# Histamine $H_3$ receptors and its antagonism as a novel mechanism for antipsychotic effect: a current preclinical & clinical perspective

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**Abstract**

Histamine $H_3$ receptors are present as autoreceptors on histaminergic neurons and as heteroreceptors on nonhistaminergic neurones. They control the release and synthesis of histamine and several other key neurotransmitters in the brain. $H_3$ antagonism may be a novel approach to develop a new class of antipsychotic medications given the gathering evidence reporting therapeutic efficacy in several central nervous system disorders. Several medications such as cariprazine, lurasidone, LY214002, bexarotene, rasagiline, raloxifene, BL-1020 and ITI-070 are being developed to treat the negative symptoms and cognitive impairments of schizophrenia. These medications works through diverse mechanisms which include agonism at metabotropic glutamate receptor (mGluR2/3), partial agonism at dopamine $D_2$, $D_3$ and serotonin 5-$HT_{1A}$ receptors, antagonism at $D_2$, 5-$HT_{2A,}$ 5-$HT_{2B}$ and 5-$HT_7$ receptors, combined dopamine antagonism with GABA agonist activity, inhibition of monoamine oxidase-B, modulation of oestrogen receptor, and activation of nuclear retinoid X receptor. However, still specific safe therapy for psychosis remains at large. Schizophrenia is a severe neuropsychiatric disorder result both from hyper- and hypo-dopaminergic transmission causing positive and negative symptoms, respectively. Pharmacological stimulation of dopamine release in the prefrontal cortex has been a viable approach in treating negative symptoms and cognitive deficits of schizophrenia symptoms that are currently not well treated and continue to represent significant unmet medical challenges. Administration of $H_3$ antagonists/inverse agonists increase extracellular dopamine concentrations in rat prefrontal cortex, but not in the striatum suggesting that antagonism via $H_3$ receptor may be a potential target for treating negative symptoms and cognitive deficits associated with schizophrenia. Further, insights are emerging into the potential role of histamine $H_3$ receptors as a target of antiobesity therapeutics which is one of the limiting adverse effects of second generation schizophrenia medications. The recent failures of two promising $H_3$ compounds in clinical trial dampened the interest in seeking antipsychotic like activities of $H_3$ receptor antagonists. However, due to the inconclusive nature of many of these studies, the development of $H_3$ compounds via $H_3$ antagonism/inverse agonism approach still hold lot of promises and may be developed as a novel class of drugs for schizophrenia and its related complications e.g. weight gain

Key words: **Schizophrenia, histamine $H_3$ receptor, $H_3$ antagonist/inverse agonist, cognitive deficits**

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## Introduction

Schizophrenia, a life-time debilitating neuropsychiatric disorder, is accompanied by a significant deficit in social functions and retardation in the quality of life. As many as 51 million people worldwide suffer from schizophrenia, with the developing nations. [1-4] According to the Saudi Arabian Ministry of Health (2008), 22.4% of outpatient of mental health services were suffering from mental and behavioural disorders caused by schizophrenia or schizotypal and delusional disorders. [5] The presence of delusions, hallucinations, suspiciousness, disorganized thinking marks the positive symptoms of the disorder, and impoverished speech and thinking, lack of social drive, flatness of emotional expression, apathy represents the negative symptoms of schizophrenia. Also, majority of patients with schizophrenia report memory and decrement in cognitive functioning. [2, 3] The first generation or the typical antipsychotic drugs (APD) have been successful in treating positive symptoms but they cause severe limiting side-effects, while the second generation (atypical) APDs ameliorated negative symptoms and positive symptoms in most patients but they had no or only moderate effects on cognition and also have adverse effects for example disturbance of metabolic profiles and weight gain. [6] Therefore, presently there is a significant unmet clinical needs for schizophrenia treatment especially, treatment of negative symptoms and cognitive deficits associated with schizophrenia.

## Pathophysiology

An increase of subcortical mesolimbic dopamine release has been reported to cause hyperstimulation of dopamine $D_2$ receptors which produces the positive symptoms, while reduced mesocortical dopamine release in the prefrontal cortex causes lowering in the dopamine $D_1$ receptors activation which produces the negative symptoms and cognitive impairment. [7-12] More recently, involvement of presynaptic dopamine receptors has also been reported, which affects the dopamine synthesis capacity, baseline synaptic dopamine levels, and dopamine release.[13] N-methyl D-aspartate (NMDA) receptor antagonists, ketamine or MK-801, induce schizophrenia-like behavioural disturbances and impaired neurocognition in rodents, produce psychotic behaviours and cognitive impairments in healthy humans and exacerbate symptoms in schizophrenia patients indicating involvement of glutamate in schizophrenia. [14-21] A recent report has demonstrated reduction in both the positive and negative symptoms with a metabotropic glutamate 2/3 (mGlu2/3) receptor agonist. [22, 23] Animal studies have reported reduced density of neurones releasing γ-aminobutyric acid (GABA) and also the abnormalities in receptors and reuptake sites in several cortical and subcortical GABA systems, and also the use of adjunctive GABA agonists have shown greater improvement in core schizophrenia symptoms. [24] Over the past decade, several basic and clinical studies have reported the involvement of brain histamine in the pathophysiology of schizophrenia. [25, 26] Increased histamine release has been recorded in several established experimental models of schizophrenia. [26, 27] In clinical studies, the levels of *N*-tele-methylhistamine, a major brain histamine metabolite, and marker of brain histamine turnover, was found to be elevated in the cerebrospinal fluid of patients, and a decrease in histamine $H_1$ receptor binding sites was also reported. Many atypical APDs were reported to increase histamine turnover in the brain, indicating that an abnormality in the histamine neuron system has a role in the extradopaminergic brain dysfunction of schizophrenia. Additionally, neurodevelopmental disturbances occurring during birth or genetic defects play critical role in schizophrenia development. [28-32]

## Limitations of the Current Antipsychotic Agents

Typical APDs have been effective in the treatment of positive symptoms and prevented psychotic relapse, but they showed only modest or no efficacy in improving negative symptoms and accompanying cognitive deficits, and frequently caused intolerable side-effects including extrapyramidal symptoms and tardive dyskinesia. The advent of the second generation, atypical APDs, significantly improved the pharmacologic treatment of schizophrenia, and caused lesser side effects. These APDs showed superior clinical outcomes, exceptional tolerability and efficacy in refractory cases, and considerably reduced psychotic symptoms, relapse rate, and

improved cognitive deficits. The disadvantages of APDs were reported to be weight gain, changes in glucose and lipid metabolism, risk of diabetes, coronary heart disease, and hypertension on prolonged use. [33] Atypical APDs also reported to have little efficacy in reversing cognitive impairments or show only modest efficacy in the treatment of negative and mood symptoms, and higher incidence of agranulocytosis especially with clozapine. Therefore, clozapine and other second generation APDs are now reserved for patients who are unresponsive to, or intolerant of, conventional APDs. Thus, there is an urgent need for newer medication for schizophrenia that is effective against a broad range of symptoms and free of such limiting safety issues. According to a document, over 36 new medications for schizophrenia are being developed by different biopharmaceutical research companies. [34] Cariprazine, a dopaminergic agent, is a novel atypical APD which has been currently approved by US Food and Drug Administration (FDA). It differs from all the current second generation APDs, which, with the exception of amisulpride, bind to $D_2$ and 5-$HT_{2A}$ receptors. It displays partial agonism at $D_2$, $D_3$ and 5-$HT_{1A}$ receptors and antagonism at 5-$HT_{2B}$ receptors. The data from animal studies suggest low that $D_2$ and $D_3$ receptors activity and high agonistic activity at 5-$HT_{1A}$. It is believed that cariprazine besides, providing an antipsychotic benefit, would mitigate some of the cognitive deficit that is often associated with schizophrenia. Lurasidone is another atypical APD which received approval at the end of 2010 by FDA. Lurasidone has high antagonistic activity at $D_2$, 5-$HT_{2A}$ and 5-$HT_7$ receptors and display partial agonism at 5-$HT_{1A}$ receptor. It is well tolerated and has few of side effects. [35] A randomized, double-blind, placebo- and active-controlled trial has reported the efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia. [36] A potential new class of treatments for schizophrenia that operate via a novel mechanism is LY2140023. It is a prodrug of the orthosteric agonist (LY-404039), which operates at the mGluR2/3 and remains active as long as bound to the receptor. It is believed that it exerts its effects by modulation of the dopaminergic system because mGluR2/3 agonists have been observed to inhibit dopamine release. Moreover, LY2140023 do not cause weight gain associated with olanzapine instead a modest weight loss has been reported. However, a double-blind, placebo-controlled comparator study in patients with schizophrenia, LY2140023 treatment demonstrated no efficacy. But the treatment with LY2140023 was generally well tolerated with no new adverse safety findings were recorded compared to previous trials. Thus, further understanding of the role of glutamate as a therapeutic target in schizophrenia is needed. [37] Rasagiline, raloxifene and Bexarotene are other schizophrenic medications being developed as adjunct therapies. Rasagiline is a selective monoamine oxidase inhibitor-B which is expected to be added to standard antipsychotic medication to treat cognitive impairment and negative symptoms associated with schizophrenia. Raloxifene is a selective modulator of oestrogen receptor, modulating the effects of oestrogen in the central nervous system which could improve emotional symptoms, memory and information processing in psychotic patients. BL-1020 is a new GABA-enhanced antipsychotic which combines dopamine antagonism with GABA agonist activity. The findings of a 6-week, randomized, double-blind, controlled, efficacy and safety study reported it to be an effective new APD with possible procognitive effects which is further being tested for short- and long-term effects. [38] Antitumor agent bexarotene act via nuclear retinoid X receptor (RXR) activation and has been reported to modulate numerous metabolic pathways involved in the pathogenesis of schizophrenia and schizoaffective disorder. A 6-week, randomized, double-blind, placebo-controlled multicenter trial evaluating bexarotene reported it to be a potential novel adjuvant therapeutic strategy for schizophrenia, particularly for the reduction of positive symptoms. [39]

ITI-007 is a new molecular entity with a pharmacologic profile which combines dose-related monoamine modulation with phosphorylation of intracellular signalling proteins. The *in vitro* and *in vivo* activities of ITI-007 have supported its development for the treatment of schizophrenia and other psychiatric and neurologic disorders. [40] ITI-007 was reported as a potent 5-$HT_{2A}$ receptor ligand having strong affinity for dopamine $D_2$

receptors and the serotonin transporter but negligible binding to receptors such histamine $H_1$, 5-$HT_{2C}$, and muscarinic receptors associated with cognitive and metabolic side effects of antipsychotic drugs. In vivo it is a 5-$HT_{2A}$ antagonist having dual properties at $D_2$ receptors. It blocks postsynaptic $D_2$ receptor and also acts as a partial agonist at presynaptic striatal $D_2$ receptors. [40] In a phase II randomized, double-blind, placebo-controlled, and active-controlled trial which was conducted at eight sites in the United States reported ITI-007 to be an effective for the treatment of schizophrenia and possess a comparable efficacy with placebo on safety measures, and improve negative and depression symptoms. Thus, it has been reported that ITI007 could have an expanded therapeutic efficacy in schizophrenia treatment in comparison with the current APDs. [41] Despite all the developments in schizophrenia treatment, specific medication to treat all of the negative symptoms and cognitive impairments remains to be developed. Thus, histamine $H_3$ ligands may be regarded as one step further in this context.

**Histamine Neurotransmission in Brain**

Histamine was first discovered in ergot extracts and subsequently isolated from tissues and shows its physiological effect on variety of cell types (including smooth muscle cells, neurons, endocrine and exocrine cells, blood cells and cells of the immune system and later demonstrated as chemical messenger in cell to cell communication, which is released from tissues (lung) producing bronchoconstriction during anaphylactic reactions. In 1970s, using radio-isotopes of histamine and its synthetic enzyme, l-histidine decarboxylase, it was confirmed that histamine acted as a neurotransmitter and there exists a well-defined histaminergic neuronal system in mammalian brain. [42]

Histamine has been reported to act as a neurotransmitter and neuromodulator in the mammalian brain, and is involved critically in the regulation of memory, cognition, emotion and sleep. [43, 44] The cell bodies of brain histamine neurons are located in the tuberomammillary nucleus (TMN) of the hypothalamus. The efferents of histamine-releasing neurons of the TMN innervate extensively to brain regions such as cerebral cortex, thalamus, hippocampus, amygdala, cerebellum, brain stem and spinal cord. [45-48] TMN receives afferent neuronal inputs from preoptic area of the hypothalamus, septum, prefrontal cortex, subiculum and dorsal tegmentum. Afferent neurons in the hippocampus release either glutamate or GABA and can stimulate or inhibit TMN neurons. Cortical afferents release glutamate and stimulate TMN neurons, via both AMPA and NMDA receptors. [48] Histamine in the brain elicit its response through 4 subtypes of receptors, $H_1$, $H_2$, $H_3$ and $H_4$ receptors and are coupled to specific G-proteins. [45, 48, 49] Histamine $H_4$ receptors are expressed in the immune system but are also present in the brain. [50]

Histamine $H_1$ receptors modulate many physiological functions such as maintaining wakefulness, sleep-wake cycle, learning and memory, stress, seizures, emotions and appetite control. [45, 48, 51] Histamine $H_2$ receptors in the central nervous system (CNS) are linked to processes of learning and memory, motor control, and thermoregulation, however, their functions are not clear. [52, 53] Histamine $H_3$ receptors are the third histamine receptor, and are presynaptic autoreceptors, which negatively regulate its synthesis and release. They are mostly restricted in the CNS, and have a wide distribution across the brain; the highest densities of $H_3$ receptors have been reported in the striatum, hippocampus and cerebral cortex. [54-58]

Histamine $H_3$ receptors also act as heteroreceptors which regulate the release of several key neurotransmitters. [48-57] Activation of $H_1$ and $H_2$ receptor leads to excitation, whereas $H_3$ receptor activation causes inhibition of histaminergic neurons, thus, $H_3$ receptors play an important role in regulating brain histaminergic neuron.

**Role of Histamine $H_3$ Receptors and Their Antagonism in Schizophrenia: Preclinical Status**

Histamine $H_3$ receptors are known to function as auto- and hetero-receptors to modulate the synthesis and release of multiple neurotransmitters critical for cognition, including histamine, dopamine and acetylcholine. [58] Histaminergic neurons containing $H_3$ receptors innervate prefrontal cortex (PFC) and hippocampus, the brain

areas involved in learning and memory processes, and $H_3$ receptor antagonists have been reported to enhance multiple cognition domains in naive animals. [59] Further, microdialysis and *in vivo* electrophysiological studies have found decrease in histamine neuronal firing following treatment with immepip, a selective $H_3$ receptor agonist. Also, increase in histamine neuronal firing and histamine release in TMN and PFC was demonstrated with the treatment of thioperamide, a $H_3/H_4$ receptor agonist. Furthermore, local perfusion of immepip into the TMN elevated histamine levels which was lowered by thioperamide in TMN but not in the PFC. However, it was observed that immepip perfused locally into the PFC lowered the extracellular level of histamine in both TMN and PFC. [61] The findings of the study suggested that histamine $H_3$ receptors in the brain, and particularly those expressed in the PFC, play key role in the regulation of histamine neurotransmission in the brain. Thus, it was suggested that histaminergic neuronal system of the brain may be critically involved in the pathophysiology of psychotic, affective and cognitive disorders among other disorders of brain. Histamine $H_3$ receptors by presynaptic feedback mechanism regulate histamine synthesis and release and thereby control brain histamine system. Hence, it may be expected that histamine $H_3$ receptor could potentially serve as a therapeutic target for novel medications for the treatment of various central nervous system disorders including schizophrenia. [45, 47, 61, 62]

In 2002, in a preclinical study, Pilot et al. showed that striatopallidal neurons of indirect pathway express $H_3$ receptors and over 70% of striatal enkephalin neurons express $H_3$ receptor messenger RNAs (mRNA). Acute administration of ciproxifan, a histamine $H_3$ receptor antagonist/inverse agonist, strongly potentiated the haloperidol-induced expression of enkephalin, c-fos and neurotensin mRNA including behavioural activities e.g. locomotor hypoactivity and catalepsy which were reduced by (R)-α-methylhistamine, a histamine $H_3$ receptor agonist. The potentiation of this effect was also found in the caudate–putamen and nucleus accumbens. The strong expression of $H_3$-receptor mRNA in enkephalin neurons indicated a direct $H_3/D_2$-receptor interactions resulting from enhanced activation of striatopallidal neurons of the indirect-pathway which in turn indicate potential interest in developing histamine $H_3$-receptor antagonists/inverse agonists in symptomatic treatment of schizophrenia. [63] In Dilute Brown Non-Agouti (DBA)/2 mouse model, impaired prepulse inhibition (PPI) was enhanced after treating with thioperamide and ciproxifan. [63] In 2006, one of the studies reported that histamine neuronal activity increased following the administration of MK-801, a NMDA receptor antagonist, further, suggests a role of histamine neurons in schizophrenia and treatment of mice with ciproxifan was reported to decrease hyperlocomotion induced by MK-801. [64] The same year, Akhtar et al. reported antipsychotic-like activities of thioperamide in several preclinical models of schizophrenia. [65] A recent study by Mahmood et al. also reported the antipsychotic and antioxidative activities of ciproxifan and clobenpropit in experimental studies. [66, 67] Reduced dopamine release in PFC has been linked to negative symptoms and cognitive impairment, and treatment with $H_3$ antagonist/inverse agonist enhanced the release of dopamine in PFC, [68] which resulted in improvement of the negative symptoms and cognitive impairment in schizophrenia. [68-70] Antagonism/inverse-agonism via histamine $H_3$ receptor has been suggested to have a dopamine sparing-effect on prefrontal function and may have an advantage over typical APDs. They may also have advantage over atypical APDs which produce side-effects including weight gain. Histamine $H_3$ receptor antagonists/inverse agonist might improve cognitive deficit leading to poor quality of life and functioning in schizophrenics and current APDs have shown poor or low efficacy in amelioration of this domain of schizophrenia. In the past, several studies investigated histamine $H_3$ antagonists in several experimental models involving cognitive deficits of schizophrenia. [65-75] However, most of the preclinical studies involving models of cognitive deficits mostly utilised mostly the imidazole-based compounds (e.g. thioperamide or ciproxifan) which could not reach clinical development stage because of undesirable effects. [75] Non-imidazole based compounds have renewed the interest in further pursuing $H_3$ compounds for possible efficacy in the amelioration of cognitive deficits. In 2007, Ligneau et al.

investigated the role of BF2.649, a high affinity, selective non-imidazole histamine $H_3$ receptor antagonist/inverse agonist in schizophrenia. [70] BF2.649 exhibited a dose-dependent cortical activation, wakening effect, in mice which probably resulted from selective activation of a sub-population of dopaminergic neurons. BF2.649 per se reduced locomotor hyperactivity mediated by methamphetamine or MK-801 without significantly affecting the spontaneous locomotor activity and abolished apomorphine-induced deficit in PPI. Accumulating evidence suggests that antagonism with non-imidazole based $H_3$ compounds could prove to be a new class of APDs with pro-cognitive properties. In 2009, Southam et al. reported preclinical study with another non-imidazole based $H_3$ receptor antagonist, GSK207040, in a series of behavioural and neurochemical paradigms to evaluate its antipsychotic potential. [77] The acute oral dose of GSK207040 was explored for its efficacy on several preclinical models which included reversal of deficit in novel object recognition memory and PPI, and hyperlocomotor activity induced by amphetamine, and acute neurochemical effects in rat anterior cingulate cortex by using microdialysates for dopamine, noradrenaline, and acetylcholine. GSK207040 at a dose of 3 mg/kg showed significant increase in object recognition memory, and decrease in isolation rearing-induced deficits in PPI at the dose of 1.0 and 3.2 mg/kg. However, it failed to reverse the amphetamine-induced increase in the locomotor activity, and did not show any evidence of interaction with haloperidol. At dose of 3.2 mg/kg, it increased the extracellular dopamine, noradrenaline, and acetylcholine levels in the anterior cingulate cortex and enhanced c-fos expression in the nucleus accumbens at doses of 3.2 and 10.0 mg/kg, respectively. [77] From the behavioural and neurochemical profile of GSK207040, it may be suggested that antagonism of histamine $H_3$ receptor could be a promising approach to treat the cognitive deficits and impaired sensory motor gating which typically observed in patients with schizophrenia. The inability of GSK207040 to reverse amphetamine-induced locomotor hyperactivity indicate that positive symptoms could not be treated with acute doses, [77] but may require a long-term treatment of histamine $H_3$ antagonists.

ABT-239 and A-431404 are other two potent non-imidazole-based $H_3$ receptor antagonists which have been studied and their efficacy compared to atypical antipsychotics risperidone and olanzapine, in animal model with impaired cognition. [78] In spontaneous alternation in cross-maze and inhibitory avoidance (IA) models of working-memory and long-term memory retention, respectively, ABT-239 and A-431404, but not risperidone and olanzapine attenuated MK-801-induced deficits on spontaneous alternation in cross-maze. ABT-239 and A-431404 on their own did not attenuate the alternation performance and IA but they ameliorate the MK-801-induced impairments in IA. It was observed that risperidone and olanzapine did not decrease MK-801-induced deficits in IA. The two typical APDs produced dose-dependent impairments when given alone. Methylazoxy-methanol acetate (MAM), a methylating agent, is a widely recognized neurodevelopmental model to study prenatal pharmacological insult, disruption of neurogenesis and neural development in rats. [79] ABT-239 significantly improves spontaneous alternation impairments in MAM treated rats in cross-maze model. [78] Another study, in 2013, reported that histamine $H_3$-receptor inverse agonist, BF2.649 (pitolisant), was effective in improving consolidation processes in fear-condition task model in rats. [80] In a study, treatment with ciproxifan at the dose of 3 mg/kg increased working memory in sleep restricted mice through specific modulation of prefrontal cortex areas. [81] A recent published study by Mahmood et al. have supported antischizophrenic activities of ciproxifan and clobenpropit on MK-801-induced schizophrenia like behaviours in rodents. [82] Another published report by Mahmood et al. reported the decrease in MK-801-induced hyperlocomotor behaviours and the modulation of dopamine and histamine levels following subchronic dosing of ciproxifan and clobenpropit indicating some antipsychotic-like activities of these $H_3$ compounds. [83]

The study by Burban et al, in year 2010, reported total absence of antipsychotic effect in several validated animal models of psychosis and rejected antipsychotic-like properties of $H_3$ receptor antagonists/inverse agonists.

However, they have supported their role in the treating cognitive deficits of SCZ as adjunct medication. [84] In 2014, Suven Life Sciences, at Alzheimer's Association International Conference reported positive data on exposure, safety, pharmacokinetics, and behavioral assays in rats. The poster claimed an increase in cortical histamine and acetylcholine levels as well as reversal of memory deficits. [85] Further preclinical data were presented at AAIC in 2015. [86] SUVN-G3031 was reported as a novel and potent histamine $H_3$ receptor antagonist developed for potential treatment of cognitive deficits. The novel compound was shown to have a receptor affinity of 8.7 nM and displays more than 100 fold selectivity against the related G-protein coupled receptors. The molecule was reported to exhibit desired pharmacokinetic properties and brain penetration and display an excellent separation between $H_3$ affinity and human hERG potassium channel inhibition. Thus, the development of such novel $H_3$ compound having desired efficacy, safety, pharmacokinetic and metabolic profiles further suggest that $H_3$ compounds still have vast therapeutic potential which need to be fully tapped using sophisticated drug discovery methods. [85]

Additionally, $H_3$ compounds could have an added advantage and edge over other pipeline drugs for schizophrenia by the fact that preclinical data have provided insights into the potential role of histamine $H_3$ receptors as a target of antiobesity therapeutics. [87] Studies on animals have revealed that brain releases histamine during the appetitive phase to provide a high level of arousal in preparation to feeding, but also mediates satiety. Furthermore, histamine is reported to regulate peripheral mechanisms such as glucose uptake and insulin function. Researches on animals have indicated that activation of $H_1$ and $H_3$ receptors is important for the regulation of the diurnal rhythm of food consumption. These receptors have been specifically recognized as mediators of energy intake and expenditure. However, no brain penetrating drugs acting $H_1$ receptor agonism could be identified as yet which could have anti-obesity effects. However, interesting results have emerged from clinical trials which have assessed the ameliorating effect of betahistine (an $H_1$ agonist/$H_3$ antagonist) on metabolic side effects associated with chronic medication of schizophrenia. [88]

In light of the present and past studies, histamine $H_3$-receptor antagonism/inverse agonism could be a promising therapeutic approach to treat schizophrenia symptomatically, and the development of $H_3$ compounds acting via $H_3$ antagonism/inverse agonism hold lot of promise but may warrant advance studies.

**Histamine $H_3$ Receptors and their Antagonism in Schizophrenia: Current Clinical Perspectives**

In post-mortem analysis of brain samples from schizophrenic patients, hippocampal CA2 region of medicated patients and prefrontal cortices show lower and higher $H_3$ receptor binding, respectively compared to controls. This indicates a correlation with psychotic symptoms suggesting that $H_3$ receptors have a role in the modulation of cognition. [89] Histamine $H_3$ compounds which were reported with almost drug-like properties included tiprolisant, ABT-239, GSK189254, and JNJ-10181457. [90]

Weight gain is a common side effect associated with some prominent antipsychotic agents affecting compliance. Histamine $H_3$ antagonists have been reported as an alternative to olanzapine to lower weight gain. In clinical studies, histamine $H_3$ antagonists have attenuated weight gain by the long-term use of antipsychotic medication e.g. olanzapine. A recent double-blind placebo-controlled study reported reduced weight gain caused by olanzapine in patients with schizophrenia following $H_3$ antagonist use. [91] In human patients on antipsychotic medication, the combined 4mg dose of reboxetine (a selective norepinephrine reuptake inhibitor), and 48 mg dose of betahistine (a potent $H_3$ receptor antagonist), administered daily significantly reduced weight compared to the placebo group. [91] A Phase II clinical trial assessed the efficacy of BF2.649 in patients suffering from APD medication induced weight-gain and found it to be effective following co-treatment with APD medication. (WO2006084833A1). Another study assessed the procognitive potential of BF2.649 in schizophrenic patients and affective disorder, and is currently underway (NCT-ID NCT00690274). A Phase1b, placebo

controlled, randomized study was initiated in April, 2009 and completed in 2010, to investigate the safety and efficacy of PF-03654746 as an add-on treatment for cognitive deficits in schizophrenic patients. The patient received 3 weeks of PF-03654746 (0.5 mg/kg/day) and 3 weeks of placebo. The results of the trial are yet to be published.

Despite promising outcomes from preclinical studies, the outcome of 3 important randomized clinical trials failed to show much the positive effect of histamine $H_3$ antagonist in the amelioration of cognitive impairment associated with schizophrenia. Phase II trial involving MK-0249 for cognitive impairments in schizophrenia found that MK-0249, 10 mg once daily dose was not superior to placebo in the treatment of cognitive impairment in patients with schizophrenia after 4-weeks. [(92)] Another randomized, double-blind, placebo-controlled, parallel-group 12-week study tested ABT-288 for efficacy in cognitive deficits in clinically stable subjects with schizophrenia. [(93)] The study participants were randomized to receive 10 mg and 25 mg of ABT-288 or placebo once daily and asked to continue their antipsychotic medication. The finding of the study showed that there were no procognitive effects with either doses of ABT-288. Additionally, the treatment was correlated with sleep disruption. [(93)] Yet another phase II exploratory trial with GSK239512, a brain penetrating $H_3$ receptor antagonist showed no overall beneficial effects of GSK239512 in cognitive deficit. [(94)]

In conclusion, the failure of histamine $H_3$ compounds in these clinical trials has dampened the confidence in developing histamine $H_3$ compounds via $H_3$ antagonism/inverse agonism. However, gathering body of evidence from preclinical studies point antagonists of histamine receptors as promising alternatives to treat brain disorders, and clinical trials are currently ongoing to assess the effects of these drugs on humans. CEP-26401 (Irdabisant) is a novel antipsychotic currently being developed by Teva Pharmaceutical Industries and is in phase I clinical trial. A considerable deal of research needs to be conducted with histamine $H_3$ compounds including CEP-26401 to verify their use in psychosis and related problems

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