Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype–targeted drugs

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Serotonin (5-hydroxytryptamine, or 5-HT) receptors mediate a plethora of physiological phenomena in the brain and the periphery. Additionally, serotonergic dysfunction has been implicated in nearly every neuropsychiatric disorder. The effects of serotonin are mediated by fourteen GPCRs. Both the therapeutic actions and side effects of commonly prescribed drugs are frequently due to nonspecific actions on various 5-HT receptor subtypes. For more than 20 years, the search for clinically efficacious drugs that selectively target 5-HT receptor subtypes has been only occasionally successful. This review provides an overview of 5-HT receptor pharmacology and discusses two recent 5-HT receptor subtype–selective drugs, lorcaserin and pimavanserin, which target the 5HT₂C and 5HT₂A receptors and provide new treatments for obesity and Parkinson’s disease psychosis, respectively.

Serotonin receptors and signal transduction

Serotonin, which was known to be the principal vasoconstricting substance found in serum, was chemically identified as 5-hydroxytryptamine by Rapport and colleagues in 1948 (1). Although the effects of serotonin on smooth muscle and other peripheral organs were long appreciated, it wasn’t until its structural similarity to lysergic acid diethylamide (LSD) was noted that serotonin and its receptors were linked to neurotransmission (2). Distinct serotonin receptor subtypes were proposed in 1957 (3), with the 5-HT₁ receptors having high affinity for serotonin and the 5-HT₂ receptors having relatively low affinity for 5-HT. The so-called 5-HT₁ and 5-HT₂ receptors identified pharmacologically by Gaddum and colleagues (3) roughly correspond to what are now known as the 5-HT₁A and 5-HT₁B families of receptors (Figure 1).

With the development of radioligand-binding technology, multiple distinct serotonin receptors were identified based principally on their differential radioligand-binding properties. Following the cloning of the β-adrenergic receptor (4), 5-HT₁A (5), the first so-called orphan GPCR, was cloned by Brian Kobilka in collaboration with Marc Caron and others (6, 7). In rapid succession, the large family of G protein–coupled serotonin receptors we now appreciate were identified by molecular cloning technology and characterized by pharmacological and biochemical studies (8, 9), including 5-HT₁B/1D (10) and 5-HT₁E (11), as well as 5-HT₂A (12, 13) and 5-HT₂C (14, 15), which have lower affinities for 5-HT than the other serotonin receptors. The 5-HT₁ receptor was also one of the early 5-HT receptor subtypes identified mainly by radioligand binding and pharmacological studies (refs. 16, 17, and see Figure 1).

In terms of signal transduction and pharmacology, we now know that all members of the 5-HT₁ family are intronless and couple to the Gi family of heterotrimeric G proteins — in keeping with the original description of the 5-HT₁A receptor (7). The 5-HT₁ family of receptors has been successfully exploited for the treatment of anxiety and depression with the development of drugs like buspirone (Table 1), which is a selective 5-HT₁A partial agonist. Likewise, 5-HT₁B and 5-HT₁D receptors represent canonical targets for antimigraine medications including various ergots (e.g., ergotamine, dihydroergotamine, and methysergide) as well as the more selective tryptans (e.g., sumatriptan and analogs) (18, 19). No selective 5-HT₁E drugs exist and though selective 5-HT₁F drugs have been developed, none of them have yet been approved by the FDA (Table 1). Theoretically, 5-HT₁F antagonists might represent novel therapeutic agents for migraine headaches.

The 5-HT₂ family receptors couple to Gq G proteins and mediate phosphoinositide hydrolysis and PKC activation (20–22). 5-HT₂ family receptors typically have lower affinity for molecular serotonin than other 5-HT receptors and are often potentely inhibited by both typical (12) and atypical (23) atypical antipsychotics (24). 5-HT₂A receptors represent the main serotonin receptors found in platelets, vascular smooth muscle, and the cerebral cortex (25, 26). As discussed below, 5-HT₂B receptors are enriched in the heart (27), and drugs likely mediate their valvulopathogenic actions on heart valves via a combination of G protein and β-arrestin signaling (27–29). The distribution and function of 5-HT₂C receptors will be summarized below when lorcaserin, a selective 5-HT₂C agonist, is discussed.

The 5-HT₄, 5-HT₅, and 5-HT₇ families of receptors are all coupled to the Gs G proteins and mediate the stimulatory effects of serotonin on cAMP accumulation. 5-HT₄ receptors represent the main site of action of many drugs used for treating gastrointestinal motility disorders (Table 1) and are found widely distributed throughout the body (18). 5-HT₅a and 5-HT₅c receptors have recently been the subject of intense investigation by pharmaceutical companies based on the discovery that many atypical antipsychotic drugs have high affinities for both receptors (30). As can be seen in Table 1, compounds that target 5-HT₅a and 5-HT₇ receptors are currently in testing for depression, cognition enhancement, and psychosis.

Drugs acting on 5-HT receptors display a range of efficacy from full agonists to inverse agonists (e.g., agonists with negative intrinsic activity). Buspirone, for instance, is a partial agonist at 5-HT₁A receptors, whereas sumatriptan is a full agonist at 5-HT₁D receptors. By contrast, both typical and atypical antipsychotic drugs have inverse agonist actions at many 5-HT receptor subtypes including...
5-HT_{2A} (31) and 5-HT_{2C} (32). Inverse agonists represent drugs that antagonize the action of full agonists (e.g., are “antagonists”) and simultaneously lower the basal level of receptor signaling (e.g., suppress constitutive receptor activity; see ref. 33 for review). Essentially, inverse agonists are antagonists with negative intrinsic activity. Finally, drugs like ergotamine display functional selectivity or signaling bias for many 5-HT receptors including 5-HT_{2B} (28, 29). Thus, ergotamine has much higher potency for activating β-arrestin pathways than for activating G protein–mediated signaling (28, 29) and as such is considered to display functional selectivity for β-arrestin signaling and to represent a β-arrestin–biased agonist.

Because of the vast effort devoted over the past five decades to studying serotonin and classifying its receptors, we now appreciate that serotonin is involved in the regulation of nearly every CNS function, including cognition, autonomic function, perception, emotion, appetite, aggression, and mood, to name but a few (18). Additionally, alterations in serotonergic neurotransmission have been implicated in nearly every neuropsychiatric disorder, including schizophrenia and related psychotic disorders, major depression, eating disorders, and so on (18). Many of the therapeutic actions, as well as serious side effects of commonly prescribed medications, are due to nonspecific actions on 5-HT receptor subtypes (18, 27, 34). Given this wealth of evidence implicating altered serotonergic neurotransmission in neuropsychiatric disease, as well as the plethora of 5-HT receptor subtypes, it has long been proposed that drugs that target distinct 5-HT receptors might provide novel and effective treatments for many neuropsychiatric disorders (Table 1).

Table 1
Listed are approved/investigational drugs targeting distinct 5-HT receptor subtypes

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Known indications (medication name)</th>
<th>Potential new indications (medication name)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT_{1A}</td>
<td>Anxiety, depression (buspirone)</td>
<td>Cognition enhancement (tandospirone)</td>
<td>77</td>
</tr>
<tr>
<td>5-HT_{1B} and 5-HT_{1D}</td>
<td>Migraine headaches (sumatriptan, rizatriptan, zolmitriptan, etc.)</td>
<td>Depression (AZD3783)</td>
<td>78</td>
</tr>
<tr>
<td>5-HT_{1E}</td>
<td>Unknown</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{1F}</td>
<td>Migraine headaches</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{2A}</td>
<td>Hypertension (ketanserin)</td>
<td>Psychosis (pimavanserin)</td>
<td>This article</td>
</tr>
<tr>
<td>5-HT_{2B}</td>
<td>Pulmonary hypertension (terguride)</td>
<td>Fibrosis (NA)</td>
<td></td>
</tr>
<tr>
<td>5-HT_{2C}</td>
<td>Obesity (lorcaserin)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{3}</td>
<td>Chemotherapy-induced nausea (odansetron, granisetron, tropisetron, etc.)</td>
<td>Psychosis, mood disorders, anxiety, metabolic syndrome</td>
<td>18</td>
</tr>
<tr>
<td>5-HT_{4}</td>
<td>Gastrointestinal motility disorders (metoclopramide)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{5}</td>
<td>Unknown</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{6}</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT_{7}</td>
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</table>
Figure 2
Structures of lorcaserin and pimavanserin in relationship to the serotonin receptor–binding pocket. Shown at the top are the structures of lorcaserin ((1R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine) and pimavanserin (N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N’-(4-(2-methylpropyloxy)phenylmethyl)carbamide), and shown below is the consensus-binding pocket of 5-HT receptors.

In this review, we focus on one newly approved 5-HT2C–selective antiobesity medication (lorcaserin) and a 5-HT2A–selective inverse agonist with efficacy in the dopamine-dependent psychosis of Parkinson’s disease (pimavanserin) that has recently been selected for expedited FDA review (see Figure 2 for structures). Currently, there is no approved treatment for this relatively common disorder. Clozapine and quetiapine, which are nonselective inverse agonists is no approved treatment for this relatively common disorder. Clozapine and quetiapine, which are nonselective inverse agonists are rarely used because of unwanted side effects. Lorcaserin (also known as APD356) (Figure 2B and ref. 45) satisfied these criteria and was entered into clinical trials for the treatment of obesity.

In 2010, the results from a large phase III clinical trial were published (46), demonstrating that lorcaserin-treated individuals (10 mg/day) achieved, on average, a 5.8-kg weight loss compared with a 2.2-kg weight loss in placebo-treated patients ($P < 0.001$) (Figure 3A). Both lorcaserin- and placebo-treated individuals were given diet and exercise guidance, with 47.5% of lorcaserin-treated patients achieving ≥5% weight loss compared with 20.3% for those treated with placebo (Figure 3B). Importantly, there was no evidence for an increase in clinically significant valvular heart disease in lorcaserin-treated patients compared with those receiving placebo. Similar results were reported in a 1-year trial that examined two doses of lorcaserin (10 or 20 mg/day); again, there was no difference in the incidence of valvular heart disease in placebo- and lorcaserin-treated individuals (2.0% in both). In both trials, headache, nausea, and dizziness were among the most frequent side effects, and there was no evidence for neuropsychiatric sequelae in either trial (46, 47). Nasopharyngitis, sinusitis, and upper respiratory infections were seen more commonly among lorcaserin-treated individuals (35). Lorcaserin appears to achieve its weight-reducing effects by diminishing caloric intake rather than by altering energy expenditure (48).

Lorcaserin — a safe and effective antiobesity drug
For many decades, it has been clear that 5-HT is a critically important neurotransmitter for the central regulation of appetite and metabolism (36) and that it is the 5-HT2C receptor that mediates the anorectic actions of 5-HT (37). The anorectic actions of the withdrawn antiobesity medication fenfluramine are due to the agonist actions of its metabolite norfenfluramine at 5-HT2C receptors (38). The combination of fenfluramine and the amphetamine derivative phentermine was demonstrated to be a highly effective appetite suppressant (39), but was withdrawn due an unacceptable rate of valvular heart disease (40). Fenfluramine was also linked to pulmonary hypertension, although the incidence was consider-ably lower than that of valvular heart disease (41). We now know that both valvular heart disease (42) and pulmonary hypertension (43) are likely due to off-target interactions of fenfluramine’s principal metabolite norfenfluramine with the 5-HT2B serotonin receptor (27). Thus, while the parent compound fenfluramine is relatively inactive at 5-HT2B Receptors (42), norfenfluramine potently activates 5-HT2B receptors (42, 44). Indeed, the EC50 of norfenfluramine is approximately 80 nM for the activation of 5-HT2B receptors in vitro. This concentration is roughly equivalent to plasma levels of norfenfluramine in individuals taking fenfluramine for obesity (18). Thus, Arena Pharmaceuticals set out to create a 5-HT2C–selective agonist devoid of 5-HT2B agonist activity, predicting that such a molecule would be an effective anorectic agent devoid of cardiovascular side effects. Lorcaserin (also known as APD356) (Figure 2B and ref. 45) satisfied these criteria and was entered into clinical trials for the treatment of obesity.
Lorcaserin has also been evaluated in obese individuals with type 2 diabetes. In a pivotal study, O’Neill et al. found that lorcaserin induced significant ($P < 0.001$) weight loss and improved glycemic control in individuals with type 2 diabetes compared with that observed in placebo-treated individuals (49). It must be noted that both groups received metformin or sulfonylurea (or both), as well as diet and exercise counseling. Thus, it cannot be concluded without further study that lorcaserin alone would be effective in producing weight loss in obese individuals with type 2 diabetes. As in all other studies, serial echocardiograms were performed, and no significant ($P > 0.05$) drug effect was noted on the incidence of valvular heart disease. Taken together, these results suggest that lorcaserin in combination with diet and exercise counseling can induce clinically significant weight loss and, perhaps, improve glycemic control in obese individuals with type 2 diabetes.

Treating Parkinson’s disease psychosis: from clozapine to pimavanserin

It has long been held that all antipsychotic drugs (APDs) achieve their antipsychotic effect primarily through blockade of dopamine (DA) D$_2$ receptors (50); however, D$_3$ receptor blockade also leads to deleterious extrapyramidal side effects (EPSs) or prolactin elevation (51). At doses of 200 to 900 mg/day, clozapine was found to produce antipsychotic action with minimal EPSs or prolactin elevation in patients with schizophrenia, an atypical profile compared with other APDs (52, 53). Comparison of the affinities of typical and atypical APDs for DA D$_1$ and D$_2$ and 5-HT$_2A$ receptors led to the hypothesis that one type of atypical APD could be identified by a higher affinity for 5-HT$_2A$ receptors than for D$_2$ receptors (54). Subsequently, a series of drugs that conformed to this hypothesis, including risperidone, olanzapine, and others, were developed for the treatment of schizophrenia (55). Unfortunately, other pharmacologic properties of these broadly acting drugs produced numerous side effects that limited their tolerability (56), including 5-HT$_2C$ inverse agonism, a major basis for metabolic side effects (57).

Typical APDs, even at ultra-low doses, cause intolerable motor impairment in patients with Parkinson’s disease psychosis (PDP), which is a common side effect of L-DOPA and direct-acting DA agonists. By contrast, clozapine, at doses of 12.5 to 75 mg/day, was found to be an effective and tolerable treatment for PDP (35); however, serious, nonmotoric side effects of clozapine limit its use in PDP (30, 35). After an examination of plasma levels of clozapine (4–6 ng/ml) in responsive PDP patients, it was concluded that clozapine’s antagonist (or inverse agonist) activity at 5-HT$_2A$ receptors was the basis for its efficacy (58). This provided further support for the suggestion that selective 5-HT$_2A$ inverse agonists might be useful as a monotherapy for some psychoses and to potentiate the antipsychotic action of subeffective doses of known APDs (24, 59). For these and other reasons, ACADIA Pharmaceuticals developed selective 5-HT$_2A$ inverse agonists (31, 35). The compound ultimately selected for clinical development was pimavanserin (60). Its pKi (–log Ki) for the human 5-HT$_2A$ receptor is 9.3, with a 40-fold selectivity over the 5-HT$_2C$ receptors and little affinity for 5-HT$_2B$ or D$_2$ receptors (60). Pimavanserin demonstrated atypical antipsychotic-like activity in a variety of preclinical models (37, 38, 60). It also reduced the release of DA in the nucleus accumbens from activated DA neurons (61), which may contribute to its antipsychotic effect, although direct effects on 5-HT$_2A$ receptors expressed on glutamatergic and GABAergic neurons may also contribute to the actions of 5-HT$_2A$ inverse agonists (55, 62).

Pimavanserin, 20–60 mg/day, was tested in a double-blind, randomized, placebo-controlled, multicenter 28-day trial in 60 patients with L-DOPA–induced PDP (63). The pimavanserin-treated patients showed markedly greater improvement in delusions and hallucinations (Figure 4). Pimavanserin did not differentiate from the placebo with regard to motor impairment, sedation, hypotension, or other side effects (39, 63). These results were recently confirmed in a 6-week, randomized, double-blind phase III study involving 198 patients, half of whom received pimavanserin (64). The FDA subsequently indicated that it will evaluate a new drug application (NDA) from ACADIA on the basis of these two studies and other safety data (65). Preclinical studies indicate that pimavanserin may also be useful for treating the psychosis of Alzheimer’s disease (66). Pimavanserin has also been shown to potentiate a subeffective dose of the atypical APD risperidone in acutely psychotic patients with schizophrenia, producing a more rapid onset of action than standard-dose risperidone or an equally effective dose of haloperidol, while producing fewer side effects (67). These results are consistent with evidence that pimavanserin, as well as other 5-HT$_2A$ inverse agonists, is able to potentiate subeffective doses of atypical, but not typical, APDs in clinically relevant animal models of psychosis and cognitive impairment (68, 69). The possibility that pimavanserin is effective as a monotherapy for some patients with schizophrenia is consistent with...
the finding that 5R43469B, another 5-HT3A inverse agonist, was reported to diminish psychotic symptoms more effectively than placebo, but slightly less so than haloperidol, in acutely psychotic patients with schizophrenia (59).

Conclusions

The approval of lorcaserin by the FDA in June 2012 marks the culmination of many years of basic science investigation in fields as disparate as the central control of appetite and drug-induced valvular heart disease. Thus, the pivotal discoveries that 5-HT2C receptors are essential mediators of both appetite (37) and the closely related serotonergic 5-HT1A is responsible for drug-induced valvular heart disease (27, 42) paved the way for the design of novel serotonergic drugs predicted to be effective in reducing appetite without cardiovascular side effects. Additionally, since it is now well established that drugs can selectively engage either G protein or β-arrestin signaling (70, 71), drugs with selective signaling bias for one pathway over another may have distinct clinical advantages over drugs without functional selectivity (72–75). It will be important to determine whether 5-HT2C agonists with signaling bias represent a therapeutic advance over drugs without functional selectivity.

The clinical studies cited here (58) are consistent with preclinical data demonstrating that selective 5-HT3A inverse agonism is a valuable mechanism for treating psychosis with fewer side effects, both as monotherapy and adjunctive treatment. One thing that is unclear, however, is the degree of inverse agonism required for therapeutic efficacy in psychosis and related disorders (76), and future studies examining drugs with a range of antagonist functional selectivity and inverse agonism will be needed to address this point. Finally, additional extensive research is needed to establish the range of disorders in which 5-HT3A inverse agonists can substitute for or augment subeffective doses of APDs. At least for PDP, pimavanserin may be considered a potential next-generation atypical APD.

Taken together, these findings underscore the importance of an in-depth understanding of the biology and pharmacology of specific subtypes of 5-HT receptors and how this may lead to the development of novel treatments with selective clinical efficacies and fewer side effects compared with prior medications.

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