Send Orders for Reprints to reprints@benthamscience.net

Current Neuropharmacology, 2021, *19*, 1545-1559

REVIEW ARTICLE

5-HT_3 Receptor Antagonism: A Potential Therapeutic Approach for the Treatment of Depression and other Disorders

Shvetank Bhatt[1,*], Thangaraj Devadoss[2], Santhepete Nanjundaiah Manjula[3] and Jayaraman Rajangam[4]

[1]Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior-474005, India; [2]Department of Pharmaceutical Chemistry, K. V. S. R. Siddhartha College of Pharmaceutical Sciences, Siddhartha Nagar, Vijayawada, Andhra Pradesh-520010, India; [3]Department of Pharmacology, JSS College of Pharmacy, Mysuru, JSS Academy of Higher Education & Research [JSSAHER], Mysuru-570015, India; [4]Department of Pharmacology, Sree Vidyanikethan College of Pharmacy – Tirupati-517 501, Andhra Pradesh, India

Abstract: ***Background*:** Depression or Major depressive disorder (MDD) is a prolonged condition of sadness. MDD is the most common mental disorder that affects more than 264 million people worldwide. According to the monoamine hypothesis, serotonin (5-hydroxy tryptamine, 5-HT), dopamine (DA) and norepinephrine (NE) are the major neurotransmitters (NTs) involved in depression.

***Methods*:** The methodology adopted for writing this review article is essentially based on the secondary literature search through a systematic literature review. This review mainly focussed on the role of 5-HT_3 receptor antagonists (5-HT_3RA) in depression and comorbid disorders like anxiety.

***Results*:** Out of three major NTs mentioned above, serotonin has a predominant role in the pathophysiology of depression. The serotonin type-3 receptors (5-HT_3R) are well renowned to be expressed in the central nervous system (CNS) in regions which have significance in the vomiting reflex, perception of pain, the reward system, cognition, depression and anxiety control. 5-HT_3R are the receptors of serotonergic family that belong to ligand-gated ion channel. 5-HT_3RA inhibit the binding of serotonin to postsynaptic 5-HT_3R and increases its availability to other receptors like 5-HT_{1A}, $_{1B}$ and $_{1D}$ as well as 5-HT_2 receptors and produces anti-depressant-like effect. 5-HT_3RA also have an important role in mood and stress disorders. Some of the studies have shown the effectiveness of these agents in stress disorder.

***Conclusion*:** The present article focussed on the role of 5-HT_3R and their antagonists in the treatment of depression and anxiety. Further studies are warranted to prove their efficacy with respect to other standard anti-depressants.

ARTICLE HISTORY

Received: June 25, 2020
Revised: September 11, 2020
Accepted: October 10, 2020

DOI:
10.2174/1570159X18666201015155816

Keywords: Co-morbid, depression, ion channel, serotonin, 5-HT_3 receptors, cognition.

1. INTRODUCTION

According to the latest report from the World Health Organization (WHO), MDD is the most common mental disorder that affects more than 264 million people worldwide [1]. The diagnostic and statistical manual for mental disorder-IV (DSM-IV) has given nine symptoms for assessment of depression. Out of these nine symptoms, if any five are present for more than 2 weeks, then the patient is said to be depressed, however, warrants further confirmation [2, 3]. The hormones like estrogen and progesterone may modulate the functioning of 5HT_3R as women are more susceptible to be affected with depression as compared to men [4-6].

*Address correspondence to this author at the Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior-474005, India;
Tel: +919414822323; Email: shvetankbhatt@gmail.com

According to this monoamine, the hypothesis level of three NTs, namely 5-HT, NE and DA, is decreased in depression [7, 8]. In addition, γ-amino butyric acid (GABA) and glutamate also have an important role in the pathophysiology of depression [9]. Moreover, recent studies also relate depression with alterations in the physiology of the brain, neuronal plasticity and reduced volume of the frontal cortex and the hippocampus [10]. Now, genetic involvement in the development of depression has also been identified. Genes such as SLC6A4 (previously known as SERT), DRDR4, SLC6A4 or 5-HTT and TPH_2 are also found to have a predominant role in the pathological progression of depression [11]. Various important causes of depression have are in (Fig. **1**). Moreover, dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis and increased oxidative stress also has a predominant role in the development of MDD [12, 13]. Imbalance in antioxidant and oxidant enzyme levels in the brain

1570-159X/21 $65.00+.00

and plasma levels of the depressed patient has also been frequently observed [13, 14]. Various studies indicated that MDD demonstrates increased levels of various peripheral inflammatory biomarkers when compared with non-depressed individuals. Increased levels of C-reactive protein, TNF- α, Interferon-α have been observed in depressed patients [15].

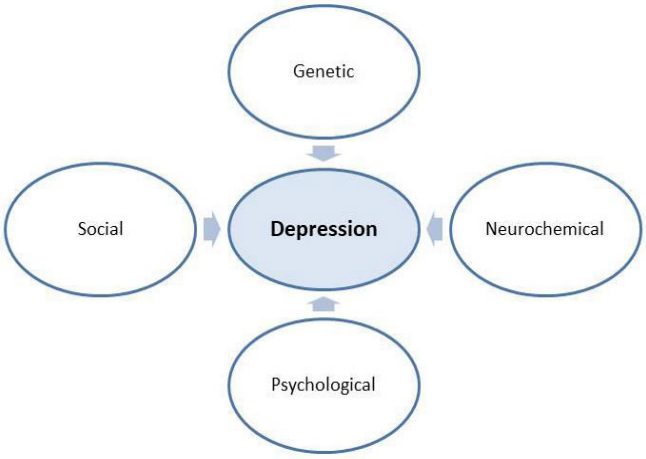

Fig. (1). Causes of depression. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Various pharmacological therapies are available for the treatment of depression and anxiety, including selective serotonin reuptake inhibitors (SSRI), noradrenaline dopamine reuptake inhibitors (NDRI), dopamine reuptake inhibitors (DARI), *etc.* [16]. However, these treatment approaches are successful to treat the symptoms of depression to some extent, but they have the drawback of ineffectiveness against treatment-resistant depression. In addition, most of the antidepressants show their effect after 1-2 months of treatment as they act through modification of the receptors [17].

Serotonin is an important neurotransmitter having a role in many physiological processes such as platelet aggregation, pain, sleep, appetite, muscle contraction, emotions and obsessions and compulsions. Targeting serotonin is an interesting strategy for the development of newer potential anti-depressants. 5- HT and its receptors are distributed in CNS, peripheral nervous system (PNS), as well as in a number of non-neuronal tissues in the gut, cardiovascular system and blood. Based on the signal transduction and amino acid sequence, now the serotonin receptors are classified into seven major types (5-HT_{1-7}) [18, 19]. All the serotonin receptors belong to the superfamily of G-protein coupled receptor (GPCR), except 5-HT_3R, which is a superfamily of ligand- gated cation channel receptor. The structure of 5-HT_3R is shown in (Fig. **2**).

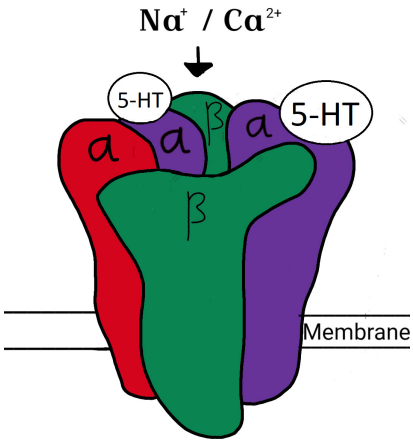

Fig. (2). Structure of the 5-HT_3 receptor. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Certain drugs and research molecules also target other 5-HT receptors. The blockade of 5-HT_{2A} receptors also seems to improve the clinical effects of SSRIs. These receptors are located postsynaptically to 5-HT axons, mainly in the neocortex. Moreover, antidepressant drugs like nefazodone, trazodone, mirtazapine are antagonists of 5-HT_{2A} or α_2-adrenoceptors [20]. Some preclinical studies have demonstrated 5-HT_{1A} receptor mediated hippocampal transmission after the chronic treatment with SSRIs as well as other antidepressant drugs [21]. However, $5HT_{1A}$ receptor agonists failed to demonstrate clinical significance in depression despite preclinical evidence. Even the effectiveness of buspirone, a 5-HT_{1A} partial agonist, is far behind as compared to standard antidepressants [22]. The other receptor is 5-HT_{1B} that may also act as a potential target for antidepressant drugs and a key determinant of stress activity. Administration of SSRIs in mice lacking 5-HT_{1B} autoreceptors exhibits increases in 5-HT levels in the ventral hippocampus (vHPC) and leads to a decrease in anxiety like behavior [23].

The expression of 5-HT_3R has been confirmed in regions having a role in the vomiting reflex, perception of pain, the reward system, memory and control of anxiety. This underlines their relevance in emesis, migraine, drug addiction, neurodegenerative and psychiatric disorders. Various behavioral and biochemical preclinical studies have reported the effectiveness of 5-HT_3R modulators in comorbid models of depression and anxiety. In addition, few clinical evidence have also shown the significance of 5-HT_3RA in CNS disorders. The effect comes in acute dose levels as well as showed inhibition of treatment resistance [24, 25]. Hence in this review, we discussed the role of 5-HT_3RA in depression comorbid with anxiety.

2. CHEMISTRY OF 5-HT_3RA

5-HT_3RA are classified into two types on the basis of binding pattern towards serotonin type 3 receptors, namely

competitive and non-competitive 5-HT_3RA. The antagonists which compete with the serotonin sites are called competitive antagonists and compounds which target allosteric sites are called non-competitive antagonists [26].

3. COMPETITIVE ANTAGONISTS

The chemical structures of competitive antagonists have similarities with serotonin. The chemical structures of serotonin and competitive 5-HT_3RA are shown in (Fig. **3**). The clinically available 5-HT_3 receptor antagonists are highly selective towards 5-HT_3 receptors than other receptors [27]. Most of the currently available competitive antagonists are in the form of salts as most of these drugs contain basic nitrogen atom(s). For example, granisetron, ramosetron, ondansetron, and palonosetron are available in the form of hydrochloride salt, while dolasetron is available in the mesylate salt form.

In old literature, as well as in recent literature, the competitive antagonists are classified into two types, namely first generation and second generation 5-HT_3RA. Ondansetron, dolasetron, tropisetron, and granisetron are classified as first-generation 5-HT_3RA, while palonosetron was categorized in second-generation 5-HT_3RA [26, 27]. In the first generation antagonists, heterocyclic systems are mostly indole or indole-like derivative, while palonosetron consists of a benzoisoquinoline (tricyclic) system.

Most of the competitive antagonists are metabolized to form the hydroxyl derivative. These metabolites are formed as the result of hydroxylation on the aryl/alicyclic system or by the reduction of the carbonyl group. For example, ondansetron, alosetron, tropisetron, granisetron, palonosetron follow hydroxylation at the aryl/alicyclic system while the dolasetron afforded hydroxyl derivative by the reduction of the ketone carbonyl group [28-32]. The formed hydroxyl metabolites are active or inactive or more active than the parent molecule. Another common pathway involved in the metabolism of competitive antagonists is demethylation, which means the removal of the methyl group from the parent molecule [32].

4. PHARMACOPHORE OF COMPETITIVE 5-HT_3RA

The pharmacophore of clinically available 5-HT_3RA and the reported molecules possesses three necessary elements [33, 34], which consists of an aromatic ring, carbonyl linking group, and a nitrogen atom. The basic pharmacophore is depicted in (Fig. **4**).

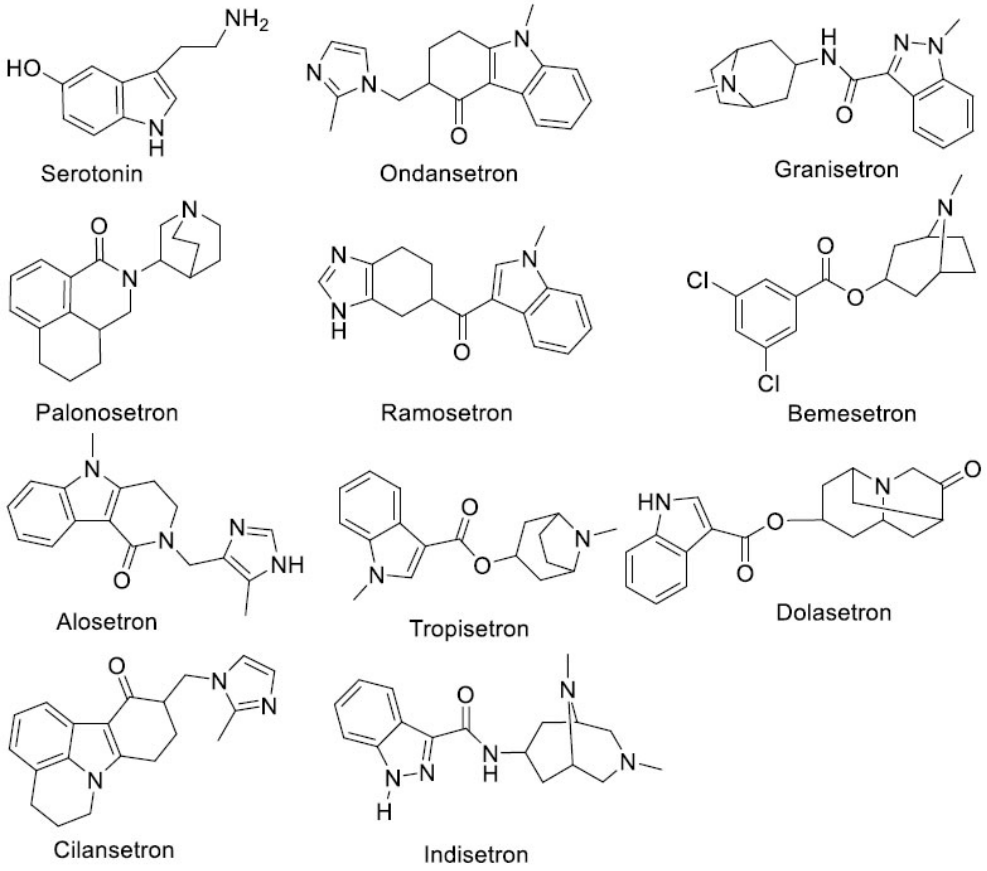

Fig. (3). Chemical structures of serotonin and competitive 5-HT_3 receptor antagonists.

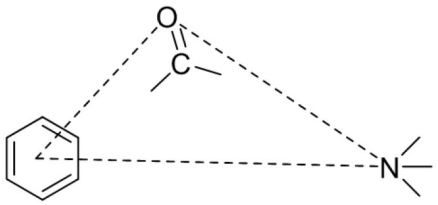

Fig. (4). Basic pharmacophore of 5-HT_3 receptor antagonists.

Several investigators have explored the role of the carbonyl group (as hydrogen bond acceptor) and the nitrogen atom (as basic nitrogen atom) in 5-HT_3RA for their interaction with 5-HT_3R [34-39]. Though a wide range of aromatic systems have been studied as 5-HT_3 receptor antagonists viz. benzothiazole, benzoxazole [40],isoquinoline [41], quinolone [42], quinoxaline [43], and indole [41], unfortunately, none of the researchers explored the role of an aromatic group in 5-HT_3RA for interaction with the receptor. In our previous study, we proposed that the possible interaction between the aromatic group and 5-HT_3R takes place through hydrophobic interaction.

Hibert *et al.* (1990) [36] proposed pharmacophoric distances between the elements: the distance between the centroid of aromatic to carbonyl oxygen ~ 3.3 Å, between the centroid of aromatic to basic nitrogen ~ 6.7 Å and the distance between carbonyl oxygen to basic nitrogen ~ 5.2 Å. In a few studies [38, 44, 45], compounds displayed potent 5-HT_3 receptor antagonism even though they deviated from the model proposed by Hibert *et al.* (1990) [36]. Similarly, in our previous study [46], many of the synthesized compounds displayed good antagonism even though the distances between the pharmacophoric elements have deviated from the model proposed by Hibert *et al.* (1990) [36].

Replacing the carbonyl group with suitable bioisotere is well tolerated; Rosen *et al.* (1990) demonstrated thiazole as hydrogen bond acceptor instead of the carbonyl group [39]. The obtained compounds maintained the 5-HT_3 antagonism, some compounds displayed antagonism greater than the standard drugs. A similar kind of results was observed when nitrogen was used as a source of hydrogen bond acceptor [47, 48].

5. NON-COMPETITIVE ANTAGONISTS

Most of the non-competitive 5-HT_3RA are obtained from natural sources [49]. The chemical structures of non-competitive 5-HT_3RA are shown in (Figs. **5A** and **5B**). The chemical structures of the non-competitive antagonists lack the similarity with serotonin.

6. PHARMACOPHORE OF NON-COMPETITIVE 5-HT_3RA

To the best of our knowledge, there is no pharmacophore model proposed/developed for the non-competitive 5-HT_3RA. Based on our observation, we identified a few common features present in non-competitive 5-HT_3RA. The common features are aliphatic residue (except vanillin) and the presence of at least one oxygen atom in the molecule. The oxygen atom may exist in the form of alcohol, aldehyde, ester, ether, amide, ketone, or phenolic functional groups. Furthermore, a set of common features is observed while comparing the phenolic derivatives. Most of the compounds except quinine contain an alkoxy or alkyl substituent present at *ortho* to a phenolic hydroxyl group and alkyl (except vanillin) substituent is located at *para* or *meta* position with respect to the phenolic hydroxyl group.

Based on this observation, we may consider these elements are necessary components (pharmacophoric elements) of non-competitive 5-HT_3RA. However, to make a conclusive statement on the pharmacophore model, an extensive study with a wide range of non-competitive 5-HT_3RA is required.

7. STRUCTURE, EXPRESSION AND PRIMARY FUNCTIONS OF 5-HT_3R

Serotonin exerts its effect through seven subfamilies of receptors, *i.e.*, 5-HT_1 to 5-HT_7 [50]. Out of these seven subtypes, only the 5-HT_3R subtype is a pentameric ion channel belonging to the superfamily of Cys-loop receptors. Long back before 50 years, '5-HT_3R' was described as the so-called 'M receptor' in the guinea-pig gut as 5-HT stimulated contractions could be blocked by the antagonist morphine [51]. It is made up of five monomer subtypes, the 5-$HT_{3A–E}$ subunits, which exhibit differences in the amino-terminal and the transmembrane region. Architecture is more or less similar for 5-$HT_{3A,\ 3B,\ 3C,\ 3E}$ subunits, whereas the 5-HT_{3D} subunit lacks most of the N-terminal domain, including the Cys-loop [52]. The functional relevance of different receptor compositions is still not clarified. These receptors work through fast synaptic transmission. Using different methods such as autoradiography, immunohistochemistry and in situ hybridization, the distribution of 5-HT_3R has been largely explained with some variance between species [53]. They are expressed in many brain regions, including the hippocampus, entorhinal cortex, frontal cortex, cingulate cortex, amygdala, nucleus accumbens (NAc), substantia nigra, and ventral tegmental area (VTA), with the highest densities in the area postrema and the nucleus tractus solitaries, regions responsible for the vomiting reflex [54-57]. The animal studies conducted to determine the expression of 5-HT_3R revealed that around 70-80% of these receptors are mainly are located in presynaptic nerve endings [58]. 5-HT_3R found within the PNS in location that includes vagal afferents from the heart and GI tract are also of physiological importance [59].

In CNS, 5-HT_3R are located in the regions involved in vomiting, pain perception, rewarding, memory and regulation of anxiety, while in the peripheral system, they are expressed on various nerve and immune cells [59, 60]. In the CNS, the density of 5-HT_3R appeared to be lower as compared to other 5-HT receptors. These receptors have their important role in emesis, particularly cancer chemotherapy in-

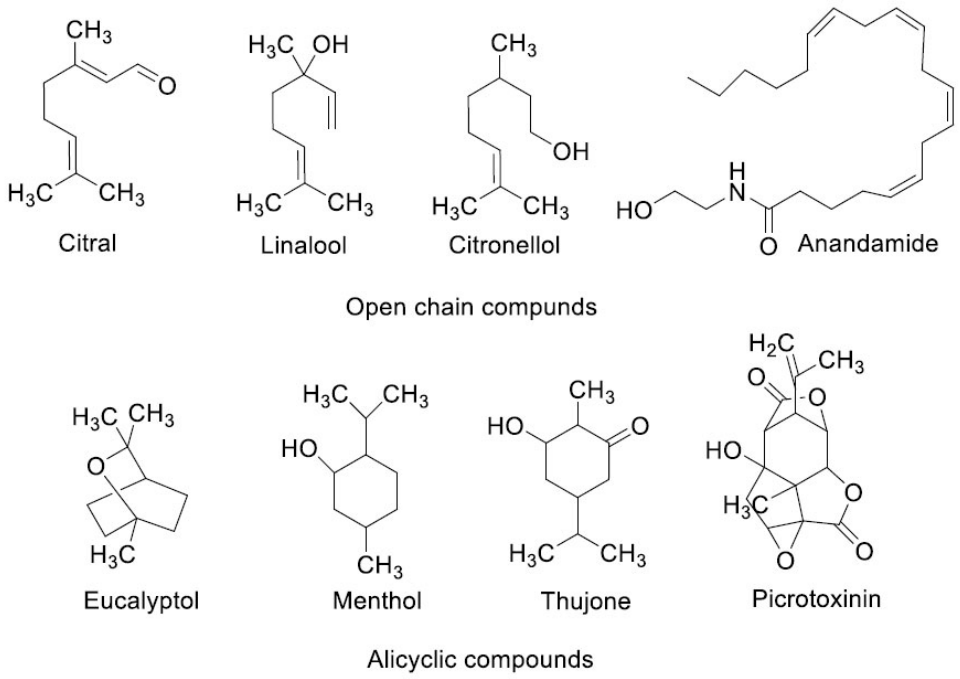

Fig. (5A). Chemical structures of non-competitive antagonists.

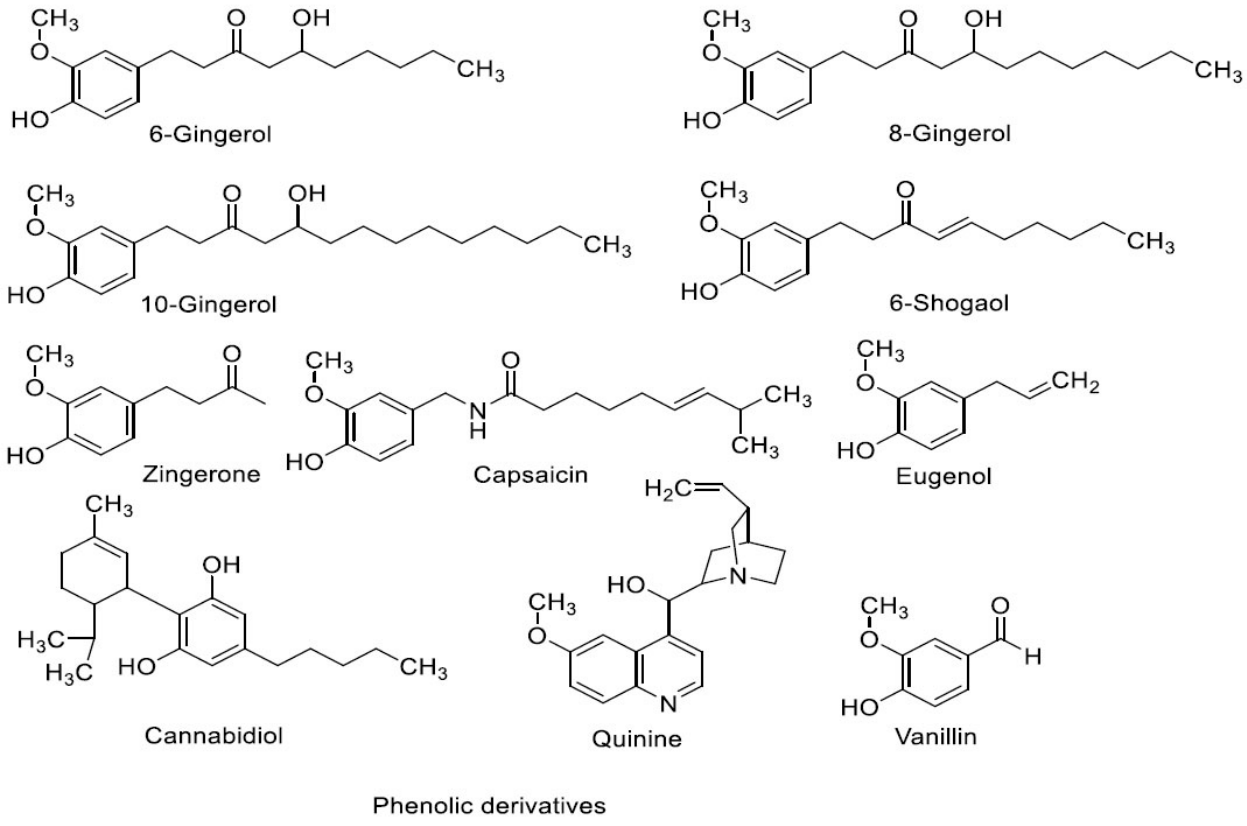

Fig. (5B). Chemical structures of non-competitive antagonists.

duced nausea and vomiting, pain sensation, addiction, psychiatric and gastrointestinal disorders [61, 62]. Moreover, the preferential localization on nerve endings is consistent with a functional role of 5-HT_3R in the control of the release of NTs such as DA, cholecystokinin, glutamate, acetylcholine, GABA, substance P, or 5-HT itself [63].

A typical subunit exhibits a large extracellular N-terminus, four TMs and a short extracellular C-terminus. Further characteristics are the large intracellular domain (ICD) between TM 3 and 4 and the Cys-loop in the N-terminus [64, 65, 66]. The transmembrane region of the channel pore is formed by the TM 2 domains of the five subunits [67]. The five subunits of 5-HT_3R cover central cation permeable pore, which facilitates the influx of $Na^+/K^+/Ca^{+2}$ ions *via* the opening of ion channel followed by fast desensitization [68]. These 5-HT_3R have a predominant role in the stimulation of nausea and vomiting and 5-HT_3RA are well recognized for their role in the reduction of cancer chemotherapy induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV) [69]. Ondansetron, granistetron, tropisetron, dolasetron, palonosetron, *etc.* are the important examples in this category [70]. Binding of three agonist molecules to homomeric 5-HT_3R leads to a fully activated ion channel [71, 72].

8. PHARMACOLOGY AND PHYSIOLOGY OF 5-HT_3R

5-HT_3R is selective for permeation of Na^+, K^+ and Ca^{2+} ions [68]. Activation of these receptors leads to the opening of ion channels and the influx of these cations, followed by depolarization of the membrane. The 5-HT_3R activation leads to the fast synaptic transmission of various NTs like 5-HT, DA or GABA [60, 73]. This activation is dependent on the location of these receptors, *i.e.*, presynaptic or postsynaptic. In particular, presynaptic 5-HT_3R displays a high permeability to Ca2+, whereas postsynaptic receptors display a lower permeability to Ca2+ compared to Na+ and K+ [74, 75].

Homomeric 5-HT_{3A} receptors are permeable to monovalent and divalent ions equally, while heteromeric receptors have lower permeability to Ca+2 [60, 76]. In addition, heteromeric receptors display faster activation and deactivation as compared to homomeric receptors. 5-HT_3RA give bell-shaped dose-response curve in case of both preclinical and clinical studies. Generally, the maximum effect is typically observed at a very low dose, in the microgram range, while higher doses are ineffective [53]. The ineffectiveness of these antagonists seen may be due to the desensitization of receptors by internalization.

9. PROBABLE MECHANISM OF 5-HT_3RA IN DEPRESSION AND COMORBID ANXIETY

In various preclinical studies, encouraging results have been obtained from the use of 5-HT_3RA in depression and comorbid anxiety models [77, 78]. These results validate the significance of 5-HT_3R in the progression of these CNS disorders. 5-HT_3RA mainly work through modulation of mainly serotonergic neurotransmission. However, it also modulates the release of DA, NE, and GABA neurotransmitter [7, 9]. Various studies conducted on 5-HT_3RA give an idea about the probable mechanism of 5-HT_3RA in depression and comorbid anxiety disorders. 5-HT_3RA, i] reduce the duration of immobility in various preclinical rodent models of depression and anxiety like forced swim test (FST), tail suspension test (TST), elevated plus maze (EPM) test and light and dark (L/D) test; ii] in a mechanistic model of depression, such as reserpine induced hypothermia, these antagonists reduce the hypothermic effect induced by reserpine due to reduction in vesicular uptake of NTs, and in 5-hydroxy tryptophan (5-HTP) induced head twitches in mice, they reduce the number of head twitches in a specified period of time; iii] In rodent models like olfactory bulbectomy and traumatic brain injury, 5-HT_3RA also showed their potential as a promising anti-depressant. These mechanisms reveal that 5-HT_3 antagonism facilitates signaling of 5-HT neurotransmission [24, 25, 68].

At a lesser concentration range, 5-HT_3RA inhibit the postsynaptic 5-HT_3R, which are involved in fast excitatory synaptic transmission in the limbic brain regions [79]. Binding of 5-HT_3R to postsynaptic receptors leads to an increase in the availability of 5-HT to other postsynaptic receptors such as 5-HT_{1B} [80], 5-HT_{2A} and 5-HT_{2C}, thereby aiding in signaling associated with serotonergic transmission and stimulating adenylyl cyclase followed by the initiation of the transformation of ATP to cAMP, that functions as a second messenger. cAMP further stimulates the phosphorylation enzyme protein kinase-A (PKA) [68]. Once PKA gets activated, phosphorylation of other intracellular protein molecules is initiated, thereby modifying the expression of CREB and BDNF in the nucleus [unpublished data]. This leads to anti-depressant-like effects by improving synaptic plasticity, neuronal survival and neurogenesis. However, at higher dose levels, the presynaptic and somatodendritic 5-HT_3 receptor blockade inhibits 5-HT release, eventually reducing the synaptic 5-HT levels that predispose to depression-like effects [81]. In addition to 5-HT, the 5-HT_3 (hetero) receptors located on nerve terminals modulate the release of other NTs such as NE, DA, Ach and GABA [68]. Various evidences gathered from previous studies suggested that inhibition of this receptor has a differential effect on the release of these NTs in the synapse. However, according to some reports, 5-HT_3RA did not show a uniform effect with respect to antidepressant action. Several studies showed that the antagonism of 5-HT3R leads to the enhancement of dopaminergic activity in mesolimbic, mesocortical and nigrostriatal pathways [27]. These pathways have importance in psychoses and Parkinson's disease, respectively. Antagonism of 5-HT_3R in presynaptic neurons tends to suppress dopaminergic transmission and an increase in depression-like symptoms [53]. Similarly, activation of presynaptic 5-HT_3R results in the facilitation of GABA release, while the same effect is inhibited by 5-HT_3RA. Hence inhibition of presynaptic receptors tends to produce depression-like effects [68]. The modu-

latory effect of 5-HT_3RA on the cholinergic system emerges from the co-localization of 5-HT3 and nicotinic receptors in striatal nerve terminals of the rat brain [82].

In addition, presynaptic 5-HT_3R stimulation inhibits ACh release, mainly in the cortex [83]. There are various evidences available to demonstrate the effect of 5-HT_3RA on NTs release or inhibition, however further studies are warranted to establish their role in various CNS disorders due to their distribution pattern and complex signaling transduction.

10. CLINICAL EVIDENCE

5-HT_3R agonist or antagonist responses are associated with a bell-shaped dose-response curve in both preclinical and clinical studies. Generally, they show good activity in the low dose range and activity decreases with an increase in dose [27]. Some clinical studies have suggested that 5-HT_3 receptors may be a relevant target in the treatment of affective disorders [53]. Evidence for the importance of 5-HT_3RA in the treatment of depression stems from clinical trials in which patients suffering from complex disorders such as fibromyalgia and bulimia showed improvement of the comorbid depression [84, 85]. A few clinical trials have exhibited the effectiveness of 5-HT_3RA monotherapy or its combination with antipsychotics in patients with psychosis and schizophrenia. Ondansetron (4 mg/day) treatment has been shown to improve the mental state and social behaviour of a schizophrenic patient [68].

11. TREATMENT RESISTANT DEPRESSION (TRD)

Despite an increase in the number of antidepressants, the pharmacotherapy of depression remains inadequate 1. At least 40% of patients do not respond well to antidepressant therapy. In general, antidepressant drugs take 8-12 weeks to show their effect as they are working through the modification of receptors, as well as the synthesis of neurotransmitter requires some time. The antidepressant drugs change the sensitivity of the receptor that, in turn, may cause externalization or internalization, change in expression of genes which involve neurogenesis and synaptic remodeling [86, 87].TRD is a complicated clinical problem caused by various risk factors. The complexities of TRD are addressed with combination strategies, which include medication optimization, a combination of antidepressant treatments, switching of therapy and augmentation with non-antidepressants, psychological therapies and non-pharmacological treatments such as deep brain stimulation, vagal nerve stimulation and trans cranial magnetic stimulation [88].

Long term treatment with classic antidepressants like SSRI, TCA, MAO inhibitors leads to the development of resistance against these drugs over a time period. In this regard, the 5-HT_3 receptor antagonists work through the fast receptors that are ligand-gated ion channel and the activation of postsynaptic 5-HT_3R is involved in fast synaptic transmission [79, 89]. These antagonists can be used in combination with classic antidepressants and antianxiety drugs [53]. Various interaction studies conducted by Bhatt *et al.*, 2014, also demonstrated the effectiveness of these antagonists in various animal models of depression and comorbid anxiety models. In addition, a study conducted by Bhatt *et al.*, 2013, has also demonstrated that 5-HT_3R antagonists also potentiated the effects of various standard drugs such as fluoxetine, bupropion, *etc.* The effect may also suggest that 5-HT_3RA may be used as an effective therapy against treatment resistant depression. 5-HT_3RA showed beneficial effect after a single dose in models like FST, TST, EPM and other models [24, 78, 90].

12. ROLE OF 5-HT_3RA IN THE REDUCTION OF OXIDATIVE STRESS

Oxidative stress plays a major role in the progression of various neuropsychiatric disorders, including depression. The brain has high metabolic activities, higher oxygen consumption, higher lipid contents, weaker antioxidative defense and more demand for glucose compared to other organs [13]. Oxidative stress or reactive oxygen species (ROS) is the main cause of neurodegeneration and its involvement in the pathogenesis of MDD is unequivocally established [91]. The imbalance between ROS and antioxidative defense leads to the deregulation of the physiology of the brain and abnormalities in nerve signaling. In depression, an imbalance in antioxidant enzymes such as SOD, catalase and reduced glutathione (GSH) and oxidant markers like peroxides and nitrates has been observed. This imbalance leads to an increase in activity of proinflammatory pathways such as TNF-α and IL-1β stimulation and other apoptotic mediators such as Caspase-3, ultimately leading to neuronal death [13, 92]. According to a study conducted by Bhatt *et al.*, 2014, compound '6g', a 5-HT_3RA, exerted antidepressant-like effects in behavioral despair paradigm in chronically stressed mice by restoring antioxidant mechanisms. The compound significantly reversed the CUMS-induced behavioral (increased immobility period, reduced sucrose preference and decreased locomotor activity) and biochemical (increased lipid peroxidation; decreased glutathione levels, superoxide dismutase and catalase activities) in mice [93]. Similarly, according to a study conducted by Gupta *et al.*, 2015, 4i, a 5-HT_3RA and fluoxetine treatment reversed the corticosterone (CORT) induced depressive-like deficits. Furthermore, 4i and fluoxetine reduced CORT induced oxidative brain insults, which may plausibly demonstrate one of the key mechanisms for antidepressant-like effects of the compounds [94]. 5-HT_3RA show neuroprotection in *in vitro* and *in vivo* studies. In fact, oxidative stress–induced injury in rat cortical neurons was counteracted through curtailing caspase-3 activation, calcium influx, reactive oxygen species generation, and excitotoxicity. The protective effect is mediated through blockade of 5-HT_3R by means of employing selective 5-HT_3RA [95]. Moreover, 5-HT_3RA tropisetron also acts as a partial agonist of α_7 nicotinic acetylcholine receptor (α_7nAChR). The activation of α_7nAChR leads to inhibition of inflammatory conditions and apoptotic signaling pathways in conditions associated with oxidative stress [96].

13. IMPORTANCE OF 5-HT3RA IN HPA AXIS DYSFUNCTION

HPA axis dysregulation is one of the main predisposing factors for the pathogenesis of depression and other comorbid disorders like anxiety. The HPA axis is involved in the release of cortisol *via* the involvement of the hypothalamus, pituitary and adrenal gland [12]. This axis works on a negative feedback mechanism where increased cortisol level in the blood conveys signals to the hypothalamus to reduce the release of a cortisol release factor. In case of depression and anxiety, the negative feedback mechanism of the HPA axis fails and increases the cortisol levels in blood [97]. However, in a normal individual, the HPA axis works perfectly fine with normal levels of cortisol. 5-HT_3RA are helpful in reducing the levels of cortisol in animal models. According to a study conducted by Kurhe *et al.*, 2015, QCM-4, a 5-HT_3RA, ameliorates the plasma HPA axis hyperactivity, leptin resistance and brain oxidative stress in depression and anxiety-like behavior in obese mice [98]. 5-HT_3R antagonism on the HPA axis, mice lacking $5HT_3$A exhibited dampened adrenocorticotropic hormone responses to acute stressors, including lipopolysaccharide and restraint, with no change in pituitary sensitivity to corticotropin-releasing hormone (CRH) [99]. According to Gupta *et al.*, 2014, Ondansetron and fluoxetine treatments significantly increased the percentage of serotonin levels in certain brain regions and attenuated HPA-axis hyperactivity, as evidenced by the low percentage of plasma CORT levels in chronic unpredictable stress (CUS) mice. These findings indicate the potential role of ondansetron (a 5-HT_3RA) in reversing CUS-induced depressive behaviour, which is possibly mediated by its modulating effects on the HPA-axis and serotonergic system [100].

14. THERAPEUTIC USE

5-HT_3RA have a variety of roles in different disorders. Various studies performed in laboratory animals suggested the important role of these antagonists in emotion, cognition, pain perception and memory process, neurodegenerative diseases and GI signaling. The role of 5-HT3 receptor antagonists in various disorders is shown in (Fig. **5A**). Due to their availability in various locations in CNS and GIT and their role in the control of emotions and memory, one can see their role in pathophysiological regulation of neurological and gastrointestinal disorders.

As discussed earlier, these 5-HT_3RA are well known for their role in CINV and PONV. In this section, we are going to discuss the role of 5-HT_3RA in schizophrenia, irritable bowel syndrome (IBS), cognitive dysfunction and substance abuse and dysfunction.

15. COGNITION AND MEMORY

5-HT_3RA play a significant role in cognition and memory. Cortex and dorsal hippocampus are the important regions associated with memory function, and antagonism of 5-HT_3R at these locations inhibits the 5-HT modulated release of acetylcholine without affecting steady state release [101, 102]. 5-HT_3RA have been shown to inhibit 5-HT3 agonist-induced ACh release in the entorhinal cortex of rats and the neocortex of guinea pigs, which are important structures for memory function [103]. A negative influence of 5-HT_3R activation on ACh release in the neocortex has also been reported in humans. Tropisetron enhances memory by activation of α7 nAChR [104]. 5-HT_3R have a substantial role in the progression of Alzheimer's disease and Schizophrenia. Overexpression of 5-HT_3R in mice has been involved in the enhancement of learning and memory as well as attention [59]. Ondansetron has been found to improve memory in patients over 50 years of age. Administration of 5-$HT_{2A/2C}$ or 5-HT_4 receptor agonists or 5-HT_{1A} or 5-HT_3 and 5-HT_{1B} receptor antagonists retards impairment in normal memory function and promotes learning in tasks that require a high cognition demand [105]. Moreover, polymorphism in the regulatory portion of 5-HT_{3A} receptor subunit has been associated with lower activity of amygdala and dorsal and medial frontal cortices, and was linked with reduced reaction time at the recognition of face [106].

16. PAIN

Serotonin causes activation of presynaptic 5-HT_3R on the central terminal of spinal afferents which are involved in the perception of pain *via* sensory and nociceptive inputs from the periphery to CNS [107]. Chronic pain in rats has been removed by ondansetron *via* antagonism at 5-HT_3R. Behavioral studies have confirmed the involvement of 5-HT_3R in pain and traumatic injury. 5-HT_3 knockout mice confirmed the involvement of antagonists in nociception after injury [107, 108]. In humans, the role of 5-HT_3RA has been confirmed in migraine and rheumatoid arthritis. The beneficial effects of 5-HT_3RA tropisetron in rheumatic diseases such as rheumatoid arthritis, tendinopathies and fibromyalgia seem promising [27, 109]. However, the role of 5-HT_3RA in chronic pain still needs to be studied in detail. Moreover, alosetron, a 5-HT_3RA, has shown its role in abdominal discomfort and pain in both male and female patients by improving stool consistency [110].

17. GASTROINTESTINAL DYSFUNCTION AND VISCERAL PAIN

5-HT_3RA are well known for their role in CINV and PONV. These antagonists block 5-HT peripherally as well as centrally in GI vagal nerve terminals and chemoreceptor trigger zone (CTZ), respectively; this blockade leads to a powerful antiemetic effect [111]. They are involved in the modulation of serotonergic transmission and regulation of GI function. In specific, they are involved in the regulation of GI motility, visceral sensation, secretion processes and perception of visceral pain. 5-HT_3RA prevent the activation of 5-HT_3R on extrinsic afferent neurons and can decrease the visceral pain associated with IBS [112]. Activation of 5-HT_3R may modulate GI excitability and activity of gastrointestinal vagal afferents at various sites and may be involved in various pathological and functional body processes, in-

cluding distention- and chemical-evoked vagal reflexes, nausea, and vomiting, as well as visceral hypersensitivity. 5-HT_3RA relieve painful colonic distention caused by increased cerebral blood flow in 5-HT_3R rich areas such as the hippocampus, amygdala and orbitofrontal cortex in IBS patients [113]. Walstab *et al.*, 2014, reported that monoterpene alcohol menthol and the aporphine alkaloid boldine combat symptoms of functional gastrointestinal disorders and work through ligand-gated ion channels [114]. In addition, they also inhibited 5-HT receptors by the 5-HT-induced activation of 5-HT_3 receptors in the low and middle micromolar range, respectively. Boldine was a competitive antagonist of both receptors being 6.5- to 10-fold more potent at 5-HT_{3A}- vs 5-HT_{3AB} receptors. Menthol non-competitively and stereoselectively inhibited both 5-HT_{3A} and 5-HT_{3AB} receptors.

18. SCHIZOPHRENIA AND NEURODEGENERATIVE DISORDERS

The role of 5-HT_3RA in psychoses is still not very clear that not all the human trials with 5-HT_3RA showed marked effect and promising results. Serotonin has a modulatory effect on dopaminergic neurons of the mid-brain area *via* 5-HT_3R and 5-HT_3RA that have been shown to decrease the hyperactivity of dopaminergic neurons in rats [115]. In clinics, 5-HT_3RA also alleviate symptoms of schizophrenia, particularly tardive dyskinesia and psychosis [116]. Some recent studies have reported the predominant role of ondansetron as a potential adjunctive therapy for the treatment of negative symptoms of schizophrenia. However, 5-HT_3RA have a limited role in the effective treatment of positive symptoms of psychoses. Interestingly, several neuroleptics and antidepressants have been shown to block 5-HT_3R in a non-competitive manner, possibly *via* interaction with the receptor–lipid interface [117]. In addition, various studies reported the predominant neuroprotective properties of ondansetron and tropisetron, consistent with their capacity for inhibiting the protein phosphatase calcineurin-involved neurodegenerative cascades [26].

19. SATIETY CONTROL

Preclinical studies suggested an important role of 5-HT_3R in the regulation of intake of food. It has been shown that the suppression of food intake by peripheral serotonin release is mediated *via* 5-HT_3R. Cholecystokinin (CCK) and peripheral serotonin suppress food intake synergistically, and blockade of 5-HT_3R attenuates the effect of CCK on food intake in combination with gastric distension [118]. Blockade of 5-HT_3R antagonised the anorexia induced by methamphetamine [119]. In addition, 5-HT_3R located centrally are involved in the regulation of blood glucose levels [120]. The significance of these pharmacological activities for the use of 5-HT_3RA in humans has not yet been investigated.

20. DRUG ADDICTION

5-HT_3RA influences the 'reward pathway'. In humans, the administration of ondansetron leads to a reduction in alcohol intake and problems associated with the intake of alcohol. 5-HT_3RA have been shown to reduce self-administration of ethanol in wild-type (WT) compared to 5-HT3A KO mice [121] and of morphine in rats [122]. In addition, ondansetron potentiated the methamphetamine induced hyperactivity in rats [119]. They have been involved in attenuation of the effect of morphine and cocaine that leads to an increase in dopaminergic activity in the mesolimbic area. These antagonists also cause locomotor activation, aggression stimulating effects and reduction in consumption of alcohol, as well as self-administration of drugs [59]. In humans, 5-HT_3RA were particularly effective in reducing the self-administration of ethanol and morphine, but a less marked effect was seen on self-administration of cocaine [123, 124]. The overall effect of 5-HT_3RA on substance abuse is inhibitory and also reduces the self-administration of abusing drugs.

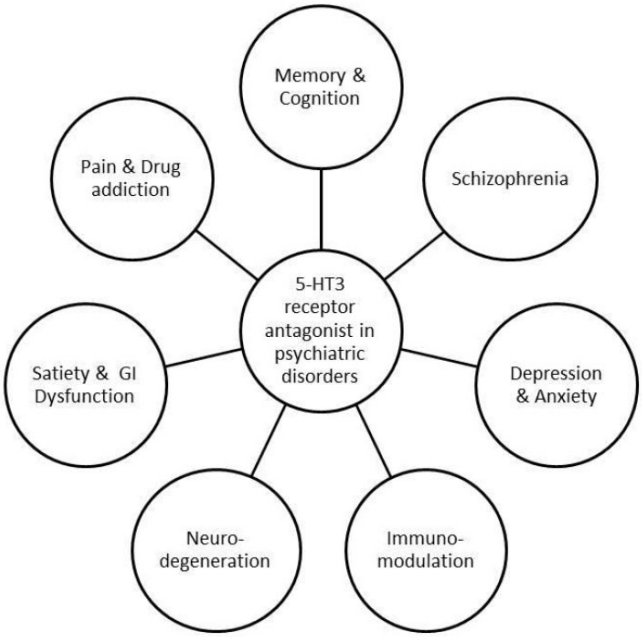

Fig. (6). Involvement of 5-HT_3 receptor antagonists in various disorders.

21. IMMUNOMODULATION

5-HT_3RA have anti-inflammatory and immunomodulatory properties, which are demonstrated by various *in-vitro* and *in vivo* studies. According to a study conducted by Bhatt *et al.*, 2017, 5-HT_3RA are able to reduce the inflammation and anxiety induced by lipopolysaccharide in mice. In addition to the anxiolytic effect, 5-HT_3RA are able to produce an anti-oxidant effect as well *via* enhancing the levels of anti-oxidant enzymes such as catalase and superoxide dismutase [125]. Tropisetron found to inhibit lipopolysaccharide induced increased levels of TNF-alpha and IL-1B in monocytes and serotonin induced prostaglandin E2 release from synovial cells [27]. It is also involved in the inhibition of calcineurin induced activation of T-cells as well as modula-

tion of Th1 cytokines in patients with the musculoskeletal disease [126]. 5-HT_3RA are also being used as adjunct therapy with intra-articular glucocorticoids for their analgesic and anti-inflammatory effects.

22. STROKE

Stroke is a leading cause of disability and death worldwide. There is a decrease in blood supply to the brain that has been taken place due to thrombus formation in the cerebral artery. The condition requires immediate hospitalization, and till date, no effective treatment requirement except tissue plasminogen activator as the only agents is approved by the U.S. Food and Drug Administration. 5-HT_3RA display a potential neuroprotective effect in various *in vitro* and *in vivo* activities. In fact, oxidative stress–induced injury in rat cortical neurons was counteracted through curtailing caspase-3 activation, calcium influx, ROS generation, and excitotoxicity [26]. A study conducted by Lee *et al.*, 2005, also observed the protection of neurons mediated through blockade of 5-HT3R. In *in vivo* models, tropisetron showed a beneficial effect in the embolic stroke model [95].

23. AUTHOR'S INSIGHT

Based on the above discussed literature, we can confirm that 5-HT_3RA have well validated role in CINV and PONV. The 5-HT_3 receptor antagonists have their role in various CNS and other disorders, including depression and comorbid disorders like anxiety. 5-HT_3RA belong to the category of ligand-gated ion channels. The ligand-gated ion channels are the second most important targets for drug discovery only after G protein–coupled receptors. The role of these receptors in these disorders is further confirmed by their expression in the CNS in regions involved in the vomiting reflex, processing of pain, the reward system, cognition, depression and anxiety control. The motivating outcomes from preliminary behavioral tests on 5-HT_3RA, their good safety profile further established the role of these drugs in depression and comorbid anxiety. We have performed some preclinical studies with 5-HT_3RA in our group and found their efficacy in both acute and chronic models of depression and anxiety. In addition, they have shown effectiveness in various rodent models of comorbidities, namely olfactory bulbectomy, traumatic brain injury, lipopolysaccharide induced depression and chronic unpredictable mild stress models. Moreover, they have also potentiated the effect of various standard drugs like fluoxetine, desipramine, bupropion as represented by various studies conducted in our lab. They worked through fast synaptic transmission effectively in very less time as compared to other standard drugs which work through some different mechanism. On the basis of the above mentioned literature, we may predict the role of these antagonists in depression comorbid with anxiety. They may also be useful and work as effective therapy against treatment resistant depression cases. These agents are very effective in addressing the issue of comorbidity very effectively. However, some detailed studies in clinics are required to prove the efficacy and exact signaling mechanisms of these 5-HT_3RA. The pharmacokinetic aspects of these drugs also need to be addressed by conducting relevant studies.

CONCLUSION

Ligand-gated ion channels are important receptors after GPCR *via* which most of the drugs showed their action. The drugs acting through these receptors have a clear advantage of fast synaptic transmission. 5-HT_3RA showed a clear advantage of fast action as well as effectiveness against various neuropsychiatric disorders when compared to other members of the serotonin receptor family. Initially, 5-HT_3RA was established as a treatment for CINV and PONV. Setrons like ondansetron, tropisetron, dolasetron, *etc.* emerged as a gold standard treatment for CINV. Nonetheless, other therapeutic effects of this class were neglected for years until recent investigations demonstrated that these compounds could alleviate the pathology of certain neurodegenerative and neuropsychiatric disorders. In this review, we have seen the role of 5-HT_3RA in other conditions like pain, addiction, eating disorders, inflammation, cognition or memory, gastrointestinal problem and schizophrenia. In addition, 5-HT_3RA showed effectiveness in depression comorbid with anxiety disorders. Various preclinical studies showed that 5-HT_3RA alleviate the symptoms of depression and anxiety in rodent models. They act through modulation of the synaptic transmission in various CNS areas. In addition, they are able to reduce the oxidative stress, cortisol levels in the plasma/brain of mice. They enhance the availability of 5-HT on 5-HT_1 and 5-HT_2 receptors and showed an anti-depressant effect *via* increasing the levels of BDNF and CREB in the brain of mice. In clinical trials, these setrons have shown their potential against the most intractable symptoms of schizophrenia like negative and cognitive symptoms. Setrons also have shown their effectiveness against early onset alcohol dependence. The condition is presumably associated with major serotonergic dysfunction, including overexpression of postsynaptic 5-HT3R in the mesolimbic DA system. These 5-HT_3RA can also be used in combination with other standard drugs and in this way, they are able to reduce the adverse effects such as abuse liability, sedation, glucose intolerance, weight gain, sexual disturbance and anticholinergic effects. In addition, the use of 5-HT_3RA in combination may also be an effective approach against treatment resistant depression cases. Given the advantageous therapeutic profile of 5-HT_3RA combined with their broad therapeutic window, more detailed studies on this class of drugs could open avenues for the development of novel pharmacophores with higher efficacy and better compliance for the management of neurologic and neuropsychiatric disorders.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] *WHO,* https://www.who.int/news-room/fact-sheets/detail/depression

[2] Center for substance abuse treatment. *Managing depressive symptoms in substance abuse clients during early recovery.,* **2008**. https://www.ncbi.nlm.nih.gov/books/NBK64063/

[3] Albert, P.R. Why is depression more prevalent in women? *J. Psychiatry Neurosci.,* **2015**, *40*(4), 219-221. http://dx.doi.org/10.1503/jpn.150205 PMID: 26107348

[4] Boivin, J.R.; Piekarski, D.J.; Wahlberg, J.K.; Wilbrecht, L. Age, sex, and gonadal hormones differently influence anxiety- and depression-related behavior during puberty in mice. *Psychoneuroendocrinology,* **2017**, *85*, 78-87. http://dx.doi.org/10.1016/j.psyneuen.2017.08.009 PMID: 28837909

[5] Shors, T.J.; Leuner, B. Estrogen-mediated effects on depression and memory formation in females. *J. Affect. Disord.,* **2003**, *74*(1), 85-96. http://dx.doi.org/10.1016/S0165-0327(02)00428-7 PMID: 12646301

[6] Karpinski, M.; Mattina, G.F.; Steiner, M. Effect of gonadal hormones on neurotransmitters implicated in the pathophysiology of obsessive-compulsive disorder: a critical review. *Neuroendocrinology,* **2017**, *105*(1), 1-16. http://dx.doi.org/10.1159/000453664 PMID: 27894107

[7] Boku, S.; Nakagawa, S.; Toda, H.; Hishimoto, A. Neural basis of major depressive disorder: Beyond monoamine hypothesis. *Psychiatry Clin. Neurosci.,* **2018**, *72*(1), 3-12. http://dx.doi.org/10.1111/pcn.12604 PMID: 28926161

[8] Heninger, G.R.; Delgado, P.L.; Charney, D.S. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry,* **1996**, *29*(1), 2-11. http://dx.doi.org/10.1055/s-2007-979535 PMID: 8852528

[9] Lener, M.S.; Niciu, M.J.; Ballard, E.D.; Park, M.; Park, L.T.; Nugent, A.C.; Zarate, C.A. Jr. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. *Biol. Psychiatry,* **2017**, *81*(10), 886-897. http://dx.doi.org/10.1016/j.biopsych.2016.05.005 PMID: 27449797

[10] Liu, W.; Ge, T.; Leng, Y.; Pan, Z.; Fan, J.; Yang, W.; Cui, R. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. *Neural Plast.,* **2017**, *2017*, 6871089. http://dx.doi.org/10.1155/2017/6871089 PMID: 28246558

[11] Shadrina, M.; Bondarenko, E.A.; Slominsky, P.A. Genetics factors in major depression disease. *Front. Psychiatry,* **2018**, *9*, 334. http://dx.doi.org/10.3389/fpsyt.2018.00334 PMID: 30083112

[12] Keller, J.; Gomez, R.; Williams, G.; Lembke, A.; Lazzeroni, L.; Murphy, G.M., Jr; Schatzberg, A.F. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol. Psychiatry,* **2017**, *22*(4), 527-536. http://dx.doi.org/10.1038/mp.2016.120 PMID: 27528460

[13] Bhatt, S.; Nagappa, A.N.; Patil, C.R. Role of oxidative stress in depression. *Drug Discov. Today,* **2020**, *25*(7), 1270-1276.

[14] Michel, T.M.; Pülschen, D.; Thome, J. The role of oxidative stress in depressive disorders. *Curr. Pharm. Des.,* **2012**, *18*(36), 5890-5899. http://dx.doi.org/10.2174/138161212803523554 PMID: 22681168

[15] Raison, C.L.; Miller, A.H. Is depression an inflammatory disorder? *Curr. Psychiatry Rep.,* **2011**, *13*(6), 467-475. http://dx.doi.org/10.1007/s11920-011-0232-0 PMID: 21927805

[16] Dunner, D.L. Combining antidepressants. *Shanghai Jingshen Yixue,* **2014**, *26*(6), 363-364. PMID: 25642112

[17] Machado-Vieira, R.; Baumann, J.; Wheeler-Castillo, C.; Latov, D.; Henter, I.D.; Salvadore, G.; Zarate, C.A. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals (Basel),* **2010**, *3*(1), 19-41. http://dx.doi.org/10.3390/ph3010019 PMID: 27713241

[18] Nichols, D.E.; Nichols, C.D. Serotonin receptors. *Chem. Rev.,* **2008**, *108*(5), 1614-1641. http://dx.doi.org/10.1021/cr078224o PMID: 18476671

[19] Lanfumey, L.; Hamon, M. 5-HT1 receptors. *Curr. Drug Targets CNS Neurol. Disord.,* **2004**, *3*(1), 1-10. http://dx.doi.org/10.2174/1568007043482570 PMID: 14965240

[20] Celada, P.; Puig, M.; Amargós-Bosch, M.; Adell, A.; Artigas, F. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. *J. Psychiatry Neurosci.,* **2004**, *29*(4), 252-265. PMID: 15309042

[21] Haddjeri, N.; Blier, P.; de Montigny, C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. *J. Neurosci.,* **1998**, *18*(23), 10150-10156. http://dx.doi.org/10.1523/JNEUROSCI.18-23-10150.1998 PMID: 9822768

[22] Blier, P.; Ward, N.M. Is there a role for 5-HT1A agonists in the treatment of depression? *Biol. Psychiatry,* **2003**, *53*(3), 193-203. http://dx.doi.org/10.1016/S0006-3223(02)01643-8 PMID: 12559651

[23] Nautiyal, K.M.; Tritschler, L.; Ahmari, S.E.; David, D.J.; Gardier, A.M.; Hen, R. A lack of serotonin 1B Autoreceptors results in decreased anxiety and depression-related behaviors. *Neuropsychopharmacology,* **2016**, *41*(12), 2941-2950. http://dx.doi.org/10.1038/npp.2016.109 PMID: 27353308

[24] Bhatt, S.; Mahesh, R.; Devadoss, T.; Jindal, A.K. Anxiolytic-like effect of (4-benzylpiperazin-1-yl)(3-methoxyquinoxalin-2-yl)methanone (6g) in experimental mouse models of anxiety. *Indian J. Pharmacol.,* **2013**, *45*(3), 248-251. http://dx.doi.org/10.4103/0253-7613.111923 PMID: 23833367

[25] Bhatt, S.; Mahesh, R.; Devadoss, T.; Jindal, A.K. Antidepressant--like effect of novel 5-HT3 receptor antagonist N-n-butyl-3-ethoxyquinoxalin-2-carboxamide (6p): an approach using rodent behavioral antidepressant tests. *Indian J. Pharmacol.,* **2013**, *45*(4), 348-353. http://dx.doi.org/10.4103/0253-7613.115014 PMID: 24014909

[26] Fakhfouri, G.; Rahimian, R.; Dyhrfjeld-Johnsen, J.; Zirak, M.R.; Beaulieu, J.M. 5-HT_3 receptor antagonists in neurologic and neuropsychiatric disorders: The Iceberg still lies beneath the surface. *Pharmacol. Rev.,* **2019**, *71*(3), 383-412. http://dx.doi.org/10.1124/pr.118.015487 PMID: 31243157

[27] Faerber, L.; Drechsler, S.; Ladenburger, S.; Gschaidmeier, H.; Fischer, W. The neuronal 5-HT3 receptor network after 20 years of research--evolving concepts in management of pain and inflammation. *Eur. J. Pharmacol.,* **2007**, *560*(1), 1-8. http://dx.doi.org/10.1016/j.ejphar.2007.01.028 PMID: 17316606

[28] Somers, G.I.; Harris, A.J.; Bayliss, M.K.; Houston, J.B. The metabolism of the $5HT_3$ antagonists ondansetron, alosetron and GR87442 I: a comparison of *in vitro* and *in vivo* metabolism and *in vitro* enzyme kinetics in rat, dog and human hepatocytes, microsomes and recombinant human enzymes. *Xenobiotica,* **2007**, *37*(8), 832-854. http://dx.doi.org/10.1080/00498250701485575 PMID: 17701832

[29] Bigaud, M.; Elands, J.; Kastner, P.R.; Bohnke, R.A.; Ernrnert, L.W.; Galvan, M. Pharmacology of the human metabolites of dolasetron, an antiemetic 5-HT_3 receptor antagonist. *Drug Dev. Res.,* **1995**, *34*, 289-296. http://dx.doi.org/10.1002/ddr.430340306

[30] Kees, F.; Färber, L.; Bucher, M.; Mair, G.; Mörike, K.; Grobecker, H. Pharmacokinetics of therapeutic doses of tropisetron in healthy volunteers. *Br. J. Clin. Pharmacol.,* **2001**, *52*(6), 705-707. http://dx.doi.org/10.1046/j.0306-5251.2001.01512.x PMID: 11736884

[31] Stoltz, R.; Parisi, S.; Shah, A.; Macciocchi, A. Pharmacokinetics, metabolism and excretion of intravenous [l4C]-palonosetron in healthy human volunteers. *Biopharm. Drug Dispos.,* **2004**, *25*(8), 329-337.

http://dx.doi.org/10.1002/bdd.410 PMID: 15378559

[32] Nakamura, H.; Ariyoshi, N.; Okada, K.; Nakasa, H.; Nakazawa, K.; Kitada, M. CYP1A1 is a major enzyme responsible for the metabolism of granisetron in human liver microsomes. *Curr. Drug Metab.,* **2005**, *6*(5), 469-480. http://dx.doi.org/10.2174/138920005774330666 PMID: 16248838

[33] Swain, C.J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E.M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. Novel 5-HT_3 antagonists. Indole oxadiazoles. *J. Med. Chem.,* **1991**, *34*(1), 140-151. http://dx.doi.org/10.1021/jm00105a021 PMID: 1992112

[34] Rizzi, J.P.; Nagel, A.A.; Rosen, T.; McLean, S.; Seeger, T. An initial three-component pharmacophore for specific serotonin-3 receptor ligands. *J. Med. Chem.,* **1990**, *33*(10), 2721-2725. http://dx.doi.org/10.1021/jm00172a007 PMID: 2145434

[35] Bermudez, J.; Dabbs, S.; Joiner, K.A.; King, F.D. 5-Hydroxytryptamine (5-HT_3) receptor antagonists. 2. 1-Indolinecarboxamides. *J. Med. Chem.,* **1990**, *33*(7), 1929-1932. http://dx.doi.org/10.1021/jm00169a017 PMID: 2362271

[36] Hibert, M.F.; Hoffmann, R.; Miller, R.C.; Carr, A.A. Conformation-activity relationship study of 5-HT_3 receptor antagonists and a definition of a model for this receptor site. *J. Med. Chem.,* **1990**, *33*(6), 1594-1600. http://dx.doi.org/10.1021/jm00168a011 PMID: 2342053

[37] Swain, C.J.; Baker, R.; Kneen, C.; Herbert, R.; Moseley, J.; Saunders, J.; Seward, E.M.; Stevenson, G.I.; Beer, M.; Stanton, J. Novel 5-HT3 antagonists: indol-3-ylspiro(azabicycloalkane-3,5'(4'H)-oxazoles). *J. Med. Chem.,* **1992**, *35*(6), 1019-1031. http://dx.doi.org/10.1021/jm00084a007 PMID: 1552497

[38] Ohta, M.; Suzuki, T.; Koide, T.; Matsuhisa, A.; Furuya, T.; Miyata, K.; Yanagisawa, I. Novel 5-hydroxytryptamine (5-HT3) receptor antagonists. I. Synthesis and structure-activity relationships of conformationally restricted fused imidazole derivatives. *Chem. Pharm. Bull. (Tokyo),* **1996**, *44*(5), 991-999. http://dx.doi.org/10.1248/cpb.44.991 PMID: 8689729

[39] Rosen, T.; Nagel, A.A.; Rizzi, J.P.; Ives, J.L.; Daffeh, J.B.; Ganong, A.H.; Guarino, K.; Heym, J.; McLean, S.; Nowakowski, J.T.; Schmidt, A.W.; Seeger, T.F.; Siok, C.J.; Vincent, L.A. Thiazole as a carbonyl bioisostere. A novel class of highly potent and selective 5-HT_3 receptor antagonists. *J. Med. Chem.,* **1990**, *33*(10), 2715-2720. http://dx.doi.org/10.1021/jm00172a006 PMID: 2213824

[40] Monge, A.; Peña, M.C.; Palop, J.A.; Calderó, J.M.; Roca, J.; García, E.; Romero, G.; del Río, J.; Lasheras, B. Synthesis of 2-piperazinylbenzothiazole and 2-piperazinylbenzoxazole derivatives with 5-HT_3 antagonist and 5-HT_4 agonist properties. *J. Med. Chem.,* **1994**, *37*(9), 1320-1325. http://dx.doi.org/10.1021/jm00035a012 PMID: 8176710

[41] Clark, R.D.; Miller, A.B.; Berger, J.; Repke, D.B.; Weinhardt, K.K.; Kowalczyk, B.A.; Eglen, R.M.; Bonhaus, D.W.; Lee, C.H.; Michel, A.D.; Smith, W.L.; Wongll, E.H.F. 2-(Quinuclidin-3-yl)pyrido[4,3-b]indol-1-ones and isoquinolin-1-ones. Potent conformationally restricted 5-HT_3 receptor antagonists. *J. Med. Chem.,* **1993**, *36*(18), 2645-2657. http://dx.doi.org/10.1021/jm00070a008 PMID: 8410977

[42] Hayashi, H.; Miwa, Y.; Ichikawa, S.; Yoda, N.; Miki, I. Ishii, A.; Kono, M.; Yasuzawa, T.; Suzuki, F. 5-HT_3 Receptor Antagonists. 2. 4-Hydroxy-quinoline carboxylic Acid Derivatives. *J. Med. Chem.,* **1993**, *36*, 617-626. http://dx.doi.org/10.1021/jm00057a011 PMID: 8496941

[43] Monge, A.; Palop, J.A.; Del Castillo, J.C.; Calderó, J.M.; Roca, J.; Romero, G.; Del Río, J.; Lasheras, B. Novel antagonists of 5-HT3 receptors. Synthesis and biological evaluation of piperazinylquinoxaline derivatives. *J. Med. Chem.,* **1993**, *36*(19), 2745-2750. http://dx.doi.org/10.1021/jm00071a005 PMID: 8410988

[44] Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. Phenylimidazolidin-2-one derivatives as selective 5-HT_3 receptor antagonists and refinement of the pharmacophore model for 5-HT_3 receptor binding. *J. Med. Chem.,* **1997**, *40*(21), 3369-3380. http://dx.doi.org/10.1021/jm970060o PMID: 9341912

[45] Kuroita, T.; Marubayashi, N.; Sano, M.; Kanzaki, K.; Inaba, K.; Kawakita, T. Benzoxazines. II. Synthesis, conformational analysis, and structure--activity relationships of 3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide derivatives as potent and long-acting serotonin-3 (5-HT_3) receptor antagonists. *Chem. Pharm. Bull. (Tokyo),* **1996**, *44*(11), 2051-2060. http://dx.doi.org/10.1248/cpb.44.2051 PMID: 8945770

[46] Mahesh, R.; Devadoss, T.; Pandey, D.K.; Bhatt, S.; Yadav, S.K. Design, synthesis and structure-activity relationship of novel quinoxalin-2-carboxamides as 5-HT3 receptor antagonists for the management of depression. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(22), 6773-6776. http://dx.doi.org/10.1016/j.bmcl.2010.08.128 PMID: 20851599

[47] Mahesh, R.; Perumal, R.V.; Pandi, P.V. Microwave assisted synthesis of 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile as a new class of serotonin 5-HT_3 receptor antagonists. *Bioorg. Med. Chem. Lett.,* **2004**, *14*(20), 5179-5181. http://dx.doi.org/10.1016/j.bmcl.2004.07.060 PMID: 15380223

[48] Verheij, M.H.P.; Thompson, A.J.; van Muijlwijk-Koezen, J.E.; Lummis, S.C.R.; Leurs, R.; de Esch, I.J.P. Design, synthesis, and structure-activity relationships of highly potent 5-HT□ receptor ligands. *J. Med. Chem.,* **2012**, *55*(20), 8603-8614. http://dx.doi.org/10.1021/jm300801u PMID: 23006041

[49] Al Kury, L.T.; Mahgoub, M.; Howarth, F.C.; Oz, M. Natural negative allosteric modulators of 5-HT□ Receptors. *Molecules,* **2018**, *23*(12), 3186. http://dx.doi.org/10.3390/molecules23123186 PMID: 30513973

[50] Cortes-Altamirano, J.L.; Olmos-Hernandez, A.; Jaime, H.B.; Carrillo-Mora, P.; Bandala, C.; Reyes-Long, S.; Alfaro-Rodríguez, A. Review: 5-HT1, 5-HT2, 5-HT3 and 5-HT7 receptors and their role in the modulation of pain response in the central nervous system. *Curr. Neuropharmacol.,* **2018**, *16*(2), 210-221. http://dx.doi.org/10.2174/1570159X15666170911121027 PMID: 28901281

[51] Gaddum, J.H.; Picarelli, Z.P. Two kinds of tryptamine receptor. *Br. J. Pharmacol. Chemother.,* **1957**, *12*(3), 323-328. http://dx.doi.org/10.1111/j.1476-5381.1957.tb00142.x PMID: 13460238

[52] Niesler, B.; Walstab, J.; Combrink, S.; Möller, D.; Kapeller, J.; Rietdorf, J.; Bönisch, H.; Göthert, M.; Rappold, G.; Brüss, M. Characterization of the novel human serotonin receptor subunits 5-HT3C,5-HT3D, and 5-HT3E. *Mol. Pharmacol.,* **2007**, *72*(1), 8-17. http://dx.doi.org/10.1124/mol.106.032144 PMID: 17392525

[53] Betry, C.; Etievant, A.; Oosterhof, C.; Ebert, B.; Sanchez, C.; Haddjeri, N. Role of 5-HT_3 receptors in the antidepressant response. *Pharmaceuticals.,* **2011**, *4*, 603-629. http://dx.doi.org/10.3390/ph4040603

[54] Barnes, J.M.; Barnes, N.M.; Costall, B.; Ironside, J.W.; Naylor, R.J. Identification and characterisation of 5-hydroxytryptamine 3 recognition sites in human brain tissue. *J. Neurochem.,* **1989**, *53*(6), 1787-1793. http://dx.doi.org/10.1111/j.1471-4159.1989.tb09244.x PMID: 2809591

[55] Abi-Dargham, A.; Laruelle, M.; Wong, D.T.; Robertson, D.W.; Weinberger, D.R.; Kleinman, J.E. Pharmacological and regional characterization of [3H]LY278584 binding sites in human brain. *J. Neurochem.,* **1993**, *60*(2), 730-737. http://dx.doi.org/10.1111/j.1471-4159.1993.tb03208.x PMID: 8419547

[56] Bufton, K.E.; Steward, L.J.; Barber, P.C.; Barnes, N.M. Distribution and characterization of the [3H]granisetron-labelled 5-HT3 receptor in the human forebrain. *Neuropharmacology,* **1993**, *32*(12), 1325-1331. http://dx.doi.org/10.1016/0028-3908(93)90027-Z PMID: 8152523

[57] Parker, R.M.; Barnes, J.M.; Ge, J.; Barber, P.C.; Barnes, N.M. Autoradiographic distribution of [3H]-(S)-zacopride-labelled 5-HT3 receptors in human brain. *J. Neurol. Sci.,* **1996**, *144*(1-2), 119-127. http://dx.doi.org/10.1016/S0022-510X(96)00211-0 PMID: 8994113

[58] Miquel, M.C.; Emerit, M.B.; Nosjean, A.; Simon, A.; Rumajogee, P.; Brisorgueil, M.J.; Doucet, E.; Hamon, M.; Vergé, D. Differential subcellular localization of the 5-HT3-As receptor subunit in the rat central nervous system. *Eur. J. Neurosci.,* **2002**, *15*(3),

449-457.
http://dx.doi.org/10.1046/j.0953-816x.2001.01872.x PMID: 11876772

[59] Walstab, J.; Rappold, G.; Niesler, B. 5-HT(3) receptors: role in disease and target of drugs. *Pharmacol. Ther.,* **2010**, *128*(1), 146-169.
http://dx.doi.org/10.1016/j.pharmthera.2010.07.001 PMID: 20621123

[60] Thompson, A.J.; Lummis, S.C. 5-HT3 receptors. *Curr. Pharm. Des.,* **2006**, *12*(28), 3615-3630.
http://dx.doi.org/10.2174/138161206778522029 PMID: 17073663

[61] Machu, T.K. Therapeutics of 5-HT3 receptor antagonists: current uses and future directions. *Pharmacol. Ther.,* **2011**, *130*(3), 338-347.
http://dx.doi.org/10.1016/j.pharmthera.2011.02.003 PMID: 21356241

[62] Navari, R.M. 5-HT3 receptors as important mediators of nausea and vomiting due to chemotherapy. *Biochim. Biophys. Acta,* **2015**, *1848*(10 Pt B), 2738-2746.
http://dx.doi.org/10.1016/j.bbamem.2015.03.020 PMID: 25838122

[63] Hannon, J.; Hoyer, D. Molecular biology of 5-HT receptors. *Behav. Brain Res.,* **2008**, *195*(1), 198-213.
http://dx.doi.org/10.1016/j.bbr.2008.03.020 PMID: 18571247

[64] Mukerji, J.; Haghighi, A.; Séguéla, P. Immunological characterization and transmembrane topology of 5-hydroxytryptamine3 receptors by functional epitope tagging. *J. Neurochem.,* **1996**, *66*(3), 1027-1032.
http://dx.doi.org/10.1046/j.1471-4159.1996.66031027.x PMID: 8769863

[65] Spier, A.D.; Wotherspoon, G.; Nayak, S.V.; Nichols, R.A.; Priestley, J.V.; Lummis, S.C. Antibodies against the extracellular domain of the 5-HT3 receptor label both native and recombinant receptors. *Brain Res. Mol. Brain Res.,* **1999**, *67*(2), 221-230.
http://dx.doi.org/10.1016/S0169-328X(99)00055-8 PMID: 10216220

[66] Unwin, N. Refined structure of the nicotinic acetylcholine receptor at 4A resolution. *J. Mol. Biol.,* **2005**, *346*(4), 967-989.
http://dx.doi.org/10.1016/j.jmb.2004.12.031 PMID: 15701510

[67] Miyazawa, A.; Fujiyoshi, Y.; Unwin, N. Structure and gating mechanism of the acetylcholine receptor pore. *Nature,* **2003**, *423*(6943), 949-955.
http://dx.doi.org/10.1038/nature01748 PMID: 12827192

[68] Rajkumar, R.; Mahesh, R. The auspicious role of the 5-HT3 receptor in depression: a probable neuronal target? *J. Psychopharmacol.,* **2010**, *24*(4), 455-469.
http://dx.doi.org/10.1177/0269881109348161 PMID: 20123937

[69] Smith, H.S.; Cox, L.R.; Smith, E.J. 5-HT3 receptor antagonists for the treatment of nausea/vomiting. *Ann. Palliat. Med.,* **2012**, *1*(2), 115-120.
PMID: 25841471

[70] Tricco, A.C.; Blondal, E.; Veroniki, A.A.; Soobiah, C.; Vafaei, A.; Ivory, J.; Strifler, L.; Cardoso, R.; Reynen, E.; Nincic, V.; Ashoor, H.; Ho, J.; Ng, C.; Johnson, C.; Lillie, E.; Antony, J.; Roberts, D.J.; Hemmelgarn, B.R.; Straus, S.E. Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. *BMC Med.,* **2016**, *14*(1), 216.
http://dx.doi.org/10.1186/s12916-016-0761-9 PMID: 28007031

[71] Mott, D.D.; Erreger, K.; Banke, T.G.; Traynelis, S.F. Open probability of homomeric murine 5-HT3A serotonin receptors depends on subunit occupancy. *J. Physiol.,* **2001**, *535*(Pt 2), 427-443.
http://dx.doi.org/10.1111/j.1469-7793.2001.00427.x PMID: 11533135

[72] Rayes, D.; De Rosa, M.J.; Sine, S.M.; Bouzat, C. Number and locations of agonist binding sites required to activate homomeric Cys-loop receptors. *J. Neurosci.,* **2009**, *29*(18), 6022-6032.
http://dx.doi.org/10.1523/JNEUROSCI.0627-09.2009 PMID: 19420269

[73] Koyama, S.; Matsumoto, N.; Kubo, C.; Akaike, N. Presynaptic 5-HT3 receptor-mediated modulation of synaptic GABA release in the mechanically dissociated rat amygdala neurons. *J. Physiol.,* **2000**, *529*(Pt 2), 373-383.
http://dx.doi.org/10.1111/j.1469-7793.2000.00373.x PMID: 11101647

[74] Nayak, S.V.; Rondé, P.; Spier, A.D.; Lummis, S.C.; Nichols, R.A. Calcium changes induced by presynaptic 5-hydroxytryptamine-3 serotonin receptors on isolated terminals from various regions of the rat brain. *Neuroscience,* **1999**, *91*(1), 107-117.
http://dx.doi.org/10.1016/S0306-4522(98)00520-X PMID: 10336063

[75] Yakel, J.L.; Shao, X.M.; Jackson, M.B. The selectivity of the channel coupled to the 5-HT3 receptor. *Brain Res.,* **1990**, *533*(1), 46-52.
http://dx.doi.org/10.1016/0006-8993(90)91793-G PMID: 1707717

[76] Barnes, N.M.; Hales, T.G.; Lummis, S.C.; Peters, J.A. The 5-HT3 receptor--the relationship between structure and function. *Neuropharmacology,* **2009**, *56*(1), 273-284.
http://dx.doi.org/10.1016/j.neuropharm.2008.08.003 PMID: 18761359

[77] Gupta, D.; Devadoss, T.; Bhatt, S.; Gautam, B.; Jindal, A.; Pandey, D.; Mahesh, R. Anti-depressant-like activity of a novel serotonin type-3 (5-HT3) receptor antagonist in rodent models of depression. *Indian J. Exp. Biol.,* **2011**, *49*(8), 619-626.
PMID: 21870430

[78] Bhatt, S.; Mahesh, R.; Devadoss, T.; Jindal, A. Anti-depressant like activity of N-n-butyl-3-methoxyquinoxaline-2-carboxamide (6o) a 5-HT3 receptor antagonist. *Indian J. Exp. Biol.,* **2013**, *51*(6), 435-443.
PMID: 23926691

[79] Sugita, S.; Shen, K.Z.; North, R.A. 5-hydroxytryptamine is a fast excitatory transmitter at 5-HT3 receptors in rat amygdala. *Neuron,* **1992**, *8*(1), 199-203.
http://dx.doi.org/10.1016/0896-6273(92)90121-S PMID: 1346089

[80] Bourin, M.; Redrobe, J.P.; Baker, G.B. Pindolol does not act only on 5-HT1A receptors in augmenting antidepressant activity in the mouse forced swimming test. *Psychopharmacology (Berl.),* **1998**, *136*(3), 226-234.
http://dx.doi.org/10.1007/s002130050560 PMID: 9566807

[81] Ramamoorthy, R.; Radhakrishnan, M.; Borah, M. Antidepressant--like effects of serotonin type-3 antagonist, ondansetron: an investigation in behaviour-based rodent models. *Behav. Pharmacol.,* **2008**, *19*(1), 29-40.
http://dx.doi.org/10.1097/FBP.0b013e3282f3cfd4 PMID: 18195592

[82] Nayak, S.V.; Rondé, P.; Spier, A.D.; Lummis, S.C.; Nichols, R.A. Nicotinic receptors co-localize with 5-HT(3) serotonin receptors on striatal nerve terminals. *Neuropharmacology,* **2000**, *39*(13), 2681-2690.
http://dx.doi.org/10.1016/S0028-3908(00)00109-X PMID: 11044738

[83] Giovannini, M.G.; Ceccarelli, I.; Molinari, B.; Cecchi, M.; Goldfarb, J.; Blandina, P. Serotonergic modulation of acetylcholine release from cortex of freely moving rats. *J. Pharmacol. Exp. Ther.,* **1998**, *285*(3), 1219-1225.
PMID: 9618425

[84] Haus, U.; Varga, B.; Stratz, T.; Späth, M.; Müller, W. Oral treatment of fibromyalgia with tropisetron given over 28 days: influence on functional and vegetative symptoms, psychometric parameters and pain. *Scand. J. Rheumatol. Suppl.,* **2000**, *113*, 55-58.
PMID: 11028833

[85] Faris, P.L.; Eckert, E.D.; Kim, S.W.; Meller, W.H.; Pardo, J.V.; Goodale, R.L.; Hartman, B.K. Evidence for a vagal pathophysiology for bulimia nervosa and the accompanying depressive symptoms. *J. Affect. Disord.,* **2006**, *92*(1), 79-90.
http://dx.doi.org/10.1016/j.jad.2005.12.047 PMID: 16516303

[86] Blier, P. Optimal use of antidepressants: when to act? *J. Psychiatry Neurosci.,* **2009**, *34*(1), 80.
PMID: 19125216

[87] Taylor, C.; Fricker, A.D.; Devi, L.A.; Gomes, I. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. *Cell. Signal.,* **2005**, *17*(5), 549-557.
http://dx.doi.org/10.1016/j.cellsig.2004.12.007 PMID: 15683730

[88] Al-Harbi, K.S. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer. Adherence,* **2012**, *6*, 369-388.

http://dx.doi.org/10.2147/PPA.S29716 PMID: 22654508

[89] Roerig, B.; Katz, L.C. Modulation of intrinsic circuits by serotonin 5-HT3 receptors in developing ferret visual cortex. *J. Neurosci.,* **1997**, *17*(21), 8324-8338. http://dx.doi.org/10.1523/JNEUROSCI.17-21-08324.1997 PMID: 9334407

[90] Bhatt, S.; Mahesh, R.; Jindal, A.; Devadoss, T. Neuropharmacological effect of novel 5-HT3 receptor antagonist, N-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n) on chronic unpredictable mild stress-induced molecular and cellular response: Behavioural and biochemical evidences. *Pharmacol. Rep.,* **2014**, *66*(5), 804-810. http://dx.doi.org/10.1016/j.pharep.2014.05.002 PMID: 25149984

[91] Maes, M.; De Vos, N.; Pioli, R.; Demedts, P.; Wauters, A.; Neels, H.; Christophe, A. Lower serum vitamin E concentrations in major depression. Another marker of lowered antioxidant defenses in that illness. *J. Affect. Disord.,* **2000**, *58*(3), 241-246. http://dx.doi.org/10.1016/S0165-0327(99)00121-4 PMID: 10802134

[92] Maes, M.; Galecki, P.; Chang, Y.S.; Berk, M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 676-692. http://dx.doi.org/10.1016/j.pnpbp.2010.05.004 PMID: 20471444

[93] Bhatt, S.; Radhakrishnan, M.; Jindal, A.; Devadoss, T.; Dhar, A.K. Neuropharmacological evaluation of a novel 5-HT3 receptor antagonist (6g) on chronic unpredictable mild stress-induced changes in behavioural and brain oxidative stress parameters in mice. *Indian J. Pharmacol.,* **2014**, *46*(2), 191-196. http://dx.doi.org/10.4103/0253-7613.129316 PMID: 24741192

[94] Gupta, D.; Radhakrishnan, M.; Kurhe, Y. Effect of a novel 5-HT3 receptor antagonist 4i, in corticosterone-induced depression-like behavior and oxidative stress in mice. *Steroids,* **2015**, *96*, 95-102. http://dx.doi.org/10.1016/j.steroids.2015.01.021 PMID: 25668613

[95] Lee, H.J.; Ban, J.Y.; Seong, Y.H. Blockade of 5-HT(3) receptor with MDL7222 and Y25130 reduces hydrogen peroxide-induced neurotoxicity in cultured rat cortical cells. *Life Sci.,* **2005**, *78*(3), 294-300. http://dx.doi.org/10.1016/j.lfs.2005.04.043 PMID: 16112139

[96] Khalifeh, S.; Fakhfouri, G.; Mehr, S.E.; Mousavizadeh, K.; Dehpour, A.R.; Khodagholi, F.; Kazmi, S.; Rahimian, R. Beyond the 5-HT3 receptors: A role for α7nACh receptors in neuroprotective aspects of tropisetron. *Hum. Exp. Toxicol.,* **2015**, *34*(9), 922-931. http://dx.doi.org/10.1177/0960327114562034 PMID: 26286524

[97] Spiers, J.G.; Chen, H.J.; Sernia, C.; Lavidis, N.A. Activation of the hypothalamic-pituitary-adrenal stress axis induces cellular oxidative stress. *Front. Neurosci.,* **2015**, *8*, 456. http://dx.doi.org/10.3389/fnins.2014.00456 PMID: 25646076

[98] Kurhe, Y.; Mahesh, R.; Devadoss, T. QCM-4, a 5-HT□ receptor antagonist ameliorates plasma HPA axis hyperactivity, leptin resistance and brain oxidative stress in depression and anxiety-like behavior in obese mice. *Biochem. Biophys. Res. Commun.,* **2015**, *456*(1), 74-79. http://dx.doi.org/10.1016/j.bbrc.2014.11.036 PMID: 25446100

[99] Bhatnagar, S.; Sun, L.M.; Raber, J.; Maren, S.; Julius, D.; Dallman, M.F. Changes in anxiety-related behaviors and hypothalamic-pituitary-adrenal activity in mice lacking the 5-HT-3A receptor. *Physiol. Behav.,* **2004**, *81*(4), 545-555. http://dx.doi.org/10.1016/j.physbeh.2004.01.018 PMID: 15178147

[100] Gupta, D.; Radhakrishnan, M.; Kurhe, Y. 5HT3 receptor antagonist (ondansetron) reverses depressive behavior evoked by chronic unpredictable stress in mice: modulation of hypothalamic-pituitary-adrenocortical and brain serotonergic system. *Pharmacol. Biochem. Behav.,* **2014**, *124*, 129-136. http://dx.doi.org/10.1016/j.pbb.2014.05.024 PMID: 24909071

[101] Harrell, A.V.; Allan, A.M. Improvements in hippocampal-dependent learning and decremental attention in 5-HT(3) receptor overexpressing mice. *Learn. Mem.,* **2003**, *10*(5), 410-419. http://dx.doi.org/10.1101/lm.56103 PMID: 14557614

[102] Preston, G.C. 5-HT3 Antagonists and dosorders of cognition. *Racagni, G.; Brunello, N.; Langer, S.Z.; editors. Recent Advances in the treatment of neurodegenerative diorders and cognitive dysfunction*; International Academy of Biomedical Drug Research: Karger, Basel, Switzerland., **1994**, 7, pp. 89-93.

[103] Ramírez, M.J.; Cenarruzabeitia, E.; Lasheras, B.; Del Río, J. Involvement of GABA systems in acetylcholine release induced by 5-HT3 receptor blockade in slices from rat entorhinal cortex. *Brain Res.,* **1996**, *712*(2), 274-280. http://dx.doi.org/10.1016/0006-8993(95)01471-3 PMID: 8814902

[104] Callahan, P.M.; Bertrand, D.; Bertrand, S.; Plagenhoef, M.R.; Terry, A.V., Jr Tropisetron sensitizes α7 containing nicotinic receptors to low levels of acetylcholine *in vitro* and improves memory-related task performance in young and aged animals. *Neuropharmacology,* **2017**, *117*, 422-433. http://dx.doi.org/10.1016/j.neuropharm.2017.02.025 PMID: 28259598

[105] Buhot, M.C.; Martin, S.; Segu, L. Role of serotonin in memory impairment. *Ann. Med.,* **2000**, *32*(3), 210-221. http://dx.doi.org/10.3109/07853890008998828 PMID: 10821328

[106] Iidaka, T.; Ozaki, N.; Matsumoto, A.; Nogawa, J.; Kinoshita, Y.; Suzuki, T.; Iwata, N.; Yamamoto, Y.; Okada, T.; Sadato, N. A variant C178T in the regulatory region of the serotonin receptor gene HTR3A modulates neural activation in the human amygdala. *J. Neurosci.,* **2005**, *25*(27), 6460-6466. http://dx.doi.org/10.1523/JNEUROSCI.5261-04.2005 PMID: 16000636

[107] Suzuki, R.; Morcuende, S.; Webber, M.; Hunt, S.P.; Dickenson, A.H. Superficial NK1-expressing neurons control spinal excitability through activation of descending pathways. *Nat. Neurosci.,* **2002**, *5*(12), 1319-1326. http://dx.doi.org/10.1038/nn966 PMID: 12402039

[108] Suzuki, R.; Rahman, W.; Hunt, S.P.; Dickenson, A.H. Descending facilitatory control of mechanically evoked responses is enhanced in deep dorsal horn neurones following peripheral nerve injury. *Brain Res.,* **2004**, *1019*(1-2), 68-76. http://dx.doi.org/10.1016/j.brainres.2004.05.108 PMID: 15306240

[109] Stratz, T.; Müller, W. The use of 5-HT3 receptor antagonists in various rheumatic diseases--a clue to the mechanism of action of these agents in fibromyalgia? *Scand. J. Rheumatol. Suppl.,* **2000**, *113*, 66-71. PMID: 11028836

[110] Zheng, Y.; Yu, T.; Tang, Y.; Xiong, W.; Shen, X.; Jiang, L.; Lin, L. Efficacy and safety of 5-hydroxytryptamine 3 receptor antagonists in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *PLoS One,* **2017**, *12*(3), e0172846. http://dx.doi.org/10.1371/journal.pone.0172846 PMID: 28291778

[111] Browning, K.N. Role of central vagal 5-HT3 receptors in gastrointestinal physiology and pathophysiology. *Front. Neurosci.,* **2015**, *9*, 413.

[112] Fayyaz, M.; Lackner, J.M. Serotonin receptor modulators in the treatment of irritable bowel syndrome. *Ther. Clin. Risk Manag.,* **2008**, *4*(1), 41-48. PMID: 18728719

[113] Mayer, E.A.; Berman, S.; Derbyshire, S.W.; Suyenobu, B.; Chang, L.; Fitzgerald, L.; Mandelkern, M.; Hamm, L.; Vogt, B.; Naliboff, B.D. The effect of the 5-HT3 receptor antagonist, alosetron, on brain responses to visceral stimulation in irritable bowel syndrome patients. *Aliment. Pharmacol. Ther.,* **2002**, *16*(7), 1357-1366. http://dx.doi.org/10.1046/j.1365-2036.2002.01287.x PMID: 12144587

[114] Walstab, J.; Wohlfarth, C.; Hovius, R.; Schmitteckert, S.; Röth, R.; Lasitschka, F.; Wink, M.; Bönisch, H.; Niesler, B. Natural compounds boldine and menthol are antagonists of human 5-HT3 receptors: implications for treating gastrointestinal disorders. *Neurogastroenterol. Motil.,* **2014**, *26*(6), 810-820. http://dx.doi.org/10.1111/nmo.12334 PMID: 24708203

[115] Ashby, C.R.; Minabe, Y.; Toor, A.; Fishkin, L.D.; Granoff, M.I.; Wang, R.Y. Effect produced by acute and chronic administration of the selective 5-HT3 receptor antagonist BRL 46470 on the number of spontaneously active midbrain dopamine cells in the rat. *Drug Dev. Res.,* **1994**, *31*, 228-236. http://dx.doi.org/10.1002/ddr.430310310

[116] Sirota, P.; Mosheva, T.; Shabtay, H.; Giladi, N.; Korczyn, A.D.

Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am. J. Psychiatry,* **2000**, *157*(2), 287-289.
http://dx.doi.org/10.1176/appi.ajp.157.2.287 PMID: 10671405

[117] Rammes, G.; Eisensamer, B.; Ferrari, U.; Shapa, M.; Gimpl, G.; Gilling, K.; Parsons, C.; Riering, K.; Hapfelmeier, G.; Bondy, B.; Zieglgänsberger, W.; Holsboer, F.; Rupprecht, R. Antipsychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner. *Mol. Psychiatry,* **2004**, *9*(9), 846-858, 818.
http://dx.doi.org/10.1038/sj.mp.4001490 PMID: 15024394

[118] Hayes, M.R.; Covasa, M. Gastric distension enhances CCK-induced Fos-like immunoreactivity in the dorsal hindbrain by activating 5-HT3 receptors. *Brain Res.,* **2006**, *1088*(1), 120-130.
http://dx.doi.org/10.1016/j.brainres.2006.03.018 PMID: 16630589

[119] Ginawi, O.T.; Al-Majed, A.A.; Al-Suwailem, A.K. Ondansetron, a selective 5-HT3 antagonist, antagonizes methamphetamine-induced anorexia in mice. *Pharmacol. Res.,* **2005**, *51*(3), 255-259.
http://dx.doi.org/10.1016/j.phrs.2004.09.002 PMID: 15661576

[120] Carvalho, F.; Barros, D.; Silva, J.; Rezende, E.; Soares, M.; Fregoneze, J.; de Castro-E-Silva, E. Hyperglycemia induced by pharmacological activation of central serotonergic pathways depends on the functional integrity of brain CRH system and 5-HT3 receptors. *Horm. Metab. Res.,* **2005**, *37*(8), 482-488.
http://dx.doi.org/10.1055/s-2005-870323 PMID: 16138260

[121] Hodge, C.W.; Kelley, S.P.; Bratt, A.M.; Iller, K.; Schroeder, J.P.; Besheer, J. 5-HT(3A) receptor subunit is required for 5-HT3 antagonist-induced reductions in alcohol drinking. *Neuropsychopharmacology,* **2004**, *29*(10), 1807-1813.
http://dx.doi.org/10.1038/sj.npp.1300498 PMID: 15162158

[122] Hui, S.C.; Sevilla, E.L.; Ogle, C.W. 5-HT3 antagonists reduce morphine self-administration in rats. *Br. J. Pharmacol.,* **1993**, *110*(4), 1341-1346.
http://dx.doi.org/10.1111/j.1476-5381.1993.tb13966.x PMID: 8306073

[123] Johnson, B.A. Role of the serotonergic system in the neurobiology of alcoholism: implications for treatment. *CNS Drugs,* **2004**, *18*(15), 1105-1118.
http://dx.doi.org/10.2165/00023210-200418150-00005 PMID: 15581381

[124] Johnson, B.A.; Roache, J.D.; Ait-Daoud, N.; Javors, M.A.; Harrison, J.M.; Elkashef, A.; Mojsiak, J.; Li, S-H.; Bloch, D.A. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug Alcohol Depend.,* **2006**, *84*(3), 256-263.
http://dx.doi.org/10.1016/j.drugalcdep.2006.02.011 PMID: 16631323

[125] Bhatt, S.; Mahesh, R.; Devadoss, T.; Jindal, A. Neuropharmacological evaluation of a novel 5-HT3 receptor antagonist (4-benzylpiperazin-1-yl)(3-methoxyquinoxalin-2-yl) methanone (6g) on lipopolysaccharide-induced anxiety models in mice. *J. Basic Clin. Physiol. Pharmacol.,* **2017**, *28*(2), 101-106.
http://dx.doi.org/10.1515/jbcpp-2016-0083 PMID: 27664773

[126] Vega, Lde.L.; Muñoz, E.; Calzado, M.A.; Lieb, K.; Candelario--Jalil, E.; Gschaidmeir, H.; Färber, L.; Mueller, W.; Stratz, T.; Fiebich, B.L. The 5-HT3 receptor antagonist tropisetron inhibits T cell activation by targeting the calcineurin pathway. *Biochem. Pharmacol.,* **2005**, *70*(3), 369-380.
http://dx.doi.org/10.1016/j.bcp.2005.04.031 PMID: 15922994