Chapter

Experimental Serotonin Syndrome: Effects of GABA-ergic Medications and 5-HT_2-Antagonists

Rumen Nikolov and Kalina Koleva

Abstract

Serotonin syndrome (SS) is a potentially life-threatening adverse drug effect that occurs after an overdose or combined administration of two or more drugs that increase the serotonin levels. In humans, SS is represented by a triad of symptoms including mental status changes, neuromuscular hyperactivity and autonomic dysfunction. The manifestations of the syndrome observed in rodents resemble the symptoms of SS in humans. Theoretically, SS can occur as a result of stimulation of any of the seven families of the serotonin receptors. However, most data support the involvement of 5-HT_{1A} and 5-HT_{2A} receptors. A number of studies indicate the effectiveness of 5-HT_2 antagonists and GABA-ergic agents in the treatment of the hyperthermia and other symptoms of SS in rats. Therefore, animal models of SS may help to further elucidate the mechanism of its development and the possibilities for its treatment.

Keywords: 5-HT_2 antagonists, GABA-ergic agents, serotonin syndrome, rats

1. Introduction

Serotonin syndrome is a drug-induced condition caused by medications that increase intrasynaptic serotonin levels. It is characterized by a triad of symptoms that includes neuromuscular hyperactivity, altered mental status and autonomic dysfunction.

The syndrome was first described in 1960 as "Indolamine syndrome" in patients on therapy with monoamine oxidase inhibitors (MAOIs) who develop symptoms of serotonin syndrome after taking tryptophan – a serotonin precursor [1]. Since then, the number of reported cases of serotonin syndrome has increased significantly. The medical community's attention to serotonin syndrome was drawn in 1984 by the unusual death of 18-year-old Libby Zion in a New York City hospital, which may have been linked to the development of serotonin syndrome after concomitant use of an MAOI and opioid analgesic. The opioid analgesic pethidine was administered to the girl suffering from depression and taking the antidepressant phenelzine, which led to the development of a fatal serotonin syndrome [2, 3].

Of all serotonergic drugs, antidepressants are the most common cause of serotonin syndrome, and recent data suggest that the most common drug combination associated with serotonin syndrome is that between selective serotonin reuptake

inhibitors (SSRIs) and opioids [2]. As a relatively rare adverse drug reaction, the incidence of serotonin syndrome is difficult to be calculated during randomized controlled trials [4]. Moreover, it is estimated that over 85% of physicians are unaware of the condition [5]. The non-specific manifestation of the syndrome leads to its difficult recognition and underreporting, which further complicates the determination of its incidence. It is considered that serotonin syndrome occurs in 15% of patients who overdose on selective serotonin reuptake inhibitors. The actual incidence of serotonin syndrome is thought to be significantly higher than reported [6–8].

2. Molecular mechanism of serotonin syndrome development

Serotonin syndrome results from an increase in intrasynaptic serotonin levels caused by overstimulation of both central and peripheral serotonin receptors [9, 10]. Theoretically, serotonin syndrome can occur as a result of stimulation of any receptor of all seven serotonin receptor families [11]. However, the role of 5-HT_{1A} and 5-HT_{2A} is most often mentioned [6, 7, 11, 12]. Moreover, the 5-HT_{2A} receptor is thought to mediate the most serious consequences of the serotonin syndrome (**Table 1**).

Some authors suggest that the development of serotonin syndrome requires the accumulation of a critical amount of serotonin. However, studies show that this level of serotonin is probably different for each patient. Experimental studies in animal models of serotonin syndrome have shown that other neurotransmitters such as noradrenaline (NA), N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA) and dopamine may also play a role in the development of serotonin syndrome but their role is not fully understood [6, 13].

It is shown that in serotonin syndrome CNS serotonin levels increase between 40 and 140 times. At the same time, dopamine levels are increased 10 to 44 times [14, 15]. Other studies indicate overactivation of the noradrenergic system with a rise in NA levels up to 15.9 times in serotonin syndrome, but the cause remains unknown. Some authors explain this increase in NA levels with activation of 5-HT2A receptors. This is supported by the fact that no significant increase in NA was observed with prior administration of ritanserin and pipamperone which act as antagonists of these receptors. On the other hand, there is evidence of the involvement of 5-HT1A receptors, although the administration of 5-HT1A antagonists does not prevent the increase in NA levels [14, 15]. The degree of NA increase may

Receptor		Function related to serotonin toxicity
Type	**Subtype**	
5-HT_1	5-HT_{1A}	neuronal inhibition, thermoregulation, hyperactivity associated with anxiety, hypoactivity associated with depression
	5-HT_{1D}	locomotion, muscle tone
5-HT_2	5-HT_{2A}	neuronal excitation, vasoconstriction, platelet aggregation
	5-HT_{2B}	smooth muscle contraction
5-HT_3	—	nausea and vomiting
5-HT_4	—	increased GIT motility

5-HT = 5-hydroxytryptamine (serotonin); GIT = gastrointestinal tract.

Table 1.
Serotonin receptors associated with the serotonin syndrome development [10–12].

be related to the prognosis of serotonin syndrome, although it is not fully understood. At the same time, some of the observed symptoms of autonomic instability may be due to an overactivated noradrenergic system [14].

3. Implicated drugs

Drugs and substances that increase serotonin levels are known as serotonergic, and a mechanism by which they do that are as follows:

- Increased serotonin synthesis
- Increased serotonin release
- Activation of serotonergic receptors
- Serotonin reuptake inhibition
- Inhibition of serotonin metabolism

The full list of all serotonergic substances is long, but antidepressants and, in recent years, some opioids take the central place. It is important to note that

Mechanism	Implicated drugs
Increased serotonin synthesis	**Dietary supplements:** L-tryptophan
Increased serotonin release	**Illicit substances:** Amphetamines **Opioids:** Tramadol, Oxycodone, Pethidine **Antidepressants:** Mirtazapine **OTC drugs:** Dextromethorphan
Activation of serotonergic receptors	**Antidepressants:** Mirtazapine, Trazodone **Opioids:** Fentanyl, Pethidine **Anxiolytics:** Buspirone **Antimigraines:** Triptans
Serotonin reuptake inhibition	**Antidepressants:** Bupropion, Nefazodone, Trazodone; **SNRIs** (Venlafaxine, Desvenlafaxine, Duloxetine); **SSRIs** (Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram); **TCAs** (Amitriptyline, Nortriptyline, Imipramine, Desipramine, Clomipramine, Amoxapine, Doxepin, Maprotiline, Trimipramine); **Opioids:** Tramadol, Pethidine, Tapentadol, Levomethorphan, Levorphanol, Methadone, Pentazocine, Dextropropoxyphen, Fentanyl, Remifentanyl **OTC drugs:** Dextromethorphan **Antiemetics:** Ondansetron, Granisetron, **Herbal supplements:** *Hypericum perforatum* (St. John's wort)
Inhibition of serotonin metabolism	**MAOIs:** Tranylcypromine, Phenelzine, Isocarboxazid, Nialamid, Iproniazid, Pargyline, Clorgiline, Moclobemide, Toloxatone **Antibiotics:** Linezolid **Dyes:** Methylene blue **Triptans:** Sumatriptan, Rizatriptan,, Zolmitriptan, Almotriptan, Eletriptan, Frovatriptan, Naratriptan **Anxiolytics:** Buspirone **Herbal supplements:** Hypericum perforatum (St. John's wort)

Table 2.
Implicated drugs [5–7, 16–19].

substances with serotonergic activity include not only antidepressants and opioids but also a number of other drugs used in everyday medical practice – some antibiotics, antiemetics, anxiolytics, antipsychotics, as well as over-the-counter drugs (OTC), dietary supplements, some illicit drugs and more [5–7, 16–19].

Some of the antidepressants, opioids, and other drugs reported in the literature causing serotonin syndrome, as well as the mechanisms by which they increase serotonin levels are listed in **Table 2**.

4. Experimental serotonin syndrome

The term "serotonin syndrome" in animals was first used in 1979 by Hwang and Van Woert [20, 21]. Manifestation of serotonin toxicity has been described in various animal species, however, most literature data, respectively most studies, are available on the development of serotonin syndrome in mice and rats [20].

In contrast to humans, in whom the symptoms of serotonin syndrome are well defined, the literature describes a wide variety of manifestations and different combinations of responses characterizing the development of serotonin syndrome in rodents.

There is considerable heterogeneity in the animal models reported in the literature. The use of different assessment methods, different response sets and different scales in assessing the effects of increased serotonergic tone limits quantitative comparisons of laboratory results. In this regard, Haberzettl et al. [20] conducted a systematic literature review of the described models of serotonin syndrome in rats and mice and evaluated the observed behavioral and autonomic manifestations. Based on the frequency of behavioral manifestations, the team divides them into traditional and additional, distinguishing those that reliably characterize the development of serotonin syndrome in rodents. The described behavioral and autonomic symptoms of serotonin syndrome in rats are presented in **Table 3**.

It is widely believed that 5-HT_{1A} receptors mediate most behavioral manifestations of serotonin syndrome in rats [22–31]. In support of this are studies demonstrating the induction of serotonin syndrome behaviors by the administration of 5-HT_{1A} agonists [26, 32, 33] and the induction of a narrower spectrum of manifestations such as hind limb abduction, a Straub phenomenon and low body posture, from the partial 5-HT_{1A}-agonist buspirone [31].

Other behavioral responses such as head weaving and wet dog shake, are mediated by 5-HT_{2A} receptors [22, 34–37]. For example, head weaving in rats induced by the administration of the non-selective MAO inhibitor phenelzine and the SSRI paroxetine was dose-dependently antagonized by 5-HT_2 antagonists [35, 37]. In addition, head weaving caused by the administration of a 5-$HT_{2A/2C}$ agonist has been antagonized by the administration of a 5-HT_{2A} antagonist, but not by a 5-$HT_{2C/2B}$ antagonist [38].

The analysis of Haberzettl et al. showed that the most common autonomic dysregulation manifestation observed in rats with serotonin syndrome is the change in the body temperature. The hyperthermic reaction observed is thought to be mainly related to the activation of 5-HT_{2A} receptors [14, 39]. Experimental studies confirmed the involvement of 5-HT_{1A} and 5-HT_{2A} receptors in thermoregulation in rats. For example, blockade of 5-HT_2 receptors by ketanserin or pirenperone causes a decrease in body temperature, while blockade of 5-HT_{1A} receptors by pindolol results in an increase in body temperature [40].

Although not a mandatory manifestation of serotonin syndrome, hyperthermia is one of the leading causes of observed mortality in experimental serotonin syndrome. In both animals and humans, it is hyperthermia that mainly causes

Behavioral manifestations		Autonomic manifestations
Traditional	**Additional**	
forepaw treading	body twitches	body temperature (increased or decreased)
head weaving	chewing	lower lip retraction
hind limb abduction	head shakes	penile erection
low body posture	head twitches	pyloric erection
Straub phenomenon	hyperactivity	salivation
tremor	hyperreactivity	
backward walking	locomotor activity (increased or decreased)	
	myoclonus	
	rearing	
	wet dog shake	

Table 3.
Serotonin syndrome manifestation in rats.

complications. Such complications in humans could include seizures, rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure, disseminated intravascular coagulation (DIC syndrome), coma and death [6].

The manifestation of serotonin syndrome observed in rodents resembles the manifestation of serotonin syndrome in humans (**Table 4**). For example, neuromuscular manifestations such as tremor and muscle rigidity have been observed in both humans and rodents. Myoclonus, which is a clinical symptom of serotonin syndrome in humans, in rodents may manifest as head twitches and forepaw treading. The Straub phenomenon observed in rodents may refer to the muscle rigidity observed in humans [21]. According to autonomic dysregulation manifestation, changes in body temperature occur in both rodents and humans.

The most difficult to differentiate in animals is the third group of symptoms typical for the manifestation of serotonin syndrome in humans - mental status changes. However, hyperactivity and to some extent the hyperreactivity observed in rodents are associated with agitation observed in humans. Moreover, it is important

Symptoms/manifestations of serotonin syndrome	Humans	Rodents
Neuromuscular disorders	clonus tremor hyperreflexia muscle rigidity myoclonus	head weaving tremor hind limb abduction Straub phenomenon low body posture backward walking
Autonomic dysfunction	diaphoresis hyperthermia (>38 °C) diarrhea shivering	change in body temperature (increase or decrease)
Mental status changes	agitation confusion hyperactivity hypomania anxiety	hyperactivity hyperreactivity

Table 4.
Symptoms and manifestations of serotonin syndrome in humans and rodents – Comparison.

to note that the current criteria for diagnosing serotonin syndrome in humans, Hunter's criteria, do not include as a mandatory diagnostic criterion changes in mental status, which confirms the validity and applicability of the animal model of serotonin syndrome [21].

Two classical models of serotonin syndrome in rats have been described in the literature induced by concomitant administration of serotonergic substances with different mechanisms of action: 5-HTP (100 mg/kg i.p.) - a precursor of serotonin and clorgyline (2 mg/kg i.p.) - selective MAO-A inhibitor [14] and fluoxetine (10 mg/kg i.p.) - a selective serotonin reuptake inhibitor and tranylcypromine (3.5 mg/kg, i.p.) - a non-selective MAO inhibitor [12].

5. Effect of GABA-ergic drugs on experimental models of serotonin syndrome

Many central neurotransmitters, such as serotonin, norepinephrine, dopamine, acetylcholine, GABA and glutamate, are involved in the thermoregulation. GABA is a major central inhibitory neurotransmitter involved in thermoregulatory processes. The role of GABA as a thermoregulatory neurotransmitter or modulator is suggested by the good distribution of the mediator in the hypothalamus, confirmed by autoradiographic and immunohistochemical studies [41–43] and its central action. In addition, GABA-ergic neurons, as well as postsynaptic $GABA_A$-ergic receptors have been identified in PO/AH (preoptic area/anterior hypothalamus) [44–46].

Potentiation of the central inhibitory effect of GABA is achieved by several different mechanisms, including allosteric modulation of GABA receptors (benzodiazepines, barbiturates, Z-hypnotics, propofol and fospropofol), direct GABA- or GABA-receptor agonist action (respectively muscimol, baclofen), increased synthesis of GABA (e.g., gabapentin, pregabalin, sodium valproate), inhibition of enzymatic degradation of GABA (e.g., vigabatrin, sodium valproate) and inhibition of neuronal or glial uptake of GABA (e.g., tiagabine).

Benzodiazepines mediate their pharmacological effects by enhancing the inhibitory effect of GABA on the CNS by binding to a specific modulating site on $GABA_A$-ergic receptors containing 1, 2, 3 or 5 alpha-subunits. Benzodiazepines have no affinity for receptor complexes containing 4 or 6 alpha-subunits [47]. Activation of specific benzodiazepine receptors by diazepam or other benzodiazepines increase the frequency of $GABA_A$-associated chloride channel opening [48].

The pharmacological activity of valproic acid is expressed in potentiation of GABA-ergic neurotransmission and prolongation of the inactivation of voltage-dependent neuronal sodium channels [49]. Sodium valproate is thought to increase brain GABA concentration by the following mechanisms: (1) inhibition of GABA-transaminase enzyme activity and decreased GABA degradation [50] 2) stimulating GAD activity [51] and increasing GABA synthesis; (3) decreased GABA turnover [52]. Vigabatrin (gamma-vinyl GABA) is a vinyl-substituted analogue of GABA that selectively and irreversibly inhibits the activity of the enzyme GABA-transaminase (GABA-T) and significantly increases the concentration of GABA in the brain [53].

After central and systemic administration of diazepam, sodium valproate, and vigabatrin dose-dependent decreases of body temperature in rats is observed [54–57]. GABA-induced hypothermia has been suggested to be mediated by $GABA_A$ and/or $GABA_B$ receptor activation [58, 59]. The hypothermic effect of sodium valproate and vigabatrin occurs later than diazepam-induced hypothermia, which can be explained by their indirect mechanism of potentiation of GABA-ergic mediation.

These results are further confirmed in our studies, where we found that substances with a GABA-ergic mechanism of action such as diazepam, sodium

valproate and vigabatrin effectively reduced the hyperthermic response in experimental serotonin syndrome in rats induced by concomitant administration of 5-HTP (100 mg/kg i.p.) - a precursor of serotonin and clorgyline (2 mg/kg i.p.) - selective MAO-A inhibitor [14]. The reduction in serotonergic-induced hyperthermia with pretreatment of GABA-mimetic drugs is most likely due to an increase in central GABA-ergic neurotransmission through activation of $GABA_A$ receptors (e.g., diazepam) as well as through indirect action by increasing GABA concentration (e.g., sodium valproate, vigabatrin). These results on the hyperthermia associated with serotonin syndrome support the hypothesis of an interaction between the GABA-ergic and serotoninergic systems in thermoregulatory processes.

In our studies, after the concomitant administration of 5-HTP (100 mg/kg i.p.) and clorgyline (2 mg/kg i.p.), a model of serotonin syndrome with typical behavioral and autonomic manifestations developed. Tremor occurs 10 minutes after injection, the hyperthermic reaction develops at 30 minutes, and the maximum value is observed 60 minutes after injection of the substances. All animals in this group died between 60 and 90 minutes after injection of serotonin. Pretreatment with diazepam at a dose of 5 mg/kg i.p. reduced the hyperthermic reaction at 30 and 60 min compared to the group with a model of serotonin syndrome, in which saline was administered prior to the injection of serotonergic agent. Administration of sodium valproate at a dose of 300 mg/kg i.p. reduced the hyperthermic reaction at 30 and 60 min compared to the group with a model of serotonin syndrome, in which saline was administered before the injection of serotonergic substances [56, 60]. Additionally, in another of our experiments, we used a modified model of serotonin syndrome induced by the concomitant administration of fluoxetine (10 mg/kg i.p.) - a selective serotonin reuptake inhibitor and clorgyline (2 mg/kg i.p.) - selective MAO-A inhibitor. Vigabatrin at a dose of 300 mg/kg i.p. significantly decreased the hyperthermic response between 150 and 300 min in rats with a serotonin syndrome model, compared to the group with a model of serotonin syndrome in which only saline was administered before the injection of the serotonergic substances [57, 61].

In summary pretreatment with diazepam (5 mg/kg i.p.), sodium valproate (300 mg/kg i.p.), and vigabatrin (300 mg/kg i.p.) decreased hyperthermia in different experimental models of the serotonin syndrome. These results suggest involvement of interactions between GABA-ergic and serotonergic systems in the processes of thermoregulation.

We assume that in addition to direct GABA-ergic mechanisms, interactions between neurotransmitters or mediator systems are involved in the influence of hyperthermia in serotonin syndrome by GABA-ergic substances. Presynaptic $GABA_B$ receptors affect the release of norepinephrine, dopamine, and 5-hydroxytryptamine [62]. Expression of predominantly $GABA_B$ receptors has been found in most of the serotonin and catecholamine neurons in the nuclei of the brainstem, which are involved in the regulation of autonomic functions [63]. Interactions between the GABA-ergic and serotonergic systems are mediated by presynaptic heteroreceptor $GABA_B$-inhibition of 5-HT release or by G-protein-coupled interaction between 5-HT_{1A} and $GABA_B$-ergic receptors [64].

6. Effect of 5-HT$_2$-antagonists on experimental models of serotonin syndrome

Hyperthermia is the most common cause of complications of life-threatening forms of serotonin syndrome in humans and is one of the leading causes of mortality reported in experimental models of serotonin syndrome [6, 7].

As already mentioned, several studies indicate the role of 5-HT_{2A} receptors in the development of a hyperthermic response in rats. In this regard, the effect of a number of 5-HT_2 antagonists in influencing the hyperthermic response in experimental serotonin syndrome has been studied. Some of the serotonin antagonists investigated are cyproheptadine, ritanserin, ketanserin, mirtazapine, some antipsychotics such as chlorpromazine, risperidone and olanzapine [8, 11–15]. Results demonstrate a significant involvement of the 5-HT_{2A} receptors in the development of hyperthermic response in experimental serotonin syndrome [65].

Studies have shown that cyproheptadine effectively affects the hyperthermic response in an experimental model of serotonin syndrome. Moreover, a comparative study demonstrates that, unlike other 5-HT_2 antagonists, it prevents both the development of serotonin syndrome and the mortality of experimental animals [14, 66].

The role of atypical antipsychotics in the treatment of serotonin syndrome has been increasingly discussed in the last few years, given that most atypical antipsychotics work primarily by blocking 5-HT_2 receptors [67].

Moreover, temperature dysregulation is a documented side effect of antipsychotic drugs [68–72]. That most often manifests in the development of hyperthermia, a life-threatening symptom characteristic of the malignant neuroleptic syndrome (MNS). Data from various clinical cases, summarized in recent years by van Marum [68] and Zonnenberg [69, 70], show that the use of classical or atypical antipsychotics carries the risk of developing another, less well-documented adverse drug reaction, namely hypothermia. In humans, hypothermia is defined as a body temperature below 35 ° C, distinguishing three degrees: mild (33–35 ° C), moderate (28–33 ° C) and severe (<28 ° C) hypothermia [69].

Although the hypothermic effect of antipsychotics is less known than the hyperthermic one expressed in MNS, analysis of the literature data shows that there are almost equal reports of hypothermia (480 cases) and hyperthermia (524 cases) associated with the use of antipsychotics. Zonnenberg et al. consider that the actual incidence of hypothermia associated with the use of antipsychotics is at least 10 times higher than the documented [69]. For the first time, the development of hypothermia after the use of antipsychotic drugs was described by Loughnane in a 26-year-old patient on chlorpromazine therapy [73].

The analyzes of van Marum et al. and Zonnenberg et al. indicate that hypothermia most often occurs one week after starting antipsychotic therapy or after increasing the dose. They also indicated that the use of atypical antipsychotics was more common (approximately 55% of cases), with risperidone being the most commonly reported [68, 69, 74]. Mild hypothermia associated with low-dose risperidone has also been observed in a child with verbal and physically aggressive behavior [75].

Analyzes by van Marum and Zonnenberg show that antipsychotics with a higher affinity for blocking 5-HT2A than D2 receptors are more often associated with the development of hypothermia [68, 69]. This is also confirmed by experimental and clinical studies which demonstrate that the atypical antipsychotics olanzapine and risperidone cause a decrease in body temperature indicating that the mechanism of hypothermic action is associated with blockade of 5-HT_2 receptors [72, 74–76].

7. Conclusion

From all data reported thus far, it can be concluded that 5-HT_2 receptors and the GABA system are strongly involved in the development of hyperthermia in serotonin syndrome and the mortality associated with it.

Drug-induced hyperthermia is resistant to the action of classical antipyretics therefore their use is not recommended. The use of acetylsalicylic acid and other classical antipyretics not only has no effect in the case of drug-induced hyperthermia but may even cause a worsening of the course of the hyperthermic reaction. In our opinion, due to the proven hypothermic effect of the mentioned GABA-ergic drugs and 5-HT$_2$-antagonists, their use in the therapeutic regimen of hyperthermia in specific hyperthermic syndromes is appropriate.

The similarity in the manifestation of the syndrome in rats and humans can serve as a basis for further elucidation of the mechanism of development of serotonin syndrome in humans. The animal model of serotonin syndrome can be used to study drugs and drug combinations that pose a potential risk of developing serotonin syndrome in humans and the possibilities for its prevention.

Author details

Rumen Nikolov* and Kalina Koleva
Department of Pharmacology and Toxicology, Medical Faculty,
Medical University, Sofia

*Address all correspondence to: rnikolov@medfac.mu-sofia.bg

References

[1] Oates, J. A., & Sjoerdsma, A. (1960). Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor. Neurology, 10, 1076-1078.

[2] Abadie, D., Rousseau, V., Logerot, S., Cottin, J., Montastruc, J. L., & Montastruc, F. (2015). Serotonin Syndrome: Analysis of Cases Registered in the French Pharmacovigilance Database. Journal of clinical psychopharmacology, 35(4), 382-388.

[3] Arora, B., & Kannikeswaran, N. (2010). The serotonin syndrome-the need for physician's awareness. International journal of emergency medicine, 3(4), 373-377.

[4] Werneke, U., Jamshidi, F., Taylor, D. M., & Ott, M. (2016). Conundrums in neurology: diagnosing serotonin syndrome - a meta-analysis of cases. BMC neurology, 16, 97.

[5] Watson, W. A., Litovitz, T. L., Klein-Schwartz, W., Rodgers, G. C., Jr, Youniss, J., Reid, N., Rouse, W. G., Rembert, R. S., & Borys, D. (2004). 2003 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. The American journal of emergency medicine, 22(5), 335-404.

[6] Volpi-Abadie, J., Kaye, A. M., & Kaye, A. D. (2013). Serotonin syndrome. The Ochsner journal, 13(4), 533-540.

[7] Boyer, E. W., & Shannon, M. (2005). The serotonin syndrome. The New England journal of medicine, 352(11), 1112-1120.

[8] Ables, Adrienne & Nagubilli, Raju. (2010). Prevention, Diagnosis, and Management of Serotonin Syndrome. American family physician. 81. 1139-42.

[9] Francescangeli, J., Karamchandani, K., Powell, M., & Bonavia, A. (2019). The Serotonin Syndrome: From Molecular Mechanisms to Clinical Practice. International journal of molecular sciences, 20(9), 2288.

[10] Scotton, W. J., Hill, L. J., Williams, A. C., & Barnes, N. M. (2019). Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. International journal of tryptophan research: IJTR, 12, 1178646919873925.

[11] Racz, R., Soldatos, T. G., Jackson, D., & Burkhart, K. (2018). Association Between Serotonin Syndrome and Second-Generation Antipsychotics via Pharmacological Target-Adverse Event Analysis. Clinical and translational science, 11(3), 322-329.

[12] Sun-Edelstein, C., Tepper, S. J., & Shapiro, R. E. (2008). Drug-induced serotonin syndrome: a review. Expert opinion on drug safety, 7(5), 587-596.

[13] Nisijima, K., Shioda, K., Yoshino, T., Takano, K., & Kato, S. (2004). Memantine, an NMDA antagonist, prevents the development of hyperthermia in an animal model for serotonin syndrome. Pharmacopsychiatry, 37(2), 57-62.

[14] Nisijima, K., Yoshino, T., Yui, K., & Katoh, S. (2001). Potent serotonin (5-HT)(2A) receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. Brain research, 890(1), 23-31.

[15] Sleight, A. J., Marsden, C. A., Martin, K. F., & Palfreyman, M. G. (1988). Relationship between extracellular 5-hydroxytryptamine and behaviour following monoamine

oxidase inhibition and L-tryptophan. British journal of pharmacology, 93(2), 303-310.

[16] Bronstein, A. C., Spyker, D. A., Cantilena, L. R., Jr, Rumack, B. H., & Dart, R. C. (2012). 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. Clinical toxicology (Philadelphia, Pa.), 50(10), 911-1164.

[17] Logan, B. K., Mohr, A. L. A., Friscia, M., Krotulski, A. J., Papsun, D. M., Kacinko, S. L., Ropero-Miller, J. D., & Huestis, M. A. (2017). Reports of adverse events associated with use of novel psychoactive substances, 2013-2016: A review. Journal of Analytical Toxicology, 41(7), 573-610.

[18] Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. (2007) New insights into the mechanism of action of amphetamines. Annual Review of Pharmacology and Toxicology; 47, 681-698.

[19] Hassan, Z., Bosch, O. G., Singh, D., Narayanan, S., Kasinather, B. V., Seifritz, E., Kornhuber, J., Quednow, B. B., & Müller, C. P. (2017). Novel Psychoactive Substances-Recent Progress on Neuropharmacological Mechanisms of Action for Selected Drugs. Frontiers in psychiatry, 8, 152.

[20] Haberzettl, R., Bert, B., Fink, H., & Fox, M. A. (2013). Animal models of the serotonin syndrome: a systematic review. Behavioural brain research, 256, 328-345.

[21] Hwang, E. C., & Van Woert, M. H. (1979). Behavioral and biochemical actions of p-chlorophenylethylamine (p-CPEA) in mice. Life sciences, 24(7), 595-601.

[22] Isbister, G. K., & Buckley, N. A. (2005). The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. Clinical neuropharmacology, 28(5), 205-214.

[23] Lucki, I., Nobler, M. S., & Frazer, A. (1984). Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. The Journal of pharmacology and experimental therapeutics, 228(1), 133-139.

[24] Zhang, G., Krishnamoorthy, S., Ma, Z., Vukovich, N. P., Huang, X., & Tao, R. (2009). Assessment of 5-hydroxytryptamine efflux in rat brain during a mild, moderate and severe serotonin-toxicity syndrome. European journal of pharmacology, 615 (1-3), 66-75.

[25] Goodwin, G. M., De Souza, R. J., Wood, A. J., & Green, A. R. (1986). The enhancement by lithium of the 5-HT1A mediated serotonin syndrome produced by 8-OH-DPAT in the rat: evidence for a post-synaptic mechanism. Psychopharmacology, 90(4), 488-493.

[26] Goodwin, G. M., & Green, A. R. (1985). A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. British journal of pharmacology, 84(3), 743-753.

[27] Goodwin, G. M., De Souza, R. J., Green, A. R., & Heal, D. J. (1987). The pharmacology of the behavioural and hypothermic responses of rats to 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). Psychopharmacology, 91(4), 506-511.

[28] Green, A. R., Guy, A. P., & Gardner, C. R. (1984). The behavioural effects of RU 24969, a suggested 5-HT1 receptor agonist in rodents and the effect on the behaviour of treatment with antidepressants. Neuropharmacology, 23(6), 655-661.

[29] Lu, J. Q., & Nagayama, H. (1996). Circadian rhythm in the response of central 5-HT1A receptors to 8-OH-DPAT in rats. Psychopharmacology, 123(1), 42-45.

[30] Lu, J. Q., & Nagayama, H. (1997). Circadian rhythm in the function of central 5-HT1A receptors is endogenous in nature. Cellular and molecular life sciences: CMLS, 53(3), 224-226.

[31] Smith, L. M., & Peroutka, S. J. (1986). Differential effects of 5-hydroxytryptamine1a selective drugs on the 5-HT behavioral syndrome. Pharmacology, biochemistry, and behavior, 24(6), 1513-1519.

[32] Assié, M. B., Bardin, L., Auclair, A. L., Carilla-Durand, E., Depoortère, R., Koek, W., et al. (2010). F15599, a highly selective post-synaptic 5-HT(1A) receptor agonist: in-vivo profile in behavioural models of antidepressant and serotonergic activity. The international journal of neuropsychopharmacology, 13(10), 1285-1298.

[33] Forster, E. A., Cliffe, I. A., Bill, D. J., Dover, G. M., Jones, D., Reilly, Y., & Fletcher, A. (1995). A pharmacological profile of the selective silent 5-HT1A receptor antagonist, WAY-100635. European journal of pharmacology, 281(1), 81-88.

[34] Peroutka, S. J., Lebovitz, R. M., & Snyder, S. H. (1981). Two distinct central serotonin receptors with different physiological functions. Science (New York, N.Y.), 212(4496), 827-829.

[35] Yap, C. Y., & Taylor, D. A. (1983). Involvement of 5-HT2 receptors in the wet-dog shake behaviour induced by 5-hydroxytryptophan in the rat. Neuropharmacology, 22(7), 801-804.

[36] Roth BL, Hyde EG. (1997) Pharmacology of 5-HT2 receptors. In: Baumgarten HGGM, editor. Handbook of experimental pharmacology, serotonergic neurons and 5-HT receptors in the CNS. Berlin, Heidelberg, New York: Springer; p.367-94.

[37] Koshikawa, F., Koshikawa, N., & Stephenson, J. D. (1985). Effects of antidepressant drug combinations on cortical 5-HT2 receptors and wet-dog shakes in rats. European journal of pharmacology, 118(3), 273-281.

[38] Willins, D. L., & Meltzer, H. Y. (1997). Direct injection of 5-HT2A receptor agonists into the medial prefrontal cortex produces a head-twitch response in rats. The Journal of pharmacology and experimental therapeutics, 282(2), 699-706.

[39] K. M., Hill, J. L., & Murphy, D. L. (1995). Evidence that 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced hyperthermia in rats is mediated by stimulation of 5-HT2A receptors. Psychopharmacology, 117(2), 193-199.

[40] Gudelsky, G. A., Koenig, J. I., & Meltzer, H. Y. (1986). Thermoregulatory responses to serotonin (5-HT) receptor stimulation in the rat. Evidence for opposing roles of 5-HT2 and 5-HT1A receptors. Neuropharmacology, 25(12), 1307-1313.

[41] Palacios, J. M., Wamsley, J. K., & Kuhar, M. J. (1981). High affinity GABA receptors-autoradiographic localization. Brain research, 222(2), 285-307.

[42] Vincent, S. R., Hökfelt, T., & Wu, J. Y. (1982). GABA neuron systems in hypothalamus and the pituitary gland. Immunohistochemical demonstration using antibodies against glutamate decarboxylase. Neuroendocrinology, 34(2), 117-125.

[43] Decavel, C., & Van den Pol, A. N. (1990). GABA: a dominant

neurotransmitter in the hypothalamus. The Journal of comparative neurology, 302(4), 1019-1037.

[44] Yasumatsu, M., Yazawa, T., Otokawa, M., Kuwasawa, K., Hasegawa, H., & Aihara, Y. (1998). Monoamines, amino acids and acetylcholine in the preoptic area and anterior hypothalamus of rats: measurements of tissue extracts and in vivo microdialysates. Comparative biochemistry and physiology. Part A, Molecular & integrative physiology, 121(1), 13-23.

[45] Herbison, A. E., Heavens, R. P., & Dyer, R. G. (1990). Endogenous release of gamma-aminobutyric acid from the medial preoptic area measured by microdialysis in the anaesthetised rat. Journal of neurochemistry, 55(5), 1617-1623.

[46] Fénelon, V. S., & Herbison, A. E. (1996). In vivo regulation of specific GABAA receptor subunit messenger RNAs by increased GABA concentrations in rat brain. Neuroscience, 71(3), 661-670.

[47] Möhler, H., Fritschy, J. M., & Rudolph, U. (2002). A new benzodiazepine pharmacology. The Journal of pharmacology and experimental therapeutics, 300(1), 2-8.

[48] Twyman, R. E., Rogers, C. J., & Macdonald, R. L. (1989). Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital. Annals of neurology, 25(3), 213-220.

[49] McNamara, J.O. Pharmacotherapy of the epilepsies. (2006) In: Hardmann, J.G., Limbrid, L.E., Gilman, A.G., editors. Godmann and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill.

[50] Löscher W. (1999). Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Progress in neurobiology, 58(1), 31-59.

[51] Bolaños, J. P., & Medina, J. M. (1993). Evidence of stimulation of the gamma-aminobutyric acid shunt by valproate and E-delta 2-valproate in neonatal rat brain. Molecular pharmacology, 43(3), 487-490.

[52] Owens, M. J., & Nemeroff, C. B. (2003). Pharmacology of valproate. Psychopharmacology bulletin, 37 Suppl 2, 17-24.

[53] Angehagen, M., Ben-Menachem, E., Rönnbäck, L., & Hansson, E. (2003). Novel mechanisms of action of three antiepileptic drugs, vigabatrin, tiagabine, and topiramate. Neurochemical research, 28(2), 333-340.

[54] Zarrindast, M. R., & Dibayan, M. (1989). Involvement of GABAA receptor sites in diazepam hypothermia. General pharmacology, 20(6), 855-859.

[55] Swiader, M. J., Luszczki, J. J., Zwolan, A., Wierzchowska-Cioch, E., Wielosz, M., & Czuczwar, S. J. (2004). Is a hypothermic effect of LY300164, valproate and phenobarbital evident in mice?. Roczniki Akademii Medycznej w Bialymstoku (1995), 49, 270-274.

[56] Nikolov R, Yakimova K. (2008). Effects of GABA-acting drugs diazepam and sodium valproate on thermoregulation in rats. Journal of Thermal Biology, 33(8): 459-463.

[57] Nikolov, R. P., & Yakimova, K. S. (2011). Effects of GABA-transaminase inhibitor Vigabatrin on thermoregulation in rats. Amino acids, 40(5), 1441-1445

[58] Zarrindast, M. R., & Oveissi, Y. (1988). GABAA and GABAB receptor sites involvement in rat thermoregulation. General pharmacology, 19(2), 223-226.

[59] Rawls SM, Tallarida RJ, Kon DA et al. (2004). GABAA-receptors modulate cannabinoid evoked hypothermia. Pharmacology Biochemistry and Behavior, 78 (1): 83-91.

[60] Nikolov, R. (2014). Effects of sodium valproate on the hyperthermic reaction in experimental serotonin syndrome. Meditsinski pregled, 50, № 2, 45-48.

[61] Nikolov, R.P., K.N. Koleva, M.H. Hristov, K.S. Yakimova. (2020). Hyperthermia in experimental models of serotonin syndrome: influence of vigabatrin. Bulgarian chemical comminications, 52(1), 138-141.

[62] Clark, W. G., & Lipton, J. M. (1985). Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents: II. Neuroscience and biobehavioral reviews, 9(2), 299-371.

[63] Burman, K. J., Ige, A. O., White, J. H., Marshall, F. H., Pangalos, M. N., Emson, P. C., Minson, J. B., & Llewellyn-Smith, I. J. (2003). GABAB receptor subunits, R1 and R2, in brainstem catecholamine and serotonin neurons. Brain research, 970(1-2), 35-46.

[64] Mannoury la Cour, C., Hanoun, N., Melfort, M., Hen, R., Lesch, K. P., Hamon, M., & Lanfumey, L. (2004). GABA(B) receptors in 5-HT transporter- and 5-HT1A receptor-knock-out mice: further evidence of a transduction pathway shared with 5-HT1A receptors. Journal of neurochemistry, 89(4), 886-896.

[65] Porcelli, S., Drago, A., Fabbri, C., Gibiino, S., Calati, R., & Serretti, A. (2011). Pharmacogenetics of antidepressant response. Journal of psychiatry & neuroscience: JPN, 36(2), 87-113.

[66] Gillman P. K. (1999). The serotonin syndrome and its treatment. Journal of psychopharmacology (Oxford, England), 13(1), 100-109.

[67] Kasper, S., Praschak-Rieder, N., Tauscher, J., & Wolf, R. (1997). A risk-benefit assessment of mirtazapine in the treatment of depression. Drug safety, 17(4), 251-264.

[68] van Marum, R. J., Wegewijs, M. A., Loonen, A. J., & Beers, E. (2007). Hypothermia following antipsychotic drug use. European journal of clinical pharmacology, 63(6), 627-631.

[69] Zonnenberg, C., Bueno-de-Mesquita, J. M., Ramlal, D., & Blom, J. D. (2017). Hypothermia due to Antipsychotic Medication: A Systematic Review. Frontiers in psychiatry, 8, 165.

[70] Zonnenberg, C., Bueno-de-Mesquita, J. M., Ramlal, D., & Blom, J. D. (2019). Antipsychotic-Related Hypothermia: Five New Cases. Frontiers in psychiatry, 10, 543.

[71] Ajayi, O. O., & Holroyd, S. (2017). Severe recurrent hypothermia in an elderly patient with refractory mania associated with atypical antipsychotic, valproic acid and oxcarbazepine therapy. BMJ case reports, 2017, bcr2017222462.

[72] Oerther, S., & Ahlenius, S. (2000). Atypical antipsychotics and dopamine D(1) receptor agonism: an in vivo experimental study using core temperature measurements in the rat. The Journal of pharmacology and experimental therapeutics, 292(2), 731-736.

[73] Loughnane T. (1968). Hypothermia in a young adult. Lancet (London, England), 2(7565), 455-456.

[74] Razaq, M., & Samma, M. (2004). A case of risperidone-induced

hypothermia. American journal of therapeutics, 11(3), 229-230.

[75] Grau, K., Plener, P. L., Gahr, M., Denzer, C., & Freudenmann, R. W. (2017). Mild Hypothermia in a Child with Low-Dose Risperidone. Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie, 45(4), 335-337.

[76] Rasnayake, L. R., Wimalarathne, H., Jayapala, R. K., Gamage, C. D., Dassanayake, D. L., Ratnayake et al. (2011). An unusual case of hypothermia associated with therapeutic doses of olanzapine: a case report. Journal of medical case reports, 5, 189.