Serotonin and panic

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Background Tricyclic (TCA) and monoamine oxidase inhibitor (MAOI) antidepressants are effective in the treatment of panic disorder. Two selective serotonin reuptake inhibitors (SSRIs) have also been licensed in the UK for this indication and studies with three other SSRIs have recently been completed. These provide further evidence for the role of serotonin in panic.

Method Review of clinical, animal and laboratory studies.

Results SSRIs have been shown to be effective in the treatment of panic disorder. The reported rates of improvement of 60–70% of patients taking SSRIs are similar to those seen with TCAs and greater than placebo. Other serotonergic agents do not appear to be effective. Animal work and human studies including measures of 5-HT in plasma, cerebrospinal fluid and platelets, challenge paradigms and tryptophan depletion show that the relationship between 5-HT and anxiety is complex.

Conclusion Clinical trials have shown that of all the serotonergic agents only the SSRIs are effective in panic disorder. They are as beneficial as the TCAs and seem to be better tolerated which may be particularly significant in view of the chronic nature of the condition. Serotonin plays a role in panic disorder and serotonergic dysfunction, however the results and evidence do not fit one theory alone. It is also likely that different brain regions and 5-HT receptors are involved in specific ways.

Interest in panic disorder has flourished over the past 20 years and as a consequence a variety of treatments are now available to the clinician. These include pharmacotherapy with tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and benzodiazepines, and psychological approaches with behaviour and cognitive–behavioural therapy. Clinical research now suggests that the selective serotonin reuptake inhibitors (SSRIs) are also effective. The development of treatments has been paralleled by advances in understanding the biology of panic (Nutt & Lawson, 1992). An underlying serotonergic dysfunction has long been postulated to be important although a working understanding of the mechanisms involved has remained elusive. The recent discovery of multiple receptor subtypes has allowed a more careful dissection of the abnormalities found in the condition.

CLINICAL EFFICACY

TCAs and MAOIs

The drug treatment of panic disorder originates from the 1960s, with reports that the TCA, imipramine and the MAOIs in general were effective in relieving panic symptoms. These were known to have powerful effects on both serotonergic (5-HT) and noradrenergic systems although the relative contribution of each to their efficacy was unclear. The MAOIs were not widely used (because of the requirement for dietary restrictions, the risk of interaction with other drugs and their poor tolerability) which meant that most studies were carried out with the tricyclic and heterocyclic groups of antidepressants. Of these, imipramine has been the most extensively studied with numerous trials confirming the initial reports of efficacy. Similar results have also been reported for clomipramine which is the most serotonergic of the TCAs, but the case for the efficacy of other TCAs is less strong. Although there have been positive reports, for example, for lofepramine (which led to it being licensed in Eire), the general trend suggests that noradrenergic agents (e.g. maprotiline) are less effective than serotonergic agents (Johnson *et al*, 1995).

SSRIs

The clinical potential of serotonergic agents arose from observations of the efficacy of other antidepressants. The development of the SSRIs over recent years has provided the tools to further examine the role serotonin plays in panic disorder. A summary of the controlled studies with SSRIs is shown in Table 1.

Zimeldine

Uncontrolled studies in the early 1980s suggested that the first SSRI available, zimeldine, was beneficial in phobic anxiety. These findings were confirmed by the one small, double-blind, controlled study that was performed before this drug was withdrawn. This compared zimeldine 150 mg/day with imipramine 150 mg/day and placebo over six weeks (Evans *et al*, 1986). Interestingly, in this study zimeldine was actually found to be superior to the comparator, imipramine although this is one of the few reports that found imipramine to be no more effective than placebo.

Fluvoxamine

The anti-panic efficacy of fluvoxamine has been demonstrated by several controlled studies lasting from six weeks to 12 months. These compared fluvoxamine 100–150 mg/day with placebo (Hoehn-Saric *et al*, 1993), clomipramine 150 mg/day (den Boer *et al*, 1987), imipramine (Bakish *et al*, 1994), the noradrenergic TCA, maprotiline 150 mg/day (den Boer & Westenberg, 1988), the reversible monoamine inhibitor, brofaromine 50–150 mg/day (van Vliet *et al*, 1996) and the 5-HT_2 antagonist, ritanserin (den Boer & Westenberg, 1990). They have generally confirmed efficacy, with 50–61% of subjects on fluvoxamine reporting improvements in panic symptoms compared with 20–42% of subjects on placebo. Two studies compared fluvoxamine with psychological treatments, that is, behaviour (de Beurs *et al*, 1995) and cognitive therapy (Black *et al*, 1993). These showed that fluvoxamine was superior to both psychological treatments on many measures but overall the most

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Table I Selective serotonin reuptake inhibitor (SSRI) studies in subjects with panic disorder

Authors	*n*	Trial	SSRI and dose (mg/day)	Length of treatment (weeks)	Response
Evans *et al*, 1986	44	Zimeldine or imipramine *v.* placebo	Zimeldine 150, imipramine 150	6	Zimeldine > imipramine=placebo
Hoehn-Saric *et al*, 1993	50	Fluvoxamine *v.* placebo	Fluvoxamine 100–150	8	Fluvoxamine > placebo
den Boer & Westenberg, 1988	44	Fluvoxamine *v.* maprotiline	Fluvoxamine 150, maprotiline 150	6	Fluvoxamine > maprotiline
de Beurs *et al*, 1995	96	Fluvoxamine or psychological treatment *v.* placebo	Fluvoxamine 100–150	12	Fluvoxamine > psychological > placebo
Black *et al*, 1993	75	Fluvoxamine or cognitive therapy *v.* placebo	Fluvoxamine up to 300	8	Fluvoxamine > cognitive–behavioural therapy > placebo
Bakish *et al*, 1994	54	Fluvoxamine, imipramine and placebo	Fluvoxamine and imipramine, both up to 300	8	Fluvoxamine=imipramine > placebo
van Vliet *et al*, 1996	30	Fluvoxamine or brofaromine	Fluvoxamine 150, brofaromine 150	12	Fluvoxamine=brofaromine
Dunbar *et al*, 1995	278	Paroxetine *v.* placebo	Paroxetine 10, 20 and 40	10	Paroxetine (40 mg/day) > placebo
Oehrberg *et al*, 1995	129	Cognitive therapy with paroxetine or with placebo	Paroxetine 20, 40 or 60	12	Paroxetine+cognitive therapy > placebo+cognitive therapy
Lecrubier *et al*, 1997*a*	367	Paroxetine or clomipramine *v.* placebo	Paroxetine 20–60, clomipramine 50–150	12	Paroxetine=clomipramine > placebo. Paroxetine more rapid onset of action
Lecrubier *et al*, 1997*b*	180	Paroxetine or clomipramine *v.* placebo	Paroxetine 20–60, clomipramine 50–150	48	Paroxetine=clomipramine > placebo. Paroxetine better tolerated than clomipramine

powerful effects were seen when drug and psychological treatments were combined.

Paroxetine

Paroxetine was the first SSRI to be licensed for the treatment of panic disorder after several clinical trials. A dose-ranging study over 10 weeks compared paroxetine (10, 20 and 40 mg/day) with placebo (Dunbar *et al*, 1995) and showed response rates (reduction of panic attacks to zero) of 76% for the subjects on paroxetine 40 mg/day compared with 40% for the subjects on placebo. Similar improvements were achieved in a large (367 subjects), multi-centre, placebo-controlled comparative study with paroxetine 20–60 mg/day and clomipramine 50–150 mg/day over 12 weeks (Lecrubier *et al*, 1997*a*). In this 76% of subjects on paroxetine, 65% on clomipramine and 60% on placebo showed a >50% reduction in the number of panic attacks by the end of treatment. Overall, paroxetine and clomipramine were found to be equally effective but paroxetine appeared to be better tolerated and to have a more rapid onset of action (by weeks 4–6 of treatment compared to weeks 10–12 for clomipramine). Subjects who completed this trial were given the opportunity to continue their treatment for a further 36 weeks, the results of which confirmed the efficacy and tolerability findings of the short-term study (Lecrubier *et al*, 1997*b*).

Sertraline

The efficacy of sertraline (50–200 mg/day) was suggested by open reports and has been further tested in four double-blind, placebo-controlled trials. These lasted for 10–12 weeks and showed significantly greater reductions in panic attack frequency for sertraline (65–79%) compared to placebo (39–59%). A large, multi-centre, randomised, controlled study comparing sertraline (50–200 mg/day) with imipramine (100–200 mg/day) and placebo has just been completed but results are not yet available.

Fluoxetine

Open trials with fluoxetine also suggested efficacy for this SSRI (Schneier *et al*, 1990). In these up to 76% of subjects experienced a moderate to marked improvement in panic attacks although there were a large number of drop-outs because of a jitteriness syndrome precipitated by the use of full doses of fluoxetine (20 mg/day) from the start of treatment. A large, multi-centre, randomised, controlled study comparing fluoxetine (20–40 mg/day) with clomipramine (100–150 mg/day) and placebo has just been completed but results are not yet available.

Citalopram

Open studies with citalopram have also suggested efficacy for this SSRI. This has recently been confirmed by a double-blind comparator study with citalopram (10–60 mg/day) and clomipramine (60–90 mg/day) over eight weeks (Wade *et al*, 1997) with a continuation phase of a further 12 months of treatment. These showed that citalopram (at doses above 20 mg/day) and clomipramine both resulted in similar improvements and were superior to placebo. As a result of these studies, citalopram has now also been licensed for the treatment of panic disorder.

Other serotonergic agents

The data on the efficacy of serotonergic drugs other than SSRIs in panic disorder are more equivocal.

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Serotonin noradrenaline reuptake inhibitors

Venlafaxine is an antidepressant that has recently been released which blocks the reuptake of both 5-HT and noradrenaline with few effects on other neurotransmitter systems. Its pharmacological profile therefore suggests that it may be useful in panic disorder although controlled studies have not yet confirmed this.

5-HT_{1a} agonists

Although the 5-HT_{1a} partial agonists, for example, buspirone, gepirone and ipsapirone have been shown to be beneficial in the treatment of generalised anxiety, evidence regarding their efficacy in panic disorder is conflicting. Buspirone was found to be ineffective as an anti-panic agent in a placebo-controlled trial (Sheehan *et al*, 1993). Another partial 1a agonist, gepirone, did reduce panic frequency in an open trial but flesinoxan, a full 5-HT_{1a} agonist, was found to result in a worsening of anxiety symptoms in the only study performed (Westenberg *et al*, 1992).

5-HT_2 antagonists

The 5-HT_2 antagonist, ritanserin was found to decrease the number of panic attacks and measures of agoraphobic avoidance in a four-week open trial in 11 people with panic disorder. This efficacy was not confirmed, however, by a larger (60 subject), double-blind comparison with fluvoxamine over eight weeks, when ritanserin appeared to be ineffective (Westenberg & den Boer, 1989).

A preliminary open study with trazodone suggested that this drug might have anti-panic and anti-phobic activity but a larger, double-blind comparison with imipramine and alprazolam showed it to be ineffective (Charney *et al*, 1986).

Nefazodone, a serotonin reuptake inhibitor with 5-HT_2 antagonist actions, was shown to be beneficial in a small open trial of people with panic disorder and comorbid depression. A controlled study is currently underway.

5-HT_3 antagonists

The 5-HT_3 antagonists, for example, ondansetron, do not appear to have significant anti-anxiety effects. Clinical trials in generalised anxiety disorder have been disappointing and as yet no studies have been performed in panic disorder.

Clinical summary

The only serotonergic agents which have been shown to be clearly effective in the treatment of panic disorder are the SSRIs. The rates of 60–70% of subjects improving (variably defined as a reduction in measures of panic symptoms, anxiety and avoidance) are similar to those seen with TCAs and greater than placebo. The placebo response is, however, frequently high (about 40%) emphasising the importance of including a placebo arm in clinical trials. The time course of symptom improvement with both TCAs and SSRIs is similar – there typically being a reduction in panic frequency over the first 3–6 weeks (possibly more rapid with SSRIs) followed later by improvements in phobic avoidance and anticipatory anxiety. The dose-range of medication is wide but doses in the higher range for both TCAs and SSRIs are frequently required. The SSRIs are generally well tolerated and are safer in overdose than the TCAs, both are important issues considering the chronicity of the condition and its association with an increased suicide risk. The problems associated with SSRIs include their characteristic side-effects, for example, nausea, headache, agitation and sexual dysfunction (which may cause some difficulty in maintaining the double-blind in trials), their relatively slow onset of action and their ability (like the TCAs) to cause an exacerbation in anxiety and 'jitteriness' early in treatment (Ramos *et al*, 1993). In this there is an initial worsening of symptoms (increase in anxiety, panic attacks and jitteriness) followed by improvement after 2–3 weeks. Interestingly, the recent clinical trials with the SSRIs have not tended to report this increase in anxiety which may in part be explained by the fact that low doses (half the recommended depression dose) were typically used initially with subsequent gradual titration according to response.

SEROTONERGIC DYSFUNCTION AND PANIC

A relationship between serotonin and anxiety has long been postulated (Nutt & George, 1990), although the mechanisms and abnormalities involved have never been clear. In this section we review the evidence for an underlying serotonergic dysfunction and discuss the two opposing hypotheses for panic disorder that are currently prevalent.

Animal studies

Early animal work suggested that increasing 5-HT resulted in increased anxiety and conversely that reducing 5-HT resulted in reduced anxiety. Examples supporting this included studies in which stimulation of 5-HT neurotransmission resulted in behavioural inhibition (freezing, a response reminiscent of anxiety) and injecting 5-HT into the ventricles of rodents which was found to block the anxiolytic effect of benzodiazepines.

It now appears that the relationship between 5-HT and anxiety is much more complex. Certain areas of the brain seem to be particularly important. These include the periaqueductal grey and amygdala which are both known to contain serotonin nerve endings. Animal studies and reports of humans during stereotaxic brain surgery showed that stimulation at these sites produced anxiety symptoms (Graeff, 1990). Subsequent work suggested that the different brain regions are involved in different aspects of anxiety – the PAG being particularly involved with panic (unconditioned fear) and the amygdala with anticipatory anxiety and avoidance (conditioned fear; Deakin & Graeff, 1991). The responses to 5-HT also appeared to be different. Increased 5-HT (with fenfluramine) in the PAG restrained panic-like responses whereas increased 5-HT in the amygdala was anxiogenic (Graeff *et al*, 1996; see Fig. 1). The receptors involved in each brain area have not been finally determined but recent animal work with newly developed 5-HT_2 agonists have suggested that these agents may have early anti-panic effects possibly through effects on the PAG (Jenck *et al*, 1996). Changes in 5-HT neurotransmission are thus expected to produce effects dependent not only on the direction of change in 5-HT but also the specific site of action.

Plasma, cerebrospinal fluid and platelet measures of 5-HT

No consistent abnormalities in plasma or cerebrospinal fluid 5-HT or its metabolite, 5-hydroxyindoleacetic acid have been reported. Platelet measures of the number and function of 5-HT uptake sites have also been inconsistent but seem to be different from the findings in depression which tend to indicate reduced functioning.

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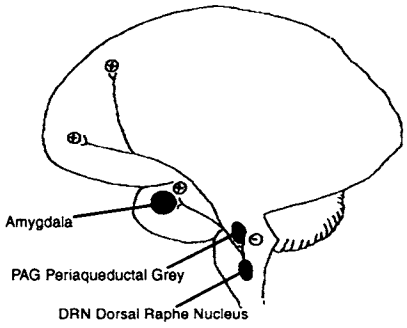


Fig. 1 Increased 5-HT in the periaqueductal grey restrains panic-like responses, whereas in the amygdala it is anxiogenic. −, decreased anxiety; +, increased anxiety.

Challenge studies

5-HT challenge studies examine the neuroendocrine and behavioural consequences of acute administration of drugs which enhance 5-HT transmission. The challenge probes used are precursors, for example, tryptophan or 5-hydroxytryptophan, reuptake blockers such as clomipramine, SSRIs, or fenfluramine (which also causes 5-HT release and has agonist effects) or agonists, for example, methylchlorophenylpiperazine (m-CPP; predominantly 5-HT_{2c} agonist), buspirone and ipsapirone.

Neuroendocrine measures

The hypothalamus and pituitary are densely innervated by 5-HT neurones and produce reliable increases in plasma concentrations of various hormones, for example, prolactin and corticotrophin when activated by 5-HT agents. Measuring the hormone response to 5-HT challenges therefore allows assessment of 5-HT receptor sensitivity in the hypothalamus. Studies with tryptophan and 5-hydroxytryptophan in subjects with panic disorder did not reveal abnormal neuroendocrine responses (Charney *et al*, 1986; Westenberg & den Boer, 1989). However, a racemic mixture fenfluramine produced abnormally elevated cortisol and prolactin responses in subjects with panic disorder compared with controls (Targum & Marshall, 1989) and m-CPP, in low oral doses resulted in an elevated cortisol response compared with controls (Kahn *et al*, 1988). Clomipramine produced no difference in neuroendocrine measures in subjects with panic disorder compared with alcoholics and normal controls (George *et al*, 1995). Only one study has been performed with a 5-HT_{1a} agonist. This challenged subjects with ipsapirone and subjects with reported panic disorder to have a blunted corticotrophin response compared with controls (Lesch *et al*, 1992).

Behavioural measures

Early challenges with tryptophan and 5-hydroxytryptophan did not find subjects with panic disorder to be unusually sensitive and actually reported a decrease in anxiety (Charney *et al*, 1986; Westenberg & den Boer, 1989). Fenfluramine and low oral doses of m-CPP induced panic attacks in subjects with panic disorder but not in controls (Targum & Marshall, 1989). High intravenous doses of m-CPP however, were not discriminative precipitating panic in both patients and normal volunteers (Charney *et al*, 1987). The 5-HT_{1a} agonist, ipsapirone produced no difference in anxiety responses between patients and controls (Lesch *et al*, 1992). The results of the challenge studies are summarised in Table 2.

Treatment studies

Empirically, the strongest support for the involvement of 5-HT in the pathogenesis of panic disorder is provided by the treatment studies described earlier.

Prior to the introduction of the SSRIs, the drugs which were found to be the most consistently effective were those with potent actions on the 5-HT system, that is, imipramine, clomipramine and the MAOIs. They all, however, also had effects on noradrenergic systems and for some time debate centred around the relative contribution of each to efficacy. Recently the picture seems to have become clearer as studies have directly compared SSRIs (fluvoxamine) with noradrenergic TCAs (maprotiline) and demonstrated that only the SSRI was effective at improving panic and anxiety symptoms (Den Boer & Westenberg, 1989). Further evidence suggestive of the role of 5-HT has been provided by a study with imipramine in which response was found to correlate with the plasma concentration of the parent compound (more serotonergic) not that of the more noradrenergic metabolite (N-desmethylimipramine; Mavissakalian & Perel, 1988). These studies confirm the clinical evidence that in general serotonergic agents are more effective than purely noradrenergic ones.

Treatment studies have also given insights into the possible role of different receptors in panic. Early studies with the non-selective 5-HT antagonist, metergoline reported an increase in anxiety in normal controls (Graeff *et al*, 1985). Similarly, a controlled trial with ritanserin, a selective 5-HT_2 antagonist, showed that it did not reduce panic attack frequency (den Boer & Westenberg, 1990), provided no additional benefit when added to an SSRI (Pols *et al*, 1993) and may actually have increased anxiety (Deakin & Graeff, 1991). These

Table 2 Serotonergic challenge studies in subjects with panic disorder compared with normal control subjects

Challenge	Behavioural response Subjects with panic disorder *v.* control subjects	Neuroendocrine response Subjects with panic disorder *v.* control subjects
Tryptophan Charney *et al*, 1986	Decreased anxiety	No difference
5-HTP Westenberg & den Boer, 1989	Decreased anxiety	No difference
Fenfluramine Targum & Marshall, 1989	Increased anxiety	Increased cortisol and prolactin
m-CPP oral Kahn *et al*, 1988	Increased anxiety	Increased cortisol
m-CPP IV Charney *et al*, 1987	Increased anxiety in both groups	No difference
Clomipramine George *et al*, 1995	Increased anxiety	No difference
5-HT_{1a} agonist Lesch *et al*, 1992	No difference	Decreased corticotrophin

5-HTP, 5-hydroxytryptophan; m-CPP, methylchlorophenylpiperazine.

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results argue against the hypothesis that decreasing neurotransmission through 5-HT_2 receptors results in anti-panic.

Although the evidence is limited and difficult to interpret (because of pre- and post-synaptic effects), studies with 5-HT_1 agonists (flesinoxan and to a lesser extent buspirone) do not seem to be effective in panic disorder and may, at least initially, worsen anxiety. The mechanisms involved are not clear but may be through actions at the 5-HT_1 autoreceptor switching off neuronal firing suggesting that reducing 5-HT promotes anxiety.

Tryptophan depletion studies

The role of the 5-HT system in various disorders can be investigated by examining the effects of acute depletion. This was originally achieved 30 years ago in subjects with carcinoid syndrome using parachlorophenylalanine. It blocks the synthesis of 5-HT and in these subjects was found to produce an increase in anxiety (Engelman *et al*, 1967). A similar but better tolerated reduction in 5-HT can be produced by rapidly reducing the availability of the 5-HT precursor, tryptophan and monitoring the results. This is achieved using an amino acid cocktail deficient in tryptophan. In subjects with remitted depression this produced a transient exacerbation of depressive symptoms in those on serotonergic drugs (Delgado *et al*, 1990). Studies in untreated subjects with panic disorder have shown that acute tryptophan depletion does not precipitate panic (Goddard *et al*, 1994) but does make subject more sensitive to challenges with CO_2 (Miller, 1995). Studies in subjects with antidepressant remitted panic disorder are currently underway which should help to clarify the situation.

DISCUSSION

As discussed above there is considerable pharmacological evidence for serotonergic dysfunction in panic disorder although the precise nature of the abnormality remains unresolved. It is also important to remember that the fact that a drug acts on a particular system does not necessarily imply that this is the source of the disorder (heart failure and diuretics). It may be that modulation of 5-HT brings about changes in other systems which are abnormal without there necessarily being any abnormality in the 5-HT system itself. Bearing these provisos in mind we will describe the two opposing theories for the involvement of 5-HT in panic disorder which are currently prevalent.

Hypothesis of excess 5-HT and panic

This is the 'classic' theory and is based on the assumption that 5-HT excess causes anxiety and suggests that subjects with panic disorder have either increased 5-HT release or supersensitive post-synaptic receptors. Antidepressant anxiety exacerbation (described above) is explained by increased 5-HT in the synapse (as a result of reuptake blockade) acting on these supersensitive receptors. Response to antidepressants is explained by gradual down-regulation of these receptors over a period of several weeks.

Hypothesis of 5-HT deficit causing panic

This derives from a theory proposed by Deakin and Graeff (1991) who suggest that in particular brain regions (periaqueductal grey) 5-HT has a restraining effect on panic and, when this restraining input is reduced panic ensues. Panic disorder is therefore seen as a consequence of a 5-HT deficit. The observed antidepressant exacerbation in anxiety is explained by proposing that there is an initial decrease in 5-HT release at the synapse (as a consequence of 5-HT acting on the inhibitory 5-HT_{1a} autoreceptor) which therefore causes more panic. Over several weeks of treatment the inhibitory 5-HT_{1a} receptor desensitises and 5-HT release at the synapse increases (Blier *et al*, 1990). It is this delayed increase in 5-HT release particularly in the periaqueductal grey which is proposed to bring about response.

The evidence for and against these hypotheses is summarised in Table 3. This illustrates the fact that some of the findings can fit both theories.

Interaction with other neurotransmitters

Although this review has concentrated on the role of 5-HT in panic it is clear that other neurotransmitters, for example γ-aminobutyric acid (GABA) and noradrenaline, are also involved.

The interaction with GABA has been shown clinically by the facts that benzodiazepines reduce 5-HT function (Nutt & Cowen, 1987) and on withdrawal cause a rebound in 5-HT function and anxiety exacerbation. Positron emission tomography studies also suggest a neuroanatomical association, as subjects with panic disorder have recently been shown to have reduced benzodiazepine binding globally (further details available from C.J.B. upon request) which demonstrates a deficiency in brain inhibition by the neurotransmitter, GABA. It is interesting that the areas specifically indicated receive considerable 5-HT inputs and may well reflect an interaction between the GABA and 5-HT systems.

The role of noradrenaline is still unclear. Studies do suggest that it is involved in panic disorder (Nutt & Lawson, 1992) and clinically, although the evidence points more in the direction of 5-HT it is not overwhelming. It may be that there is a subgroup of patients who have a particular noradrenergic abnormality and respond to noradrenergic agents. A synergistic effect between 5-HT and noradrenaline has also been suggested but, as yet, there is no evidence that pure serotonergic agents are more or less effective than those with combined effects.

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Table 3 Evidence for and against hypotheses of 5-HT excess and deficiency in panic disorder

5-HT marker	Putative 5-HT mechanism	Effect (differences compared with normal control subjects)	Supports 5-HT excess theory	Supports 5-HT deficit theory
Pre-synaptic				
Tryptophan depletion/pCPA	Decreases 5-HT pre- or post-synaptically	Increased anxiety sensitivity	No	Yes
Tryptophan or 5-HT challenge	Increases 5-HT pre- or post-synaptically	Decreased anxiety	No	Yes
Post-synaptic m-CPP challenge	Agonist at 5-HT 2, 1a, 3, a2 receptors	Increased anxiety. Increased neuroendocrine response	Yes Evidence increased sensitivity post-synaptic receptors	?Yes Evidence increased sensitivity pre-synaptic 1a receptors – switch off neurone firing. Alternative explanation – increased post-synaptic sensitivity is indicative of reduced 5-HT availability
Fenfluramine challenge	5-HT release, uptake blocker, agonist	Increased anxiety. Increased neuroendocrine response	Yes Evidence incresed pre-synaptic activity or post-synaptic receptor sensitivity	?Yes As above explanation – increased post-synaptic sensitivity is indicative of reduced 5-HT availability
Clomipramine challenge	5-HT uptake blocker	Increased anxiety	Yes Evidence increased sensitivity post-synaptic receptors	?Yes As above explanation – increased post-synaptic sensitivity is indicative of reduced 5-HT availability
5-HT_{1a} agonists Ipsapirone challenge	Partial agonist effects at post-synaptic 5-HT_{1a} receptors	Decreased neuroendocrine response	?Yes Reduced sensitivity 5-HT_{1a} receptors possibly down-regulation in response to excess 5-HT	?Yes Reduced sensitivity 5-HT_{1a} receptors possibly indicative reduced 5-HT function is anxiogenic
Buspirone	Agonist at pre- and post-synaptic 5-HT_{1a} receptors	Suggestion clinically of initial nervousness and delayed general anxiolytic response	No	?Yes Initial nervousness explained by effects at autoreceptor switching of firing. Anxiolytic response at 5-HT function recovers and post-synaptic 1a effects
Flesinoxan	Full agonist at pre- and post-synpatic 5-HT_{1a} receptors	Clinically increases anxiety	?Yes Agonist effects on post-synaptic receptors cause increase in anxiety	?Yes Initial increase in anxiety through effects at autoreceptor switching of firing. Anxiolytic response as 5-HT function recovers and post-synaptic 1a effects
5-HT antagonists				
Metergoline	Non-specific 5-HT antagonist	Produced anxiety in normal control subjects	No	Yes
Ritanserin	5-HT_2 antagonist	Not effective in panic disorder	No	?Yes Expect increase in anxiety – some reports of this

pCPA, parachlorophenylalanine; 5-HTP, 5-hydroxytryptophan; m-CPP, methylchlorophenylpiperazine.

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