SSRIs as Antihypertensives in Patients With Autonomic Panic Disorder

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The cardiovascular properties of serotonin (5-HT) have been known for some time—its name reflects its presence in serum and its action in increasing vascular tone. Serotonergic medications are routinely used to treat depressive and anxiety disorders, and the association of depression with cardiovascular disease has become well established. Recent studies have confirmed the colloquial wisdom that anxiety (especially panic) and hypertension are linked.

We would like provisionally to name it serotonin, which indicates that its source is serum and its activity is one of causing constriction. Rapport M, et al

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In this article, we examine the trinity of serotonin—serotonergic dysfunction, autonomic panic, and normal-weight essential hypertension—and the evidence that hypertensive individuals who experience panic with autonomic symptoms may be a group of patients in whom serotonergic dysfunction plays a key role. We discuss implications of this model, including the potential utility of SSRIs as antihypertensives in this cohort.

The role of serotonin
SSRIs are well established as first-line treatments of clinical anxiety disorders.3 Their wide availability, relative safety in overdose, limited adverse effects, and broad clinical effectiveness have contributed to their popularity. Indeed, their categorization as antidepressants seems increasingly inadequate because these agents have been found to be clinically useful in a range of psychiatric conditions.

In recent years, there has been much concern about emergent suicidality in adults and children
treated with SSRIs.

Such fears appear to have eroded clinical confidence in these medications, despite some methodological concerns.4-6 Sadely, a parallel decrease in prescribing of SSRIs appears to be associated with increased suicide rates—a powerful reminder of the need to closely monitor all patients for whom these powerful medicines are prescribed and the complex implications of health policy modification.7 Most authorities continue to advocate considered use of SSRIs and/or cognitive-behavioral therapy (CBT) in clinical anxiety states, although the evidence base supporting combination therapy over SSRIs alone is surprisingly sparse.8 Patients are commonly told that SSRIs work by “correcting” an abnormality in the 5-HT system, but only recently has evidence emerged to support this correlation with anxiety. One difficulty has been competing theories that patients with anxiety disorders have either too little or too much 5-HT in the synaptic cleft.9

The 5-HT deficit model proposes that 5-HT reuptake blockade leads to increased availability of 5-HT, which, in turn, rapidly leads to a decreased rate of firing of the raphe nucleus. The initial net result is little overall change in cortical 5-HT concentration. After a few weeks to months, however, the raphe firing rate recovers, and eventually 5-HT cerebral concentration reaches levels that are therapeutic. This model accounts for the delayed onset of antidepressant and anxiolytic action as well the initial transient increase in anticipatory anxiety.

An alternative (5-HT excess) model proposes that increased levels of 5-HT produce an increase in anticipatory anxiety initially; however, a gradual down-regulation of supersensitive postsynaptic receptors (or a decrease in presynaptic excitability) produces an anxiolytic effect.

We have tested these theories by transiently depleting central 5-HT by the dietary technique of acute tryptophan depletion (ATD) coupled with anxiety-specific challenges, and by neuroimaging subjects with anxiety disorders pre- and post-SSRI treatment.10,11 Using the first method, we have demonstrated that patients who have SSRI-remitted social anxiety disorder, panic disorder, or posttraumatic stress disorder experience a transient return of anxiety symptoms when central 5-HT is depleted. This supports the 5-HT deficit model.12 We have not elicited significant anxiety symptoms in subjects with SSRI-remitted generalized anxiety disorder, obsessive-compulsive disorder, or CBT-remitted panic disorder. Thus, according to this pharmacological dissection technique, it would appear that there is more to recovery than maintaining central 5-HT in these disorders.

Neuroimaging has demonstrated down-regulation of cerebral 5-HT1A receptors in patients with panic disorder and social anxiety disorder.11,12 A study by Nash and colleagues showed that the receptor down-regulation was localized to regions known to play an important role in anxiety states (ie, amygdala, orbitofrontal cortex, and temporal cortices), with some evidence of normalization of 5-HT1A binding with SSRI treatment.

Clearly, other neurotransmitter systems are also important in the treatment of anxiety disorders.
Anxiety with norepinephrine reuptake properties or g-aminobutyric acid–A (GABA) agonism, for example, are in common use, and cross talk between neurotransmitter systems is well described. Recent interest in neuropeptides (which are virtually always co-localized in the CNS with at least 1 of the classic neurotransmitters) and neurotrophic factors adds additional complexity. While recognizing the broader context in which serotoninergic agents operate, we focus our attention on more direct modification of 5-HT via SSRI medications.

Panic disorder and hypertension

Philosophical distinction between mind and body can be traced back to the ancient Greeks; however, it is Ren Descartes14 to whom we owe credit for the first systematic account of mind/body dualism. Discrimination between mental and physical phenomena characterized psychiatry and medicine until the end of the 20th century (some would suggest that it continues to this day). The rise of a voice for consumers, deliberate moves to destigmatize mental illness by a range of interest groups, and a trend away from traditional medical models of health care have prompted more integrated approaches.

The interface between psychiatry and cardiovascular medicine is a topic of immense current research interest, and although the past 15 years have seen scientific evidence catch up with the common wisdom linking depression to cardiovascular disease, anxiety and cardiovascular comorbidity has been little studied.2 In fact, there is considerable evidence that people with anxiety disorders have elevated cardiovascular mortality.25 When patients with panic attacks present to the emergency department fearing imminent cardiovascular collapse, their valid concerns often fall on deaf ears—panic disorder recognition rates as low as 2% have been reported in this setting!16,17 Hypertension is an independent risk factor for cardiovascular disease. It may be a cause or a consequence of endothelial dysfunction. An increase in blood pressure over the optimal 120/80 mm Hg increases the risk of cardiovascular events. Several authors have demonstrated an epidemiological association between cardiovascular disorders and anxiety disorders. Two large controlled studies have provided evidence for an association of hypertension with panic attacks and panic disorder, including one conducted by members of our group in Sheffield, England. This was a study of 891 patients in 3 groups—hypertensive patients in primary care, matched normotensive controls from the same primary care practice, and hypertensive patients attending a hospital clinic. Davies and colleagues18 found that 37% of the hypertensive patients had experienced panic attacks compared with 21% of normotensive controls—a highly significant difference (P < .001). Panic disorder was significantly more common in hypertensive patients in primary care than in matched normotensive controls. Prospective studies have also reported on this association, although none of these studies had combined a robust method for diagnosing panic disorder and robust methods for diagnosing cardiovascular end points.

Why might an association between panic disorder and hypertension exist? A possibility is that patients with panic disorder have higher blood pressures because of a greater “white coat” (health-anxiety-related) hypertension response compared with patients without panic disorder. Davies and colleagues19 have also looked at this, finding that although a white coat effect exists, there was no difference in this effect in patients with panic disorder and in those without, making this explanation unlikely. The issue of whether normal-weight essential hypertension can be caused by chronic mental stress, such as panic disorder, is debated; however, Esler and colleagues20 have argued persuasively that in both conditions the increase in levels of plasma cortisol, (stress-induced) tissue nerve growth factor, subcortical norepinephrine turnover, and epinephrine cotransmission in sympathetic nerves support this assertion. It follows that the interplay of 5-HT with autonomic nervous system abnormalities in these patients warrants careful scrutiny.

Autonomic dysfunction and serotonin

For many years, the majority of cases of hypertension were classified as “essential hypertension,” which simply means of unknown etiology. Because there is substantial evidence for autonomic dysfunction in both hypertension and panic, a parsimonious explanation for the association between these 2 conditions in at least some cases of essential hypertension is common autonomic dysfunction.21 Davies and colleagues22 tested this hypothesis by considering panic attack symptom profiles in people who had experienced a panic attack. Hypertensive participants (with resting blood pressure greater than 160/90 mm Hg) were more likely to report experiencing sweating (64.6% vs 46.2%) and flushing (54.9% vs 39.7%) during their worst attack than were normotensive patients. In addition, factor analysis revealed a 4-factor solution with a dominant autonomic symptom factor containing sweating, flushes, and shaking—and only this factor was significantly associated with hypertension.
An explanation of these data may be that experiencing panic attacks with autonomic symptoms is a marker for a specific kind of hypertension in these people—one in which there is a dysregulated central 5-HT system. A range of diverse data relates to this assertion, including the clinical utility of SSRI antidepressant medications in patients with cardiovascular conditions. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) group reported that sertraline was a safe and somewhat effective antidepressant in subjects with ischemic heart disease and major depression, and a post hoc analysis hinted at an improvement in severe cardiac events.\(^23\) The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) investigators demonstrated a psychological benefit in post-myocardial infarction patients with cognitive therapy (plus sertraline for some patients) with no impact on cardiovascular morbidity or mortality.\(^24\) Depression rather than anxiety was examined in these studies and neither study reported a significant improvement in blood pressure. SSRI-induced inhibition of platelet 5-HT uptake is known to reduce platelet plug formation, which could be of additional benefit. Animal data also exist that support putative 5-HT (ie, sympathetic) anxiety circuits and provide a plausible preclinical biological model.\(^25\)

Using the ATD procedure, we demonstrated that people with SSRI-remitted anxiety disorders—including panic disorder—show an increased cardiovascular (independent of anxiety measures) and psychological response to a disorder-specific stressor when depleted of tryptophan in comparison with a control (nondepleted) condition.\(^10,12,26,27\) Healthy volunteers, however, do not show an increased response to a single-breath 35% carbon dioxide stress challenge when they are tryptophan-depleted, which suggests that they have a more robust 5-HT system.\(^28\) The integrity of the 5-HT system in people with dysregulated blood pressure control, as determined by the ability to buffer the stress response under the tryptophan-depleted versus nondepleted condition, has yet to be assessed.

**SSRIs as antihypertensives**

If patients with hypertension and autonomic symptoms of panic are susceptible to a pressor effect by acutely depleting central 5-HT, might not the addition of SSRIs improve their blood pressure control? We already have some intriguing early data that suggest that this may indeed be true. Polyk\(^29\) has presented the results of a study of 107 adults with both hypertension and anxiety who were taking a range of antihypertensive medications. Low-dose (mean, 39 mg/d) sertraline was added to their diverse antihypertensive regimens, and the effects on blood pressure was checked at 1 month and at 6 months. At both points, a significant improvement in systolic blood pressure of about 10 mm Hg and diastolic blood pressure of about 5 mm Hg were seen. Although this case series has not been replicated and subjects with autonomic panic were not specifically identified, these data cannot easily be ignored.

We propose conducting a series of follow-up studies to explore the utility of SSRI therapy in people with hypertension and the related condition of prehypertension, and to evaluate the evidence for serotonergic dysfunction and altered blood pressure response to stress in people with prehypertension and panic attacks via serotonergic manipulation. Until such work is undertaken, this interesting therapeutic option will remain largely a research interest.

**Conclusions**

An association between 5-HT, panic, and hypertension has long been noted and is now the subject of active research interests. Manipulating 5-HT may have clinical implications for blood pressure control in people with panic attacks and anxiety. Our data suggest that panic attacks comorbid with hypertension may be distinct from panic attacks uncomplicated by hypertension—and it may be that hypertension complicated by panic attacks has specific biological features compared with hypertension uncomplicated by panic. Serotonergic manipulation of hypertension has largely been ignored or dismissed since the isolation of serotonin in 1948; however, we believe that by focusing on patients with key autonomic panic symptoms such as sweating and flushing, we may clarify this issue with potential therapeutic benefits.

**References:**


Psychoneuroendocrinology. 2006;31:1087-1097.

**Evidence-Based References**


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