



## The effect of selective serotonin reuptake inhibitors on the hemostasis in patients with craniocerebral trauma

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### Abstract

**Background.** Due to the increased prevalence of depressive disorders, the demand for antidepressants also increases. One of the most popular pharmacological groups is selective serotonin reuptake inhibitors. Although, their admission not always can be safe in some categories of patients, among formers can be patients with head injuries.

**Aim.** Main mechanisms of SSRI negative influence on hemostatic system analysis in patients with depression and TBI. Finding ways to solve this problem.

**Methods.** The bibliographic databases such as Pubmed, Web of Science and Google Scholar for keywords: organic depression, disorder, depression, SSRI, TBI, hemostasis changes were analyzed.

**Results.** The general information about serotonin, its role in neurotransmission and the influence on the hemostatic system were studied. There're shown the main mechanisms of SSRI influence on intra-thrombocytes serotonin. The main risk factors for SSRI admission in patients with depression with TBI were studied. We also have studied the SSRI admission in these painful patients. Some ways of solving the problem of treatment of patients with depression on the background of TBI are proposed.

**Keywords:** depression, craniocerebral trauma, SSRI, hemostasis

## 1 Background

Today medicine widely uses psychopharmacology that is affine to various neurotransmitter systems. The most used among such drugs are antidepressants. This is due to a significant prevalence of depression among the mental disorders.

According to the data information from the World Health Organization (WHO), in Ukraine, about 2.8 million people suffer from depression that is 6.3% of the entire population. This indicator is higher in Europe [1].

Some American researchers state that such antidepressants as selective serotonin reuptake inhibitors (SSRI) are prescribed at a frequency of 6 per second, 24/7, throughout the year [2]. However, despite the general prevalence, availability, and effectiveness of these drugs, there is some negative impact beyond their target properties.

## 2 General facts about of neurotransmission

For any neurosynaptic transmission, regardless the type of neurotransmitter system, the following factors are always the same: the neurotransmitters presence in the postsynaptic neuron and, as a rule, uneven mediator distribution in the nervous system. Indispensable is a presence in the presynaptic neuron of molecular neurotransmitters' precursors, enzymes for their synthesis or specific transport systems. A prerequisite for removing the mediator from the intersynaptic gap is the presence of specialized inactivation systems of the secreted mediator, which allow completing the functioning of the mediator: enzymes degradation system (monoamine oxidase - MAO), presynaptic neuron reuptake system, etc. [3]. And the serotonergic system is not an exception.

## 3 Serotonin, general information

Initially, the researchers did not detect the proper function of *5-hydroxytryptamine* (5-HT) serotonin as a neurotransmitter, but only that this compound is capable of causing vasoconstriction and the fact that it is the part of platelets [4]. Despite the fact that the platelets themselves contain a significant amount of 5-HT, serotonin is synthesized in the intestine. It released after the activation of presynaptic neurons and stimulation of enterochromaffin cells. Serotonin is an intermediate product of tryptophan metabolism. After penetrating the bloodstream, serotonin is sequestered inside the platelets by sodium-dependent serotonin transporters SERotonin Transporter (SERT), which subsequently enters the secretory granules with the help of *vesicular monoamine transporter* (VMAT) [5].

The serotonin function is not only a part of hemostasis system. It has been proved that it can inhibit the molecular growth activity of some neuronal cones. This suggests that serotonin plays a significant role in the regulation of neuronal architecture, in addition to its classical neurotransmitter and hemostatic functions [6].

## 4 SSRI influence on intra-platelet serotonin

Serotonin is the structural part of human platelets and cumulates in the cytoplasm of their inactive form. Serotonin is stored in one of four types of granules, which are called "dense" [7].

Selective serotonin reuptake inhibitors inhibit the function of its transporters (5-HTT or SERT), blocking the absorption of synaptic serotonin by the presynaptic neuron (for re-use or disposal). Similarly, SSRIs prevent the serotonin entry from the bloodstream into the thrombocyte. Since platelets are not able to synthesize this neurotransmitter independently, the use of SSRI can reduce the volume of dense granules for intra-platelets serotonin cumulation, thus reducing the effectiveness of mediated platelet hemostasis [8], [9]. According to this, it can be assumed that patients with depression, with a background of craniocerebral trauma (CCT) who take SSRI, are at higher risk of "vascular damage."

The treatment of patients with SSRI after cerebrovascular accident (due to ischemia or hemorrhage) with subsequent development of depression symptoms remains poorly understood [9].

## 5 The use of SSRI in patients with CCT

A common phenomenon in patients with CCT is an ischemic disorder of cerebral circulation. In about 90% of deaths after CCT on the brain autopsy are revealed the areas of ischemia with varying severity. Among patients with CCT, signs of brain ischemia are also noted, and cerebral hemodynamic disorder is noted in the delayed time intervals [10]. Therefore, neurosurgeons often use the anticoagulants with such complications as thrombosis of central and cerebral arteries, intracranial venous thrombosis and thrombophlebitis of central veins.

The use of antiplatelet agents, in this case, can often be carried out for a sufficiently long time and with co-administration of SSRI can significantly increase the risk of blood coagulation impairment.

Moreover, among mental disorders that arise as a result of CCT, depressive disorders are most common 30-40% [11]. That is, almost all patients in this category may be potential applicants for the SSRI use.

Also, the patients with CCT have disturbances of sodium balance. The main reasons for this may be the syndrome of inadequate antidiuretic hormone secretion (ADH) (Parhon syndrome), cerebral mineral loss syndrome, etc., due to central sodium autoregulation disturbances [12]. In our opinion, these phenomena can affect not only the work of the sodium-dependent serotonin transporter but also potentiate other side effects of SSRIs.

## 6 Influence of fatty acids on the hemostasis

There is an assumption that when the platelets reach a very high concentration of arachidonic acid, the acid exchange between the platelets and the brain becomes impossible. When the level of arachidonic acid increases in brain and neurons, the platelet membrane begins to lose its viscosity, significantly impairing the serotonin absorption by platelets and neurons. Since serotonin is not able to penetrate the blood-brain barrier as in normal conditions, the described mechanism may explain the low serotonin concentrations in depression, both in platelets and neurons [13].

The severe traumatic, ischemic and hemorrhagic lesions of the brain are accompanied by the development of local inflammatory reactions. Cytokines are essential inflammatory response mediators, powerful immunoregulatory pro- and anti-inflammatory agents. They stimulate the formation and release of many secondary mediators such as free radical molecules, neuropeptides, and derivatives of arachidonic acid (prostaglandins, thromboxanes, prostacyclin, and leukotrienes) [14], [15].

It can be assumed that due to CCT additional arachidonic acid concentration in brain structures (an element of proinflammatory response) is further increased, triggering a cascade of fatty acid metabolism and serotonin metabolism.

## 7 Pain syndrome and SSRI

Such biological factors as an impairment of the serotonergic system are not limited by causing depression but also characterize the pain modulation. Patients who are simultaneously suffer from pain and depression are often attenuated and have a higher level of suffering [16].

It has been proved that the use of antidepressants, including the SSRI class, can efficiently reduce the level of pain syndrome, in particular, the headache. SSRIs mitigate the severity of pain in 70-80% of patients with chronic pain [17], [16].

It is known that CCT of any severity is a chronic stress reaction accompanied by pain, often hyperthermia syndrome and inflammation [18]. As a remote CCT consequence, the headache often occurs, and the SSRI group may be involved in its reduction.

Also, patients with CCT often fall into the intensive care departments, where receive non-steroidal anti-inflammatory drugs, with adverse gastrointestinal effects. Prolonged use of the non-steroidal anti-inflammatory drugs in combination with SSRI considerably increases the risk of gastrointestinal bleeding.

## 8 Conclusion

Consequently, side effects using SSRIs in patients with CCT should always be considered and weighted. There most risks are associated with hemostasis impairments, which can often lead to negative consequences and delayed recovery. Alternatively, for patients with secondary depression after CCT can be used antidepressants of another pharmacological group, such as tricyclic antidepressants. In the circumstances of the mandatory appointment of SSRIs, patients must be warned about the adverse effects on the blood coagulation system. A specialist prescribing SSRI drugs should take into account the possibility of interaction with other medications and take timely preventive measures.

## 9 Additional information

### 9.1 Competing interests

The author declares that no competing interests exist.

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