such as major depression, substance abuse, cardiovascular disease or bipolar disorder. An algorithm for the systematic approach to treatment of panic disorder is presented in figure 1, but the skilful use of each treatment requires a careful assessment of risks and benefits as outlined in this article.

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