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 $5\text{HT}_{2C}$ and $5\text{HT}_{2A}$ receptors and provide new treatments for obesity and Parkinson’s disease psychosis, respectively.
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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-HT1c 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-HT3 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 intransone 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., sumatryptan 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 medulate 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 potently inhibited by both typical (12) and atypical (23) antipsychotic drugs (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-HT6, 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-HT4 and 5-HT7 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-HT4 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., antagonists 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-HT₂A (31) and 5-HT₂C (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-HT₂B (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).

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-HT₁A</td>
<td>Anxiety, depression (buspirone)</td>
<td>Cognition enhancement (tandospirone)</td>
<td>77</td>
</tr>
<tr>
<td>5-HT₁B</td>
<td>Migraine headaches (sumatriptan, rizatriptan, zolmitriptan, etc.)</td>
<td>Depression (AZD3783)</td>
<td>78</td>
</tr>
<tr>
<td>and 5-HT₁D</td>
<td>Unknown</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT₁E</td>
<td>Migraine headaches</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT₁F</td>
<td>Hypertension (ketanserin)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5-HT₂A</td>
<td>Pulmonary hypertension (terguride)</td>
<td>NA</td>
<td></td>
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<tr>
<td>5-HT₂B</td>
<td>Obesity (lorcaserin)</td>
<td>NA</td>
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<tr>
<td>5-HT₂C</td>
<td>Chemotherapy-induced nausea (odansetron, granisetron, tropisetron, etc.)</td>
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</tr>
<tr>
<td>5-HT₃</td>
<td>Gastrointestinal motility disorders (metoclopramide)</td>
<td>NA</td>
<td></td>
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<tr>
<td>5-HT₄</td>
<td>Unknown</td>
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<tr>
<td>5-HT₇</td>
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</tr>
</tbody>
</table>

Figure 1
Sites of action of 5-HT therapeutics. Shown in the middle is a table listing the major families of 5-HT receptors (viz. 5-HT₁ to 5-HT₇). As shown, the 5-HT₁ family has five members (5-HT₁A, 5-HT₁B, 5-HT₁D, 5-HT₁E, and 5-HT₁F), while the 5-HT₂ family — the topic of this review — has three: 5-HT₂A, 5-HT₂B, and 5-HT₂C. Each member of the 5-HT₂ family displays distinct brain and tissue distributions. The 5-HT₂A receptor is enriched in pyramidal neurons in layer V of the cerebral cortex, where it mediates the actions of pimavanserin and other atypical antipsychotic drugs. The 5-HT₂B receptor is enriched in interstitial cells of the heart valves, where it mediates the valvulopathic actions of certain drugs like fenfluramine. The 5-HT₂C receptor is enriched in the hypothalamus, among other areas, particularly in nuclei engaged in regulating feeding behavior, where it mediates the actions of the appetite suppressant lorcaserin.
pharmacologically distinct 5-HT₁B and 5-HT₂B receptors (refs. 19, 29, and Figure 2), many of the key amino acids essential for ligand binding by the G protein–coupled 5-HT receptors are identical. Until recently, this high degree of structural conservation made it challenging for medicinal chemists to create subtype-selective 5-HT receptor–active drugs. As is evident from Table 1, and as has been briefly reviewed earlier, several selective serotonergic drugs have now survived the gauntlet of clinical trials and are approved for treating a number of diseases, including obesity, migraine headaches, psychosis, anxiety, depression, chemotherapy-induced nausea, and even Alzheimer’s disease.

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 at the 5-HT₂A receptor, are rarely used because of unwanted side effects caused by their actions at other receptors (35).

**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.

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, 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 in one trial (46), but not in the other (47). Lorcaserin appears to achieve its weight-reducing effects by diminishing caloric intake rather than by altering energy expenditure (48).

**Figure 3**

Lorcaserin induces significant weight loss. (A) Average weight loss versus placebo with lorcaserin treatment (n = 1,538 in lorcaserin group vs. 1,489 in placebo group; $P < 0.001$). (B) Percentage of patients in each group who achieved ≥5% weight loss (P < 0.001 lorcaserin vs. placebo). Data republished with permission from ref. 46.
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) D2 receptors (50); however, D3 receptor blockade also leads to deleterious extrapyramidal side effects (EPSs) and 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 D1 and D2 and 5-HT2A receptors led to the hypothesis that one type of atypical APD could be identified by a higher affinity for 5-HT2A receptors than for D2 receptors (54). Subsequently, a series of drugs that conformed to this hypothesis, including risperidone, olanzapine, and others, were developed for 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 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-HT2A 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

Figure 4
Pimavanserin significantly improves delusions and hallucinations in PDP. Baseline and 28-day scale for the assessment of positive symptoms (SAPS) of global delusions (A) and hallucinations (B) ratings for 30 patients per group with PDP treated with pimavanserin or placebo (P < 0.05), respectively. Data republished with permission from ref. 63.
the finding that SR43469B, another 5-HT_{2A} inverse agonist, was shown to reduce the range of disorders in which 5-HT_{2A} 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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