

## REVIEWS

# Pharmacodynamics of Serotonin. Emphasis on 5HT-3 Antagonists and SSRI Medication (II)

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## Abstract

This paper is a specialized literature review of the pharmacology of serotonin, that focuses on pharmacodynamics. The main aspects discussed here are the metabolism and transport of serotonin, along with the structure and functions of 5-HT receptors and their clinical implications. We also included the substances that influence the serotonin neurotransmission and the autacoid function, which may be prove useful in treating various disorders. In this second part of the review, we present the types of 5-HT receptors (5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>), along with the tendencies and prospects in influencing serotonin transporter (SERT) through selective serotonin reuptake inhibitors (SSRIs). In order to achieve better safety and effectiveness of antidepressant therapy, recent research is studying substances that not only target SERT, but can also act on certain serotonergic receptors.

**Keywords:** serotonin, 5-HT receptors, cisapride, selective serotonin reuptake inhibitors (SSRI), tedatioxetine, vortioxetine, vilazodone, amitifadine

## Rezumat

Acest articol reprezintă o recenzie de literatură privind farmacologia și, în special, farmacodinamia serotoninei. Principalele aspecte abordate sunt metabolizarea, transportul serotoninei, precum și structura, funcțiile receptorilor 5-HT și implicațiile clinice ale acestora. S-au inclus date despre substanțe care influențează neurotransmisia serotonergică și funcția de autacoid a serotoninei, care se pot dovedi utile în tratamentul anumitor afecțiuni. În această a doua parte a recenziei, sunt prezentate celelalte tipuri de receptori serotonergici (5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>), alături de tendințele și perspectivele actuale în influențarea transportorului serotoninei prin inhibitori selectivi ai recaptării serotoninei. Pentru a obține o mai mare siguranță și eficacitate a tratamentului antidepresiv, studii recente au descris substanțe care, pe lângă efectul asupra transportorului serotoninei, acționează direct și asupra unor anumiți receptori serotonergici.

**Cuvinte cheie:** serotonină, receptori serotonergici, cisapridă, inhibitori selectivi ai recaptării serotoninei, tedatioxetină, vortioxetină, vilazodonă, amitifadină

## SEROTONERGIC RECEPTORS AND THEIR IMPLICATIONS IN THERAPY (PART II)

5-HT<sub>4</sub> receptors are a G-protein-coupled family of receptors coupled with G<sub>s</sub> protein that stimulates the production of the intracellular signaling molecule cAMP.

It has two isoforms (5-HT<sub>4S</sub> and 5-HT<sub>4L</sub>), differing in the length and sequence of their C-termini<sup>1</sup>. 5-HT<sub>4</sub> are present both in the central nervous system and peripheral tissues; in the brain, are found mostly in basal ganglia and the hippocampus<sup>2</sup>. In the periphery, 5HT<sub>4</sub> play an important role in the functioning of gastrointestinal tract, urinary bladder, heart and adrenal gland.

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Gastrointestinal 5-HT<sub>4</sub> receptors potentiate peristalsis, and electrolyte secretion. In the urinary bladder, activation of 5-HT<sub>4</sub> receptors modulates cholinergic and purinergic transmission. Stimulation of atrial 5-HT<sub>4</sub> receptors produces tachycardia and arrhythmias. In the adrenal gland, activation of 5-HT<sub>4</sub> receptors releases cortisol, aldosterone and corticosterone<sup>3</sup>.

**Cisapride** is a 5-HT<sub>4</sub> agonist that increases motility of the upper gastrointestinal tract. It was widely prescribed as a prokinetic agent. Cisapride was withdrawn in 2000 because of reports of the side-effect long QT syndrome, which may cause arrhythmias, e.g. torsade des pointes<sup>4</sup>. Other 5-HT<sub>4</sub> agonists are supposed to be antidepressants with early onset of effects<sup>5</sup>. Cisapride's mechanism of action include increasing the phosphorylation of the CREB protein, desensitization of 5-HT<sub>1A</sub> autoreceptors and promoting neurogenesis in the hippocampus<sup>6</sup>.

Because of their properties, 5-HT<sub>4</sub> receptor agonists and antagonists may also be useful in the treatment of cardiac arrhythmias, urinary incontinence, irritable bowel syndrome and gastroparesis<sup>3</sup>. However, because of the severity of the adverse effects, extensive research is being done in finding a safe new-generation 5-HT<sub>4</sub> receptor ligands that can be used in medical treatments<sup>7</sup>.

For the clinical treatment of IBS-C (irritable bowel syndrome with constipation predominance) 5-HT<sub>4</sub> receptor agonists are sometimes employed. 5-HT<sub>4</sub> receptor agonists (e.g. tegaserod) potentiate peristalsis, initiated by 5HT<sub>1</sub> receptor stimulation, eases the abdominal pain and increases the number of bowel movements and decreases stool consistency<sup>8</sup>.

5-HT<sub>4</sub> receptor agonists (e.g. tegaserod) have been associated with cardiovascular adverse events probably because of changes in the function of the cardiac hERG (human Ether-à-go-go Related Gene) potassium channel. New-generation 5-HT<sub>4</sub> receptor agonists (e.g. prucalopride, velusetrag) are devoid of these adverse effects<sup>9</sup>.

**The 5-HT<sub>5A</sub> receptors** are Gi/Go coupled proteins, that inhibit the manufacture of the cAMP intracellular signaling molecule<sup>10</sup>. Despite the fact that humans have also a gene coding for the 5-HT<sub>5B</sub> subtype, the 5-HT<sub>5A</sub> subtype is the only one expressed in the human brain. This is because the coding sequence of 5-HT<sub>5B</sub> subtype is interrupted by stop codons, making the gene non-functional<sup>11</sup>. The 5-HT<sub>5</sub> receptors have not been extensively characterized pharmacologically. LSD (lysergic acid diethylamide) appears to act as a partial agonist at the 5-HT<sub>5A</sub> receptor. Another partial agonists are valerian extract and valerianic acid<sup>12</sup>. However, few highly

selective agonists or antagonists are commercially available for the 5-HT<sub>5A</sub> receptor, but extensive research is being done in this direction<sup>13</sup>.

**The 5-HT<sub>6</sub> receptors** are Gs coupled proteins and are present in the brain, most prominently in the caudate nucleus, but also in striatum, olfactory tubercle, nucleus accumbens and hippocampus<sup>14,15</sup>. Because of its abundance in limbic and cortical regions, it has been suggested that 5-HT<sub>6</sub> receptors play a role in regulating glutamatergic and cholinergic neuronal activity and are involved in the cognition, feeding and, possibly, affective state and seizures<sup>16</sup>. Indeed, studies with 5-HT<sub>6</sub> receptor antagonists have shown encouraging results in improving cognitive performance in patients with Alzheimer's<sup>17</sup>. 5-HT<sub>6</sub> receptor antagonists potentiate the antidepressant effects of SERT inhibition. Also, it has been suggested that co-administration of a lower dose of an antidepressant with a 5-HT<sub>6</sub> receptor antagonist might speed up the onset of action and reduce the side-effects<sup>5</sup>. Stimulation of 5-HT<sub>6</sub> receptors might play a role in some of the behavioral and chemical effects of antidepressants such as fluoxetine<sup>18</sup>.

**The 5-HT<sub>7</sub> receptors** are receptors coupled with protein Gs protein<sup>19</sup>. The 5-HT<sub>7</sub> receptors are found especially in the brain, the gastrointestinal tract, in blood vessels and in the intestinal immune cells<sup>20</sup>. There is also evidence that 5-HT signaling (including 5-HT<sub>7</sub>) plays an important role in various gut disorders such as inflammatory bowel diseases, IBS, and enteric infections<sup>21</sup>.

**5-HT<sub>7</sub> receptors** control body temperature, regulate sleep and circadian rhythms. Preclinical data also support the antidepressant actions of 5-HT<sub>7</sub> receptor antagonists, but clinical efficacy has not been yet established. Other evidences have implicated the 5-HT<sub>7</sub> receptor in learning and memory. Blockade of this receptor may be beneficial against schizophrenia-like cognitive deficits; other possible indications include pain, epilepsy, migraine, and autism spectrum disorders<sup>22</sup>.

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

Selective serotonin reuptake inhibitors (SSRIs) modulates serotonin levels and are one of the most used class of antidepressants, probably because they induce fewer adverse effects than classical tricyclic agents<sup>23</sup>. SSRI generics include fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine and escitalopram.

## MECHANISM OF ACTION

SSRIs inhibit the reuptake of serotonin and, as a result, serotonin lasts longer in the synaptic cleft and can stimulate several times the presynaptic and postsynaptic receptors. The supposed mechanism of the antidepressive effect is the serotonergic reinforcement.

Serotonergic reinforcement does not take place immediately after the initiation of treatment, as increased serotonin levels stimulate 5-HT<sub>1A</sub> autoreceptors as negative feedback, inhibiting the release of serotonin at presynaptic terminals. However, persistent rise of 5-HT levels following repeated SSRI administration subsequently induces desensitization of 5-HT<sub>1A</sub> autoreceptors, and the firing frequencies of 5-HT neurons gradually recover resulting in the delayed appearance of antidepressant effects. In practice, this delayed therapeutic benefit of SSRIs has been a source of distress for both depressive patients and psychiatrists<sup>24</sup>.

## INDICATIONS

SSRIs are proved to be effective in treating conditions like depression, generalized anxiety disorder, stroke recovery, and obsessive compulsive disorder<sup>25</sup>, binge eating disorders<sup>26</sup>, premature ejaculation<sup>27</sup> or IBS (Irritable Bowel Syndrome)<sup>28</sup>.

For the patients with depression, SSRI may only work for those with severe depression. Studies show that there is little to none benefit for those patients who have mild or moderate symptoms of depression, like all other antidepressant<sup>29</sup>.

In obsessive compulsive disorder, SSRIs remain the pharmacological treatment of choice, although a substantial minority of patients fail to respond to SSRI and may need dose elevation or adjunctive antipsychotic<sup>30</sup>. Also, for the patients with stroke, SSRIs appeared to improve disability, dependence, neurological impairment, anxiety and depression<sup>31</sup>.

## ADVERSE REACTIONS

The SSRIs are not without adverse reactions, but they are usually predictable, mild and typically ameliorate with continued treatment. Decreasing the dose of the SSRI for a short time may be helpful. Adverse reactions include gastrointestinal dysfunction (diarrhea, constipation, nausea, epigastric discomfort), central nervous system effects (anxiety, tremor, somnolence), sexual dysfunction (delayed ejaculation and anorgasmia)<sup>32</sup>.

Other side effects of SSRIs include **akathisia**<sup>33</sup>, **increased risk of bone fractures**<sup>34</sup> and **photosensitivity**<sup>35</sup>.

In addition, SSRIs in higher dosage than recommended **worsen preexistent suicidal ideation**<sup>36</sup>. Epidemiologic studies show that SSRI treatment is linked with upper gastrointestinal bleeding; other bleeding sites has been less commonly reported, as has a possibly increased risk of bleeding associated with surgical procedures<sup>37</sup>. Patients who take both SSRI and blood thinners and/or NSAIDs (nonsteroidal anti-inflammatory drugs), as well as those suffering from liver failure or cirrhosis are more vulnerable to these side-effects<sup>38,39</sup>. Treatment with SSRIs during pregnancy is **associated with slightly increased risk of cardiovascular malformations**<sup>39</sup> and higher incidence of pulmonary hypertension in the newborn child, especially if the child was exposed to SSRIs in late pregnancy<sup>40</sup>.

SSRIs are relatively safe in overdose despite serotonin syndrome being common<sup>41</sup>. The most important symptoms for diagnosing serotonin syndrome are tremor, extreme aggressiveness, akathisia, or clonus (spontaneous, inducible and ocular)<sup>42</sup>. The exception are citalopram and sertraline. Studies show that sertraline and citalopram are associated with cardiovascular disease and the occurrence of arrhythmias<sup>43</sup>. Citalopram was significantly associated with QTc prolongation and even death<sup>41,44</sup>.

## PERSPECTIVES. INFLUENCING THE SEROTONIN SYSTEM BY ANTIDEPRESSANTS

The serotonin syndrome and withdrawal syndrome are important aspects considered in the research and management of depression using SSRIs. The **withdrawal syndrome** (met especially in substances with short half-lives, can be counteracted using substances with longer half-life as fluoxetine).

Recent research has focused on obtaining additional antidepressant effects by manipulating specific type of 5-HT1 receptor, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, 5-HT7. Substances already discovered (vilazodone, vortioxetine), and others that are under study or in the pipeline may not increase the overall tonus of serotonin and may be more efficacious and safe.

Drugs that influence both 5-HT3 and SERT are already on the market. Thus, tricyclic antidepressant (TCA) **imipramine**; the SSRI **fluoxetine**; the non-selective  $\alpha_2$ -adrenoceptor antagonist **mirtazapine** and the MAOI **phenelzine** block in a dose-dependently manner the inward current mediated by 5-HT3 receptors expressed in cultured cells<sup>45,46</sup>.

**Buspiprone** is part of the azapirone chemical class and is a partial agonist for 5-HT<sub>1A</sub> receptor, that has

anti-anxiety and antidepressant properties<sup>47</sup>. Additionally, buspirone is a dopamine antagonist at the D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors<sup>48,49</sup>. It was firstly synthesized in 1968 and marketed in 1986, and it is used for treating generalized anxiety and depression (either alone or combined with an antidepressant drug)<sup>50</sup>.

**Flibanserin** is a benzimidazole that has a high affinity for serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist). Flibanserin decreases the amount of serotonin in the brain, while elevating the levels of noradrenaline and dopamine. The substance has a very mild antidepressant activity and was initially developed for the treatment of hypoactive sexual desire disorder (HSDD)<sup>51</sup>.

**Several drugs that target the serotonergic system have recently been approved in major depressive disorder treatment (MDD)**. MDD is the leading cause of disability worldwide, and only 33% of patients with MDD responded to initial drug therapy<sup>52</sup>.

**Vilazodone** is a partial agonist of 5-HT<sub>1A</sub> receptor and a serotonin transporter, that shown efficacy versus placebo in improving depression symptoms in several double-blind, placebo-controlled trials<sup>53</sup>. Vilazodone's adverse reactions are nausea and diarrhoea<sup>54</sup>.

**Vortioxetine** is an antidepressant with multimodal activity, with effects on multiple 5-HT receptors and on the serotonin transporter, which has shown efficacy in MDD patients<sup>55</sup>. It has been shown to combine 5-HT<sub>3</sub> and 5-HT<sub>7</sub> receptor antagonism, 5-HT<sub>1B</sub> receptor partial agonism, 5-HT<sub>1A</sub> receptor agonism, and serotonin transporter inhibition<sup>56</sup>. Vortioxetine offers a comparable tolerability and efficacy (assessed by MADRS/HAM-D tests) when compared with other antidepressants used in major depressive disorder<sup>57</sup>.

The area is still one of interest for many researchers. Some drugs that target serotonergic system are on the

pipeline and waiting for approval. Unfortunately, not all of them proved to be safe and effective.

**Amitifadine** (EB-1010), now in a clinical phase III trial NCT0131843458, is a triple monoamine uptake inhibitor which inhibits transporters of dopamine, serotonin and norepinephrine<sup>59</sup>.

**DSP-1053** is a serotonin reuptake inhibitor with 5-HT<sub>1A</sub> partial agonistic activity which seem to generate a rapid antidepressant results with negligible adverse events<sup>60</sup>. The clinical study of this substance was terminated in 2014, after a clinical phase I trial, because of financial reasons<sup>61</sup>.

**Tedatioxetine** (Lu AA24530) is a multimodal antidepressant agent, which is used for generalized anxiety disorder or other anxiety disorders and for depression<sup>62</sup>. In the international patent application WO 03/029232, the compound is believed to be an inhibitor of the serotonin transporter, and to manifest affinity for the serotonin receptor 5-HT<sub>2C</sub><sup>63</sup>. In 2007, the substance was investigated in a clinical phase II trial for treating major depressive disorder NCT00599911<sup>64</sup>. The study showed promising results<sup>65</sup>. However, the drug never reached phase III trial stage. In May 2016, the trial was discontinued<sup>66</sup>.

## CONCLUSIONS

Influencing serotonergic receptors and focusing on serotonin synthesis, transportation and serotonin degradative enzymes represent important and interesting topics for the research. Recent research involving serotonin aims to improve the safety and effectiveness of antidepressant therapy. To achieve this, scientists developed drugs that not only target SERT, but can also act as a full or partial agonist or antagonist on certain serotonergic receptors.

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