

Antidepressants in Panic Disorder: Clinical and Preclinical Mechanisms

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Advances have been made in understanding the biology of panic disorder and the role of the underlying serotonergic dysfunction. This review summarizes the biological evidence for the involvement of serotonin in the pathogenesis of panic disorder and considers the 2 opposing theories that are currently prevalent (5-HT excess and 5-HT deficit). The serotonin selective reuptake inhibitors are increasingly considered as first-line treatment for panic disorder, and the interaction of these agents with the serotonergic system is considered. *(J Clin Psychiatry 1998;59[suppl 8]:24-28)*

A number of theories have been proposed to explain the etiology of panic disorder, including dysfunction of 1 or more neuronal systems (serotonin [5-HT], norepinephrine, γ -aminobutyric acid [GABA], cholecystikinin), the "false suffocation response," and cognitive and behavioral mechanisms. To some extent these theories have developed from an understanding of the differing time courses and withdrawal reactions from antipanic therapies. The mode of action of the benzodiazepines in alleviating the symptoms of panic disorder has been ascribed to an interaction with the central GABA system; however, the mechanism by which antidepressants exert their antipanic activity is still the matter of some debate. Nevertheless, a central role for 5-HT in mediating the antipanic activity of the serotonin selective reuptake inhibitors (SSRIs) would appear to be indicated.

Early evidence in support of the role of 5-HT in panic disorder came from a number of observations. Imipramine, clomipramine, and the monoamine oxidase inhibitors (MAOIs), all of which have demonstrated efficacy in the treatment of panic disorder, increase the availability of serotonin as well as that of norepinephrine. Furthermore, the response to imipramine correlates with the plasma concentration of the parent compound (serotonergic) rather than with that of the active metabolite *N*-desmethyl-imipramine (noradrenergic).¹ Further support for the importance of 5-HT in panic disorder came from the finding

that maprotiline, a tetracyclic antidepressant that has selective action on norepinephrine uptake sites, was found to be ineffective in the treatment of panic disorder, whereas the SSRI fluvoxamine significantly reduced the mean state anxiety score (Figure 1).² The noradrenergic selective drug lofepramine has also been reported to be ineffective in panic disorder, although some studies have found it effective.³

This review describes the biological evidence for an underlying serotonergic dysfunction in panic disorder and discusses the 2 opposing hypotheses of serotonin action.

BIOLOGY OF PANIC DISORDER

Brain Regions and Panic

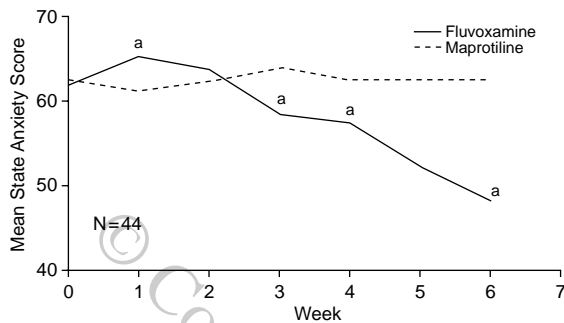
Serotonin is widely distributed throughout the brain and in certain regions, particularly in the amygdala and possibly also the frontal cortex; serotonergic inputs are anxiogenic. Animal studies and observations during brain surgery have shown that stimulation of these areas induces anxiety symptoms (reviewed in Graeff⁴). Subsequent work has suggested that different areas of the brain are involved in different aspects of anxiety: Deakin and Graeff⁵ have proposed that serotonergic input to the periaqueductal gray (PAG) may be particularly involved in the mediation of panic (unconditioned fear), while the amygdala is involved in the pathogenesis of anticipatory anxiety and avoidance (conditioned fear). The PAG receives serotonergic innervation from the dorsal raphe nucleus, and 1 theory proposes that an increased availability of serotonin in this part of the brain increases inhibition in the PAG and thereby restrains paniclike responses.^{6,7} Stimulation of the PAG in animals evokes paniclike behavior: the animals show terror, try to jump out of the cage, and have autonomic activation, all of which can be attenuated by SSRIs or by the direct action of serotonin agonists.

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Figure 1. The Reduction in the Mean State Anxiety Score in 44 Patients With Panic Disorder Who Were Treated With Either Maprotiline or Fluvoxamine*



*From reference 2, with permission.

*p < .01.

There is evidence to support the view that increased levels of serotonin in the PAG inhibit panic behavior, whereas in the amygdala and possibly the frontal cortex, increased levels of serotonin may induce anxiety. Thus, it is clear that there are multiple sites of action for serotonin and that the relationship between serotonin and anxiety is complex. These reasons underlie the inability of researchers at present to clearly pinpoint a serotonergic lesion in panic.

Neuronal Sites of Action

The interaction of drugs with serotonergic neurons can occur at a number of different levels, and serotonin uptake sites exist not only at the nerve terminals but also on the cell bodies. Serotonin can be released from the dendrites as well as from the terminal vesicles and can therefore act at both the level of the cell body or the postsynaptic membrane. Serotonin released from the dendrites acts on inhibitory 5-HT_{1A} autoreceptors to attenuate the firing rate of the neuron, while serotonin released from the nerve terminals can act either postsynaptically on 5-HT_{1A} and 5-HT₂ receptors or presynaptically on the 5-HT₁ autoreceptor. Blockade of serotonin uptake sites by SSRIs increases the availability of serotonin at the axonal terminal regions in the amygdala, PAG, and frontal cortex and also at the cell bodies in the raphe, leading to activation of the presynaptic serotonergic autoreceptors and a decrease in cell firing (Figure 2). This effect wears off in 3 to 6 weeks as the presynaptic receptors desensitize, which explains the delayed time course of action of the antidepressants in depression and may also explain the gradual development of the antipanic response by these drugs.

Challenge Studies

Studies that examine the behavioral and neuroendocrine consequences of acute administration of serotonergic agents are currently the most effective way of studying the role of 5-HT in panic. The challenge probes commonly

Figure 2. A Schematic Representation of the Effect of SSRI Administration on Raphe Firing Rate and of 5-HT Concentration in the Cortex

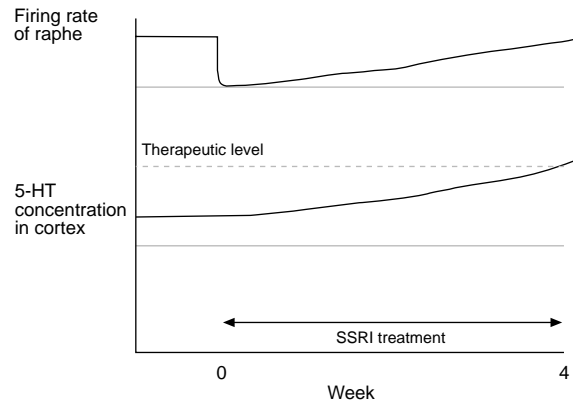


Table 1. Challenge Studies*

Challenge	Behavioral Response	Neuroendocrine Response	Reference
Tryptophan	Decreased anxiety	No difference	Charney et al, 1986 ⁸
5-HTP	Decreased anxiety	No difference	Westenberg and den Boer, 1989 ⁹
Fenfluramine	Increased anxiety	Increased cortisol and prolactin	Targum, 1990 ¹⁰
Clomipramine	Increased anxiety	No difference	George et al, 1995 ¹¹
<i>m</i> -CPP (5-HT ₂)	Increased anxiety	Increased cortisol	Charney et al, 1987 ¹²
Ipsapirone (5-HT _{1A})	No difference	Increased cortisol	Lesch et al, 1992 ¹³

*Abbreviations: 5-HT = 5-hydroxytryptamine (serotonin), 5-HTP = 5-hydroxytryptophan, *m*-CPP = *m*-chlorophenylpiperazine.

used are precursors (tryptophan or 5-hydroxytryptophan), reuptake inhibitors (clomipramine), 5-HT releasers (fenfluramine), or agonists (*meta*-chlorophenylpiperazine [*m*-CPP], buspirone and ipsapirone).

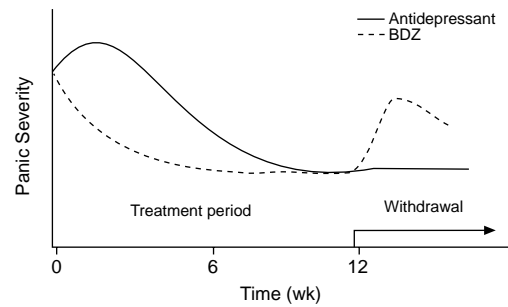
Precursors, releasers, and reuptake inhibitors. Early challenge studies with tryptophan or 5-hydroxytryptophan were found, paradoxically, to reduce anxiety and did not support the view that increased levels of 5-HT were anxiogenic (Table 1). Furthermore, there was no suggestion that challenges with these precursors discriminated between patients with panic disorder and controls.^{8,9} Fenfluramine, which induces the neuronal release of serotonin, was reported by Targum¹⁰ to increase the level of anxiety in panic disorder patients as well as concomitantly increase the postsynaptic neuroendocrine response to cortisol and prolactin. These findings lent support to the suggestion that a supersensitive postsynaptic receptor was present, although this has not been verified in further studies. After administration of intravenous clomipramine to patients with panic disorder, an increase in anxiety was noted and about one third of the patients experienced a

panic attack.¹¹ Nevertheless, it is still not clear whether increasing the synaptic concentration of serotonin elicits panic attacks; in the fenfluramine study,¹⁰ patients experienced an increased level of arousal without any overt panic attacks.

5-HT agonists. Several studies have been conducted with *m*-CPP, which is a relatively nonselective 5-HT₂ agonist. The behavioral response is an increase in anxiety in normal volunteers as well as in patients who have panic disorder,¹² although there is some suggestion that lower oral doses are anxiogenic only in patients with panic.¹⁴ In this latter study, an elevated cortisol response in patients with panic compared with controls was also observed after the oral *m*-CPP challenge. The 5-HT_{1A} agonist ipsapirone has also been used in challenge studies, although it is not clear whether it is acting at the presynaptic or postsynaptic level. It does not produce a behavioral response in patients with panic, and there is no evidence to support the view that it is anxiogenic¹³; nevertheless, the cortisol response is increased in these patients compared with controls. This response supports the suggestion that postsynaptic receptor supersensitivity may be involved, but it does not clarify whether the change in the postsynaptic receptor is the primary event or whether the changes are a direct result of up-regulation of the postsynaptic receptor population caused by presynaptic dysfunction.

5-HT depletion. Depletion of brain 5-HT has been utilized by researchers to gain insight into the role of serotonin in panic. The methodology employed involves feeding patients a low tryptophan diet for 1 day and then saturating the tryptophan transport system into the brain with a high dose of large neutral amino acids. Since the enzyme tryptophan hydroxylase is not saturated, the reduced availability of precursor results in reduced synthesis of 5-HT. This methodology has been used extensively in research into depression where it has been shown that depleting 5-HT in depressed patients receiving an SSRI means depression is likely to recur. These results suggest that increased levels of 5-HT are required in the synapse for the SSRIs to be effective.¹⁵ In obsessive-compulsive disorder (OCD) the situation differs, and depletion of 5-HT in OCD patients who have recovered while taking an SSRI does not cause relapse, so receptor adaptation is considered to be more important. Studies in untreated panic disorder patients have shown that acute tryptophan depletion does not precipitate panic¹⁶; however, it does make patients more sensitive to a panicogenic challenge.¹⁷ A study is presently under way, with paroxetine, to assess if treated patients with panic in remission are more vulnerable to panic attacks when in a tryptophan-depleted state. If effective treatment of panic disorder with SSRIs requires an increased level of 5-HT in the synapse, then tryptophan depletion should result in relapse. Conversely, if the primary action of the SSRIs is to cause receptor adaptation, then tryptophan depletion should not elicit a relapse to the panic state.

Figure 3. The Biphasic Course of Antidepressant Response



HYPOTHESIS OF 5-HT EXCESS AND DEFICIT

Clinical and experimental findings point toward a serotonergic dysfunction in panic disorder, and 2 competing theories have been proposed. At present, a distinction cannot be made between the 2 theories, as both are able to explain some, but not all, of the experimental findings.

5-HT Excess

The premise in the 5-HT excess theory is that patients with panic disorder either have an increased level of 5-HT release or have supersensitive postsynaptic receptors. The well-documented biphasic course of the antidepressant response in panic disorder (Figure 3) can be explained by this theory in the following way: initial anxiety exacerbation is related to an increased level of 5-HT in the synapse (due to the uptake blockade) acting on supersensitive post-synaptic receptors; gradual down-regulation of these post-synaptic receptors over a period of several weeks, or possibly alteration in presynaptic excitability, explains the antipanic response to antidepressants. The antipanic effect of high-potency benzodiazepines is thought to support this theory, as these drugs inhibit 5-HT turnover and so reduce 5-HT function overall.¹⁸

5-HT Deficit

The converse theory is that of 5-HT deficit. This theory proposes that in particular brain regions such as the PAG, 5-HT has a restraining effect on panic behavior, and when there is a deficit in 5-HT, this restraint is reduced and panic ensues. Initial anxiety exacerbation with antidepressants, according to this theory, is related to an initial decrease in 5-HT release due to the action of 5-HT on the presynaptic inhibitory autoreceptor. Antidepressant response, however, is related to a gradual desensitization of these autoreceptors and the resultant increase in 5-HT release.¹⁹

The action of antidepressants, according to the 5-HT deficit theory, can be understood by considering the effect of the SSRIs on the raphe cells (Figure 2). Within minutes of acute administration of an SSRI, the firing rate of the

Table 2. Evidence in Support of the 5-HT Excess or Deficit Theories*

Agent	Anxiety	Supports Excess 5-HT	Supports 5-HT Deficit
5-HT depletion	↑	No	Yes
5-HT precursors	↓	No	Yes
5-HT releaser	↑	Yes	No
5-HT ₂ agonist	↑	Yes	No
5-HT ₂ antagonist	No change	No	No
SSRI	↑→↓	Yes	Yes
Benzodiazepine	↓	Yes	No

*Based on data from references 8 to 18. Abbreviation: SSRI = serotonin selective reuptake inhibitor. Symbols: ↑ = increases; ↓ = decreases; ↑→↓ = increases at first, then decreases.

Table 4. Selectivity of the SSRIs for 5-HT Versus Norepinephrine Uptake*

Drug	IC ₅₀ (nM)	
	5-HT Uptake	Norepinephrine Uptake
Paroxetine	0.3	81
Fluvoxamine	3.8	620
Fluoxetine	6.8	370
Sertraline	0.2	160
Citalopram	1.8	6100
Clomipramine	1.5	21

*Based on data from reference 20.

Table 3. Receptor Binding Profile of the SSRIs and Clomipramine*

Drug	IC ₅₀ (nM)							
	α ₁ Praz	α ₂ Idaz	β DHA	D ₂ Spip	H ₁ Mepy	5-HT _{1A} 8-OH-DPAT	5-HT _{2A} Ketan	5-HT _{2C} Ly 278584
Paroxetine	19,000	8900	35,000	52,000	19,000	> 100,000	18,000	20,000
Fluvoxamine	4800	1900	89,000	66,000	11,000	> 100,000	12,000	6700
Fluoxetine	14,000	2800	18,000	32,000	3200	79,000	710	1600
Sertraline	2800	1800	14,000	24,000	10,000	100,000	8500	No data
Citalopram	1600	18,000	> 100,000	33,000	350	15,000	5600	630
Clomipramine	60	1800	22,000	430	54	28,000	54	No data

*Based on data from reference 20. Abbreviations: DHA = dihydroalprenolol, Idaz = idazoxan, Ketan = ketanserin, Mepy = mepyramine, Praz = prazosin, Spip = spiperone. All receptor ligands were [³H]. The higher the IC₅₀, the weaker the effect at the receptor.

raphe cells is greatly reduced. This reflects uptake blockade at the cell body, increasing the availability of dendritically released 5-HT to interact with the inhibitory autoreceptor. Although the firing rate of the neurons decreases, uptake blockade at the terminal regions means that the 5-HT that is released lasts longer, and, therefore, at the level of the cortex, there is little overall change. Over a period of a few weeks, the firing rate of the raphe gradually recovers, and the level of 5-HT in the cortex begins to rise. By about 4 weeks, the concentration of 5-HT in the cortex is predicted to reach a level at which a therapeutic effect is obtained.

The evidence from the challenge studies⁸⁻¹⁸ for and against these 2 opposing theories is summarized in Table 2; it is clear that both theories are capable of explaining some of the findings. The challenge for future researchers is to design experiments to critically differentiate between the 2 theories and so resolve this confusion.

ARE THERE DIFFERENCES BETWEEN SSRIs IN PANIC?

The SSRIs are increasingly considered as first-line treatment for panic disorder (see other articles in this supplement). Pharmacologic differences (both dynamic and kinetic) exist within the drug class, which can be of relevance in treating panic, and these are summarized below.

The SSRIs have demonstrated low affinity for adrenergic, dopaminergic, and histaminergic receptors in contrast with clomipramine, which has a relatively high affinity for both the α₁ adrenoceptor and the H₁ histamine receptor (Table 3). The affinity of clomipramine for these receptors, in addition to those for the cholinergic class, results in many of the unwanted side effects with this drug, which can eventually lead to pa-

tient noncompliance and may contribute to the slower onset of therapeutic effect compared with paroxetine.²¹ In addition, clomipramine is a relatively potent antagonist at the 5-HT_{2A} receptor, while fluoxetine, at clinically effective doses, may act as an agonist at this receptor subtype, which could lead to greater initial anxiety or jitteriness early in treatment (Table 3). The relative affinity of the SSRIs to inhibit 5-HT and norepinephrine uptake sites is displayed in Table 4. Paroxetine, citalopram, and sertraline are the most selective of the SSRIs for 5-HT uptake; clomipramine would appear to be more selective for 5-HT uptake than for norepinephrine uptake, but the clinical picture is more complex, as its principal metabolite is predominantly selective for noradrenergic uptake sites. The selectivity ratio in clinical practice is therefore lower than would be suggested from Table 4. Future studies are required to determine the contribution of additional norepinephrine uptake in the treatment of panic; at present, there is no evidence that it confers benefit. It may lead to increased jitteriness early in treatment and so have a negative impact.

Pharmacokinetic variations within the SSRI class are apparent and deserve consideration, especially when termination of treatment is required or when there is a need to switch between drugs (Table 5). Fluoxetine has the longest half-life of any of the SSRIs, and the problems this can cause are further compounded by the long half-life of its active metabolite, desmethylfluoxetine. For this reason,

Table 5. Comparative Pharmacokinetics of the SSRIs*

SSRI	Half-Life	Metabolite		
		Active	Half-Life	Potency Relative to Parent
Paroxetine	24 h	No
Fluvoxamine	15 h	No
Fluoxetine	1–3 d	Yes	7–15 d	Equipotent
Sertraline	25 h	Yes	66 h	8 × less
Citalopram	33 h	Yes	49 h	2–4 × less

*Based on data from references 22 to 25.

switching from fluoxetine to an MAOI can be problematic, and care must be taken when prescribing another drug that is metabolized by the enzyme system that fluoxetine blocks.

CONCLUSIONS

There is evidence to support a role for serotonin in the biology of panic disorder, but at present, the available evidence does not differentiate between the theories of 5-HT excess or deficit. The precise serotonergic dysfunction in panic disorder remains unclear, and it is likely that multiple brain regions and 5-HT receptors are involved. SSRIs are increasingly being used in the treatment of panic disorder, and they can be differentiated with respect to serotonin versus norepinephrine uptake selectivity, binding affinity for 5-HT receptor subtypes, and pharmacokinetic profiles.

Drug names: bupirone (BuSpar), clomipramine (Anafranil), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), paroxetine (Paxil), sertraline (Zoloft).

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