Schizophrenia: Synthetic strategies and recent advances in drug design

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Abstract

Schizophrenia is a complex and unpredictable mental disorder which affects several domains of cognition and behaviour. It is a heterogeneous illness characterised by positive, negative, and cognitive symptoms, often accompanied by signs of depression. In this tutorial review, we discuss recent progress in understanding the target sites and mechanisms of action of second-generation antipsychotic drugs. Progress in identifying and defining target sites has been accelerated recently by advances in neuroscience, and newly developed agents that regulate signalling by the main excitatory neurotransmitters in the brain are surveyed. Examples of novel molecules for the treatment of schizophrenia in preclinical and clinical development and their industrial sponsors are highlighted.

Introduction

Schizophrenia is one of the most mysterious disorders in psychiatry owing to its complex nature and unpredictable course. The very start of the disorder goes back to the early brain development stage and is known to result from genetic and environmental risk factors. The anatomical changes seen in the brains of patients diagnosed with schizophrenia include differences in volume and alterations of various regions of the brain such as the global, cortical, subcortical regions, white and grey matter. Its complex pathology includes abnormalities in the dopaminergic, serotonergic, glutamatergic and GABAergic (related to the function of γ-aminobutyric acid (GABA) neurotransmitter) systems. Such an heterogeneous (symptoms, course, response to treatment and outcome greatly vary with patients[1;2]) and complex mental disorder is challenging to cure, but recent progress in genomics, epidemiology and neuroscience[2] have opened up new avenues for the design of suitable medications for the minimisation of schizophrenia effects and symptoms. A significant number of clinical trials now involve novel molecules for the treatment of schizophrenia. Some of the current (February 2018) clinical trials are listed in Table 1.

Table 1. Some examples of industries/sponsors with molecules in development or clinical trials or approved for clinical use. In many cases more details can be found on the Clinical Trials website: http://www.clinicaltrials.gov/

Industry/ Sponsor	Drug	Type of drug/mechanism of action	Targeted outcome	Stage
Eli Lilly (Generic since 2011)	Olanzapine	Dopamine antagonist	To reduce symptoms of schizophrenia, to treat acute exacerbations, and to treat early-onset schizophrenia	Approved
Generic	Risperidone	Dopamine antagonist	To reduce the overall symptoms of schizophrenia	Approved
Janssen Pharmaceutica.	9-hydroxyrisperidone (Paliperidone)	Dopamine antagonist and Serotonin 2A antagonist	To treat schizoaffective disorder	Approved
Otsuka	Aripiprazole	Partial dopamine	To treat acute exacerbations	Approved

		agonist	of schizophrenia and for maintenance treatment (relapse prevention)	
ACADIA Pharmaceuticals Inc.	Pimavanserin (Nuplazid)	Selective inverse agonist of the serotonin 2A receptor	To treat positive and negative symptoms	Phase III
Alkermes, Inc.	Samidorphan and olanzapine (ALKS 3831)	Mu opioid receptor antagonist and Dopamine antagonist	To provide patients with the strong efficacy of olanzapine and a differentiated safety profile with favourable weight and metabolic properties	Phase III
Sumitomo Dainippon Pharma Co., Ltd.	Blonanserin (DSP-5423P)	Dopamine 2 receptor antagonists; Serotonin 2A receptor antagonists	To treat positive and negative symptoms	Phase III
Beth Israel Deaconess Medical Center	Tiagabine	GABA reuptake inhibitor	To correct the brain deficits associated with the disease	Phase III
VA Office of Research and Development	3-[2,4 dimethoxybenzylidene] anabaseine (DMXB-A)	Orally administered nicotinic cholinergic agonist	To improve attention and other neuropsychological dysfunctions in schizophrenia, leading to improved psychosocial outcome	Phase II
Indiana University and Eli Lilly	LY500307	Selective estrogen receptor beta agonist	To treat negative symptoms and cognitive impairment associated with schizophrenia	Phase II
Sunovion Pharmaceuticals Inc.	SEP-363856	Serotonin 1A receptor agonist; Trace amine-associated receptor 1 agonist	To treat the positive and negative symptoms of schizophrenia, as well as hallucinations and delusions	Phase II
Avraham Reichenberg	L-Carnosine (β-alanyl-L-histidine)	Advanced glycation end-products production inhibitor	To increase the performance of patients with schizophrenia on memory and learning training tasks	Phase II
Merck Sharp & Dohme Corp.	MK-8189	Undisclosed	To treat acute episode	Phase II
Massachusetts General Hospital	Sodium nitroprusside	Release of nitric oxide	To treat positive and negative symptoms	Phase II
China Medical	D-amino acid	NMDA-enhancing	To treat treatment-resistant	Phase II

University Hospital	oxidase inhibitor (DAAOI-2)	agent	Schizophrenia	
Central Institute of Mental Health, Mannheim	Cannabidiol	Cannabinoid receptors 1 and 2 inverse agonist	For maintenance treatment of schizophrenia	Phase II
Astellas Pharma Inc.	ASP4345	Undisclosed	To treat cognitive impairment associated with schizophrenia	Phase I
Otsuka Pharmaceutical Development & Commercialization, Inc.	Brexpiprazole	Dopamine 2 partial agonist	To treat positive and negative symptoms	Phase I
Autifony Therapeutics Limited	AUT00206	Selective modulator Kv3 potassium channels	To treat positive, negative and cognitive symptoms of schizophrenia	Phase 1
Brian Miller	Siltuximab	Chimeric monoclonal antibody	Adjunct to antipsychotic medications	Phase 1
University of California, San Diego	Memantine (3,5-dimethyl-1-adamantanamine)	NMDA receptor antagonists	To improve cognitive impairment and symptoms in schizophrenic patients	Phase I
University of Maryland	L-tetrahydropalmatine	Dopamine 1, 2, 3 receptors antagonist	Treatment of Schizophrenia with anti-inflammatory and antiprotozoal activity	NCT02118610 In development
University of Colorado, Denver	Levetiracetam (LEV: (S)-α-ethyl-2-oxo-pyrrolidine acetamide)	Anticonvulsant and antiepileptic drug	To reduce hippocampal activity in schizophrenia	NCT02647437 In development

The development of antipsychotics started in the 1950s with the approval of chlorpromazine and other ‘typical’ antipsychotics (such as haloperidol). Such a discovery allowed for the first time the de-institutionalisation of patients suffering from psychosis. A second generation of antipsychotics (also named as “atypical”), such as clozapine, became available in the late 1980s. The large number of clinical trials currently recruiting and the continuing quest for finding drugs with novel mechanisms of action arise from the fact that both typical and

atypical antipsychotics, although having demonstrated some efficacy, do not treat all symptoms of the disease. Furthermore, the treatment of schizophrenia with antipsychotics is impaired by a number of side effects, such as motor side-effects, weight gain, and sedation. The treatment of the symptoms of schizophrenia is therefore of the utmost complexity, and is a task that can only be undertaken *via* interdisciplinary collaborations and concerted research efforts between chemists, biologists, and clinicians.

In this tutorial review, we provide a brief overview of schizophrenia for non-specialist researchers that have interest in anti-schizophrenia chemical drug design or in the biological evaluation of such drug candidates. In order to introduce some emerging approaches for the treatment of schizophrenia, we survey the synthesis, mode of action, effectiveness and limitations of some of the most clinically used typical and atypical antipsychotics, and we highlight some of the current interests in antipsychotic design. We attempt to focus especially on their interactions with target sites, including glutamatergic signalling and inhibition of key transporters. Owing to the inter-individual variation in antipsychotic drug response, tailoring the design of drugs to target specific sites is likely to be a major part of future personalised medicine, which will include genomic and proteomic profiling of individuals.

1. Schizophrenia in a nutshell

1.1. Clinical signs and symptoms

Schizophrenia is characterised by positive, negative, and cognitive symptoms; around 20% of diagnosed individuals have permanent and severe symptoms which cause disability, and more than 50% have non-persistent symptoms which follow a long-course.[2]

Positive symptoms, also called psychotic symptoms, mainly occur during acute episodes of the disorder[1;3] and include delusions, hallucinatory experiences, thought insertion or

withdrawal, and extraordinary behaviour. These symptoms tend to relapse and remit but some individuals report residual long-term symptoms.[2] Antipsychotic drugs are used to help with positive symptoms and the outcome is usually positive.[4]

Negative symptoms are more persistent than positive symptoms, and these can be divided into primary and secondary negative symptoms.[5] The primary negative symptoms are likely to occur before the onset of the disorder and between psychotic episodes.[6] Secondary negative symptoms occur along with the psychotic episodes or during depression.[5] Negative symptoms include flat affect (decreased emotional response such as less movement and monotonic speech), alogia (poverty of speech), lack of volition, apathy and social withdrawal. Antipsychotic drugs have only minor effect on negative symptoms.[3]

Cognitive symptoms are often seen before the onset of other symptoms of schizophrenia[1;7] and they are associated with poor performance of patients in a broad range of cognitive domains.[2;3] These symptoms include thought disorder (core symptom of schizophrenia), thought blocking, derailment (patient cannot make a logical connection between words and sentences), poor attention, illogicality, clanging, neologism and echolalia (repeating of words, phrases or sounds).[4] Between 20 and 30% of individuals diagnosed with schizophrenia do not show cognitive deficits.[3] However, for individuals with cognitive symptoms, these tend to be chronic and often do not improve even if positive symptoms show good response to medications.[3;8]

Other symptoms of schizophrenia include episodes of depression (observed in over 50% of cases),[3] anxiety, hostility and aggression, and self-injury.[4] The most frequent symptoms of acute schizophrenic disorder include lack of insight at 97%, auditory hallucinations at 74%, suspiciousness at 66%, voices speaking to the patient at 65% and thoughts spoken aloud at 50%.[8]

1.2. Statistics

Schizophrenia is known to begin in late adolescence and early adulthood, with typical age of onset for men - 23 years and for women - 28 years. However, the very start of the disorder goes back to the early brain development stage and is related to genetic and environmental risk factors. Genetic factors such as abnormalities of dopamine signalling and glutamatergic dysfunction are the core features of schizophrenia[2] but these are also related to other mental illnesses such as autism and bipolar disorder.[8] Environmental factors such as risk factors during pregnancy (maternal stress, infections, birth complications, growth retardation for example, immigration, birth in late winter, misuse of compounds with high content of tetrahydrocannabinol (cannabis), all contribute to schizophrenia, especially for individuals who are susceptible to the disorder.[2]

Life expectancy is reduced by 15-20 years,[2] where 40% of mortality account for suicide cases and 60% for health problems such as cardiorespiratory, infectious and musculoskeletal diseases.[3] The duration of the illness is at least 6 months, with at least one month of severe symptoms known as 'active-phase symptoms'. However, if the disorder is successfully treated with medications and psychological therapies, the duration of these severe symptoms can be reduced.[1] Statistics show that only 11.5% of the people diagnosed with schizophrenia in the UK are working, which means that unemployment for schizophrenia is really high (*ca.* 80 - 90%). The number of schizophrenic individuals in the UK who had experienced homelessness in their lifetime, reaches 32.8%.[9]

1.3. Neurobiology of Schizophrenia

Anatomical changes in the brains of people diagnosed with schizophrenia include differences in volume and alterations of not only white and grey matter, but also of different regions such as the global, cortical, subcortical regions (Figure 1).[1;10]

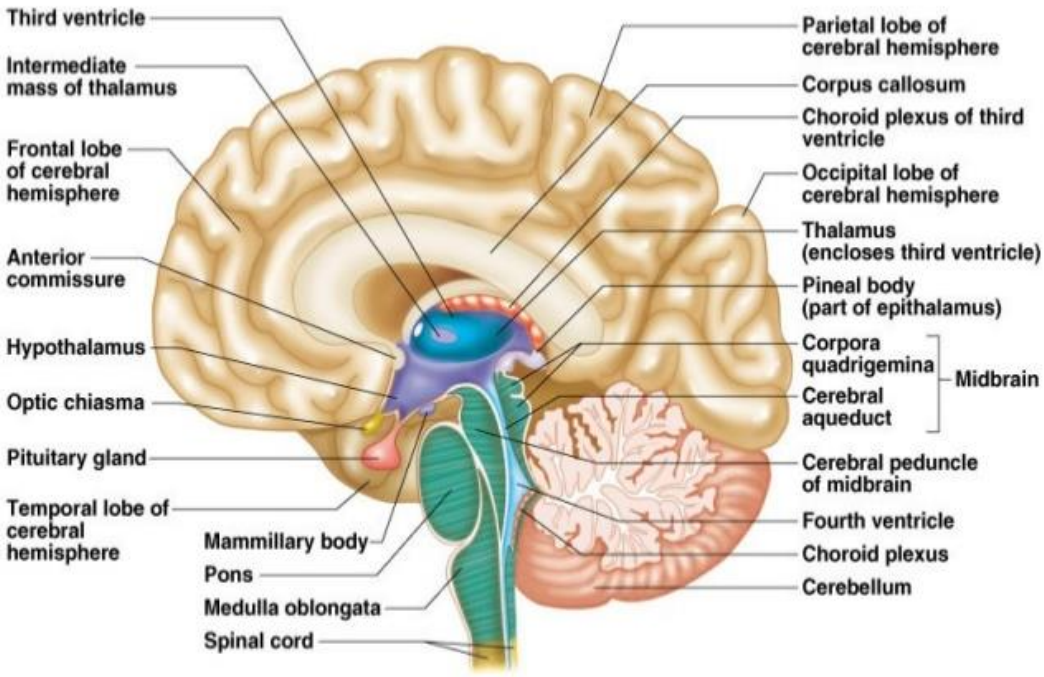


Figure 1. Schematic representation of a cross section of a human brain. Reproduced with permission from reference.[11]

Figure 2 summarises some of the most important changes observed in the brains of individuals diagnosed with schizophrenia.

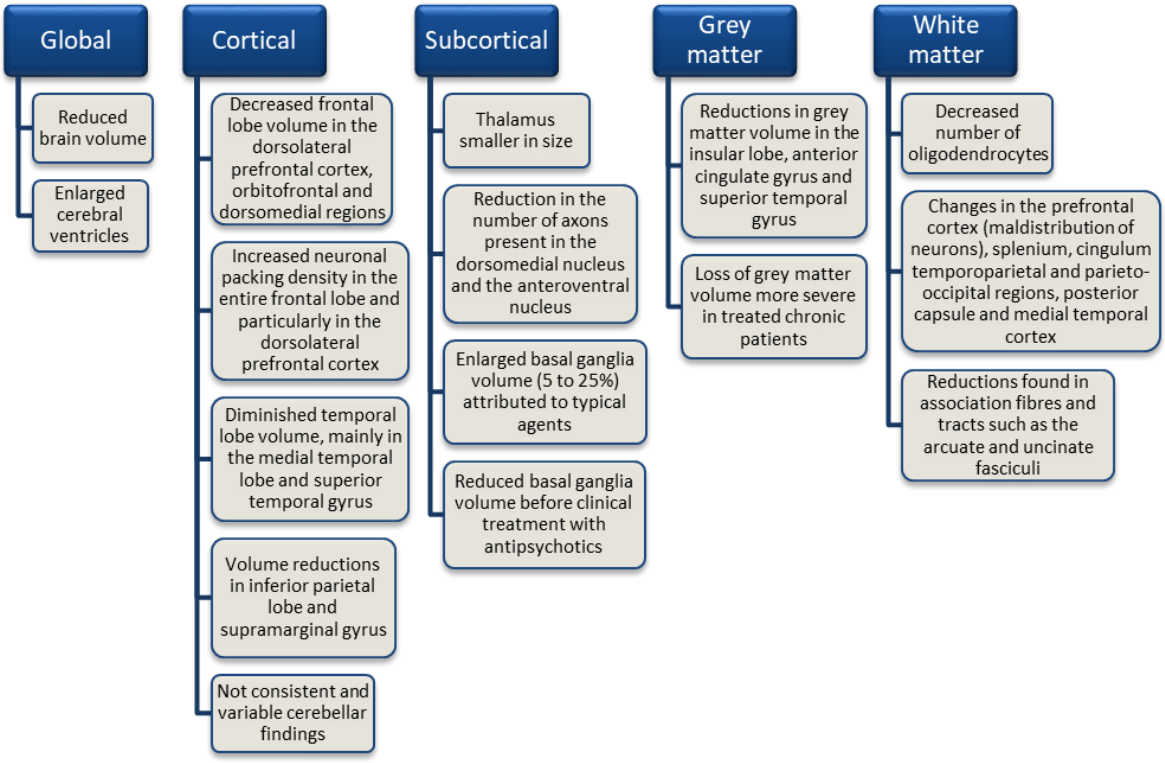


Figure 2. Summary of the different alterations found in the brains of patients diagnosed with schizophrenia.

Global brain findings include a 2% reduced brain volume, and enlarged cerebral ventricles.[1;10] Some studies show increases in ventricle size from 20 to 75% which are associated with schizophrenia. Ventricle enlargement supports the idea that schizophrenia is a progressive disorder because it has been found that this particular problem progresses with time if the individual does not follow the treatment. Patients with largest ventricles show most severe symptoms with small chances for positive outcomes.[10]

Cortical findings include changes and alterations in the prefrontal cortex (PFC), temporal lobe and parietal lobe. The neuronal packing density, but not the number of neurons, is found to be higher in the entire frontal lobe and specifically in the dorsolateral prefrontal cortex (DLPFC). The DLPFC is of significant importance for investigations related to schizophrenia owing to its association with a number of symptoms and cognitive deficits. Analysis of the temporal lobe shows alterations in the medial temporal lobe, the superior temporal gyrus (STG) and the planum temporale. Positive symptoms of schizophrenia have been related to alterations of the temporal lobe and negative symptoms have been related more specifically to reductions in the left medial temporal lobe volume. Severity of auditory hallucinations and thought disorder are related to changes in the left anterior and left posterior STG. The medial temporal lobe includes the amygdala (responsible for emotions, and fear in general) and the parahippocampal gyrus (related to memory). A number of imaging studies and post-mortem investigations found that the volume of the medial temporal lobe of individuals diagnosed with schizophrenia is reduced.[10] Volume decreases in amygdala-hippocampal complex are observed in both chronic and first-episode patients but these losses are also present in anxiety disorders, mood disorders and as a result of aging. Volume reductions in the parietal lobe,

particularly located in the inferior parietal lobe and supramarginal gyrus are associated to schizophrenia.[10]

Subcortical findings include changes in the thalamus and basal ganglia of patients diagnosed with schizophrenia. The thalamus is responsible for the transmission of sensory impulses from various receptors throughout the body to the cerebral cortex and is smaller in size in patients with schizophrenia as compared to healthy subjects. When the thalamus is being subdivided, a decrease in the number of axons present in both the dorsomedial nucleus and the anteroventral nucleus is observed.[10] When considering basal ganglia in patients diagnosed with schizophrenia, it has been found that there is an increase in its volume (with around 5 to 25%)[1] and this is considered to be a medication effect attributed to typical (first-generation) antipsychotic drugs.[10]

The reduced brain volume in patients diagnosed with schizophrenia is related to a decrease in grey and white matter volume.[12;13] Reductions in grey matter volume could be found in different regions of the brain and in different structures such as frontal and temporal areas, including the insular lobe, anterior cingulate gyrus, and superior temporal gyrus. The loss of grey matter volume results from cortical thinning and progresses with time. It is more severe in treated chronic patients than in medication-naive patients. White matter volume changes are also distributed across various brain regions and are mainly found in association fibres and tracts such as the arcuate and uncinate fasciculi.[12] These findings support the theory of dysconnectivity in schizophrenia where symptoms, course and severity of the disorder are believed to result from the disconnections between different brain structures and their poor communication.[14;15] Diffusion Tension Imaging (DTI) study, which is a special type of Magnetic Resonance Imaging (MRI) analysis related to white matter, confirmed white matter changes in the PFC (maldistribution of neurons), splenium, cingulum, temporoparietal and parieto-occipital regions, posterior capsule and medial temporal cortex.[10] Reductions in white

matter volume in patients diagnosed with schizophrenia do not progress after the onset of the disorder and could even improve over time. One of the main reasons for white matter deficits in patients diagnosed with schizophrenia is believed to be the dysfunction of oligodendrocytes and these are responsible for the production of myelin which protects the nerve fibres in the central nervous system (CNS).[12]

1.4. Neurochemistry of Schizophrenia

Schizophrenia is a severe mental illness combining abnormalities of different neurotransmitters and receptors in the brains of patients diagnosed with the disorder. Its complex pathology includes alterations in the dopaminergic, serotonergic, glutamatergic and GABAergic (related to the function of γ-aminobutyric acid (GABA) neurotransmitter) systems. Dopamine hypothesis of schizophrenia is the oldest theory related to the disorder. Abnormalities of the dopamine receptors, dopamine synthesis and release, are observed in patients diagnosed with schizophrenia.[16] Dopamine (Figure 3) is a neurotransmitter synthesised in neurones from extracellular tyrosine *via* dihydrophenylalanine.[17]

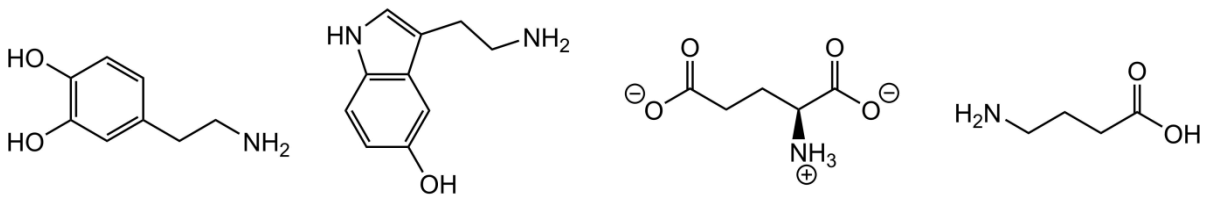


Figure 3. Molecular structures of dopamine (a), serotonin (b), L-glutamate (c), and GABA. (d).

The molecule interacts with different postsynaptic receptors from D_1 dopamine family (including D_1 and D_5 receptors) and D_2 dopamine family (including D_2, D_3 and D_4 receptors).[18] Dopamine is associated with a number of behaviours owing to its role in the control of motor activities, reward and pleasure, and thus contributes to cognition and volition.[1] Schizophrenia could be partly characterised by prefrontal dopamine hypofunction

and subcortical dopamine hyperfunction.[19] The prefrontal dopamine hypofunction (mainly in the PFC and anterior cingulate)[1] is known to result in negative and cognitive symptoms of the disorder such as flat affect, lack of volition and thought disorder.[19;20] The subcortical dopamine hyperactivity (mainly in Broca's area, STG, cingulate gyrus and hippocampus)[1] is thought to result in positive symptoms such as hallucinations and delusions. Evidence supporting this theory comes from the observation of higher dopamine levels correlating to greater positive symptoms and the response of patients to antipsychotic drugs.[19] Positron emission tomography (PET) studies demonstrated reduced cerebral blood flow in the frontal cortex (hypofrontality)[1;19] which is related to low cerebrospinal fluid dopamine metabolite levels, indicating dopamine hypofunction in the frontal region of the brains of patients diagnosed with schizophrenia.[19, 21] Studies investigating striatum region in the brains of schizophrenic individuals or people at high risk for psychosis, found increased dopamine synthesis capacity, increased dopamine release and increased dopamine occupying the $D_{2/3}$ receptors.[16;19] $D_{2/3}$ dopamine receptor binding in the thalamus was also found to be reduced and the dopamine synthesis capacity in the temporal and limbic regions increased.[16, 22]

Serotonergic systems are also involved in the neurochemistry of schizophrenia, interacting closely with the dopaminergic systems.[23] Serotonin (or 5-hydroxytryptamine or 5-HT, Figure 3), is a neurotransmitter synthesised from L-tryptophan, one of the essential amino acids. The 5-HT systems are involved in mood balance and emotional processing, they are sensible to stress and therefore 5-HT dysfunction results in depression (a common symptom in schizophrenia).[20] Post-mortem and *in vivo* molecular imaging studies of the serotonergic system show abnormal serotonin receptor function in patients diagnosed with schizophrenia.[24] These studies reported reduction in $5HT_{2A}$ receptors density (20 to 50%) and increase in $5\text{-}HT_{1A}$ receptors density (20 to 90%).[20, 24] The $5\text{-}HT_{2A}$ receptors are of interest in schizophrenia as many of the newly developed (second-generation) antipsychotic drugs

display potent antagonism activity for this particular receptor subtype,[1;20] but they also bind to other 5-HT receptors such as 5-HT_{1A}, 5-HT_{2C} and 5-HT_7 receptors.[24]

Glutamatergic systems also take part in the neuronal pathology of schizophrenia and it is believed that schizophrenia results from dysfunctional glutamate and glutamine neurotransmission which further damages other neuronal systems.[25] Glutamate (Figure 3~~2~~c) is the main excitatory transmitter in the brain and it is synthesised in neurones or glial cells from glutamine. Glutamatergic systems can influence dopamine function and either stimulate or inhibit dopamine release.[1;26] Proton magnetic resonance spectroscopy (^{1}H MRS) and single-photon emission computed tomography (SPECT) studies reported changes in the concentrations of glutamate, glutamine and a combination of both glutamate and glutamine (GLX) levels, in patients diagnosed with schizophrenia.[27] These studies show increased GLX levels in the medial prefrontal cortex, thalamus, basal ganglia (BG), parietal region, occipital region and anterior cingulate.[28] Glutamine concentrations are found to be elevated in the thalamus, anterior cingulate and medial prefrontal cortex, whilst Glutamate levels are found to be decreased in the thalamus but increased in the basal ganglia.[29] The increased levels of glutamine and decreased levels of glutamate in the thalamus represent dysfunctional conversion of glutamine to glutamate in this region in the brains of patients diagnosed with schizophrenia. The increased concentrations of glutamate in GLX and basal ganglia are seen in patients before the first episode of psychosis and could be used as an indication of the schizophrenic syndrome.[30] When patients are treated with antipsychotic drugs these levels decrease back to normal.[16] *N*-methyl-D-aspartic acid (NMDA) receptor is one of the glutamate receptors and it is known to be involved in the mechanism of schizophrenia.[31] It is an ionotropic receptor and it has a gated cation channel.[1] NMDA receptors located on the dopaminergic neurons regulate extracellular dopamine. Reduction in the NMDA receptor

function in patients diagnosed with schizophrenia results in dysregulation of dopamine release – subcortical dopamine hyperfunction and prefrontal dopamine hypofunction.[16]

GABA (Figure 3) is another important neurotransmitter involved in the neuronal pathology of schizophrenia.[32] GABA is synthesised from glutamate by the enzyme glutamate decarboxylase. It is the main inhibitory transmitter in the brain and it binds to a range of postsynaptic receptors such as $GABA_A$, $GABA_B$ and $GABA_C$.[1] Post-mortem and *in vivo* imaging studies demonstrated decreased GABA activity in the cortex and mesolimbic systems of patients diagnosed with schizophrenia.[1;20] As GABA is the main inhibitory neurotransmitter in the brain, its decreased activity is believed to result in dopamine hyperactivity.[1;33]

1.5.Treatment

The treatment of schizophrenia combines medications, psychological sessions and therapies, rehabilitation and social support. After the first episodes of psychosis, when treated with medications, around 20% of individuals report encouraging results, recovery and a positive outcome. Around 35% of individuals report symptoms that relapse and remit, with a good condition between episodes. Around 35% of individuals report chronic positive and negative symptoms, with a need for further treatment and psychological care. Around 10% of individuals report severe symptoms, with a need for a long-term treatment and special care.[3] Antipsychotic drugs have been used for many years and remain the mainstay for both the acute and long-term treatment of schizophrenia. This class of drugs could be divided in two major categories – first-generation antipsychotics (FGAs) (also called typical or conventional) and second-generation antipsychotics (SGAs) (also called atypical antipsychotic drugs).[2] Here, we will explore the structures of clinically approved typical and

atypical antipsychotics, their modes of action, metabolism, effectiveness and limitations. We will also survey recent advances made in the chemical synthesis of antipsychotic drugs.

2. Clinically-approved drugs

2.1. Chlorpromazine

Chlorpromazine (Figure 4) is the first antipsychotic drug developed and was discovered in 1950 following a collaborative work between the Laboratoire d'Eutonologie at Boucicault Hospital (Paris, France) and the pharmaceutical company Rhône-Poulenc.[34] It has been used in the treatment of psychoses, severe anxiety, psychotic aggression, resistant and severe hiccups, as well as for pre-anaesthetic conditioning.

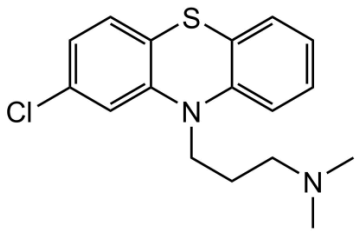


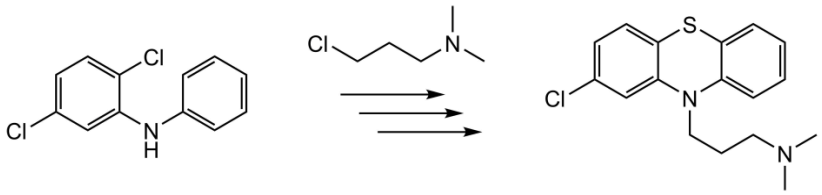
Figure 4. Molecular structure of chlorpromazine.

Chlorpromazine is a neuroleptic agent which is on the World Health Organisation (WHO)'s list of essential medicines.[35] It also exhibits some sedative and antiemetic activities, and has led to the discovery of antidepressants.[36] This drug had a tremendous impact on psychiatric patients, and its role was compared to the role of penicillin on infectious diseases.

2.1.1. Synthesis

Chlorpromazine is usually found as a salt: CPZ hydrochloride. Within its molecular structure, the nitrogen from the side chain can act both as a hydrogen bond donor and acceptor. Its synthesis was developed in 1950 by the French pharmaceutical company Rhône-Poulenc and CPZ went through clinical development with surgeons and psychiatrics in France in the early

1950's. The first clinical trial was published in 1952 on the use of CPZ as a sedative agent before CPZ was approved for the treatment of many psychotic disorders, including schizophrenia a few years later.



Scheme 1. Synthesis of chlorpromazine from the original 1953 patent.[37]

The synthesis of CPZ involves the condensation of the chlorophenothiazine cyclic compound with the tertiary aminoalkyl halide 3-dimethylamino-1-chloropropane in the presence of an acid-binding agent, such as sodium amide, using xylene as solvent. The 2-chlorophenothiazine compound is prepared by cyclisation of the corresponding 2,5-dichloro-*N*-phenylaniline with sulfur, with the use of iodine as catalyst.[37]

2.1.2. Mode of action and metabolism

Chlorpromazine is an antagonist on several dopamine receptors (D_1, D_2, D_3, and D_4). The particular blocking of D_1 dopamine receptors diminishes neurotransmitter binding in the forebrain, and creates a feedback loop that causes the release of more dopamine after the first intake of the drug. Both the productive and unproductive symptoms are affected as a result. CPZ also strongly acts as an antagonist of serotonin receptors, 5-HT_1 and 5-HT_2,[38] which is highly unusual for typical antipsychotics, and similar to atypical antipsychotics (with anxiolytic, anti-depressive, and anti-aggressive properties, attenuation of extra-pyramidal side-effects as well as some drawbacks such as weight gain, blood pressure fall, sedation and ejaculation difficulties).[39] Chlorpromazine is one of the most potent agent at α-adregenic receptors, as reported for other antipsychotics with sedative properties, which accounts for sympatholytic properties, lowering of blood pressure, reflex tachycardia, vertigo, sedation,

hypersalivation, incontinence and sexual dysfunction. This property coupled with its antagonist effect on histamine H1 receptors (accounting for sedation, antiemetic effect, vertigo, and weight gain) has led to the pharmaceutical development of CPZ as a anti-histaminic agent.[40] Other neurotransmitters are affected: epinephrine, norepinephrine, acetylcholine. This can lead to dry mouth, blurred vision, constipation, difficulty to urinate, loss of memory; however a positive impact on extrapyramidal side effects is reported.

Chlorpromazine is metabolised by different pathways, including hydroxylation and conjugation with glucuronic acid, *N*-oxidation, *S*-oxidation, and dealkylation, all being part of the "first pass" metabolism. The highest concentrations of unconjugated metabolites are found in the lung and in the liver (almost 40% of the administered dose), which may lead to rare but severe idiosyncratic toxicity (hepatic injury).[41] Cytochrome P450 plays a major role in its metabolism. Numerous metabolites are secreted (more than fifty have been reported), with various half-lives and pharmaceutical levels of activity.[42-44]

2.1.3. Effectiveness

Chlorpromazine was the first effective treatment available for schizophrenia to become available on the market in 1952 and is still one of the most commonly used antipsychotics owing to its low production cost.[45, 46] However, the important weight gain is a major drawback, as well as the sedation effect.[47, 48] In addition, CPZ exhibits the same levels of extrapyramidal side-effects (EPSEs) than most second-generation antipsychotics, which is unusual for a first-generation product.

2.1.4. Limitations

The administration of chlorpromazine leads to a number of side effects: Parkinsonism, jaundice, hypotension, convulsions, confusion, dermatitis, constipation, sedation.[49, 50] The latter effect can be of benefit in the initial stages of treatment; some other side effects

disappear when the treatment is stopped and do not appear again when the treatment resumes.[51]

2.2. Haloperidol

Haloperidol (Figure 5) is a first-generation antipsychotic drug which has been in clinical use for more than fifty years and it has been involved in a huge number of studies all contributing to the development of neuroscience and playing an important role in psychiatry.[52;53]

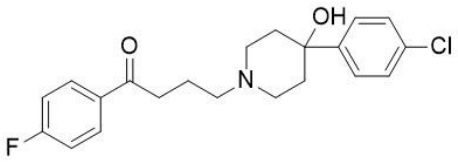
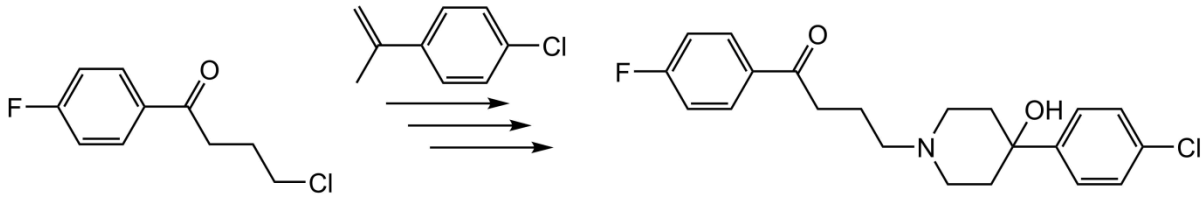


Figure 5. Molecular structure of haloperidol.

Haloperidol is a strong neuroleptic agent which is included in the World Health Organisation's list of essential medicines.[53] It is proven to be effective for the treatment of positive symptoms associated with schizophrenia but it causes extrapyramidal side effects (for nearly 50% of all patients)[52] and accentuates negative symptoms of the disorder.[54] Among the typical antipsychotic agents, haloperidol is the most widely prescribed drug with over 2.48 million prescriptions in 2008.[55] Nowadays, it is also used for the treatment of hyperactivity, chorea associated with Huntington disease, obsessive-compulsive disorder, psychosis agitation associated with dementia, and rarely for nausea and vomiting induced by chemotherapy or surgery.[52] There has been an ongoing comparison between typical and atypical drugs for years, and a recent study showed that patients treated with second-generation antipsychotics continue their treatment for longer than subjects treated with haloperidol; moreover, atypical drugs seem to be more protective against recurrences when compared to haloperidol.[54]

2.2.1. Synthesis

Haloperidol is part of the butyrophenone family (6-membered aromatic cycle conjugated with a ketone and an aliphatic chain). Within its molecular structure, the hydroxyl group acts as both a hydrogen bond acceptor and donor; the ketone oxygen and the piperidine nitrogen serve as two additional hydrogen bond acceptors. Due to these properties, haloperidol demonstrates high biological activity in humans.[52] Its synthesis (Scheme 2) was developed in 1958 by the Belgian company Janssen Pharmaceutica and it went through a clinical development by the psychiatric research team at the University of Liège where it was confirmed that it is effective for the treatment of different mental disorders such as chronic schizophrenia, mania and acute or chronic paranoid psychosis.[53]



Scheme 2. Synthesis of haloperidol adapted from reference[52]

The synthesis of haloperidol involves a substitution reaction between a piperidine derivative and 4-chlorobutanoyl chloride in the presence of potassium iodide. The piperidine derivative is synthesised in four steps from an aromatic chloride compound. 4-chlorobutanoyl chloride is synthesised in one step from fluorobenzene.[52]

2.2.2. Mode of action and metabolism

Haloperidol demonstrates high affinity for dopamine D_2 receptors[52;56] particularly in the basal ganglia as the concentrations of D_2 receptors in this region are high.[52] It shows an approximately 100 fold higher affinity for the D_2 receptor as compared to clozapine and also high residence time which both account for the occurrence of EPSEs.[52] Haloperidol also demonstrates additional antagonist activity at serotonin 5-HT_{2A} receptors, α_{1A} and α_{1B}

adrenergic receptors,[52] and little affinity for muscarinic cholinergic and histamine receptors.[56] Two recent studies demonstrated the ability of haloperidol to bind to dopamine D_3 receptors.[57;58] Zanatta *et al*. performed computer simulations at the molecular level for haloperidol and its binding patterns. They have demonstrated the important role of the axial orientation of the hydroxyl group within haloperidol's structure which contributes to the favourable interaction with Tyr365 and Thr369 residues further increasing haloperidol's binding to dopamine receptors.[57]

Zhuravliova and co-workers showed that haloperidol induces neurotoxicity of neuronal cells as it interacts with the glutamate NMDA receptor which is known to be involved in excitotoxic neuronal cell death that occurs in many neurological disorders.[59]

Haloperidol can be administered orally (haloperidol tablet or haloperidol lactate liquid), intravenously (haloperidol lactate) and as a long-acting intramuscular injection (haloperidol decanoate). It shows plasma protein binding of approximately 92% and plasma half-life of 24 hours after it has been administered orally, 14 hours following an intravenous administration and 21 hours after it has been administered as an intramuscular injection.[52] Haloperidol is metabolised by uridine 5'-diphospho-glucuronosyltransferases (UGTs) including UGT1A4, UGT1A9, UGT2B7[60] and cytochrome P450 (CYP450) enzymes including 3A4,[61] 2D6 and 1A2 enzymes.[52] Nine different metabolites of haloperidol have been observed but the main one is known to be haloperidol glucuronide[52] (Figure 6).

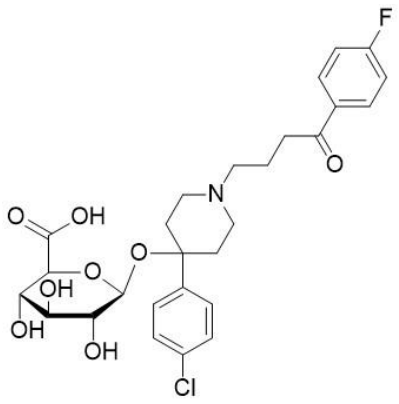


Figure 6. Molecular structure of haloperidol glucuronide.

When haloperidol is being metabolised only around 1% of the administered dose is detectable in urine. Smoking has been shown to increase the clearance of haloperidol by 44% whilst decreasing its serum concentrations by 70%.[52]

2.2.3. Effectiveness

Statistics show that 35 years after haloperidol was approved for the treatment of schizophrenia, 250 million people were treated with this agent. Since haloperidol is a strong dopamine D_2 receptor antagonist, it is effective for the positive symptoms of schizophrenia such as delusions and hallucinatory experiences. Its discovery also contributed to the development of new theories related to schizophrenia and other mental disorders.[53] Nowadays, after the introduction of second-generation antipsychotics, haloperidol is rarely prescribed. Its strong potency for the dopamine D_2 receptor may help with the positive symptoms of schizophrenia but it suffers from severe side effects.[52] Newly developed antipsychotics drugs have different binding profiles and most of them offer better treatment for patients diagnosed with schizophrenia when compared to haloperidol.[54]

2.2.4. Limitations

Haloperidol is associated with a range of adverse events but the most common ones are EPSEs including dystonia, akathisia, dyskinesia and parkinsonism.[52] Intravenous haloperidol can induce arrhythmias observed by electrocardiograms such as QT interval prolongation which can lead to incidents of irregular heart rhythms.[62;63] Haloperidol is also associated with dysphoria which is characterised by depression, anxiety or agitation.[52] It has been shown to be cytotoxic to neurons and to induce apoptosis in rodents by reducing cell survival signaling.[56;64] Park *et al.* performed a study to assess the effects of antipsychotic agents on cell viability and autophagy (process of self-digestion by a cell) in rat primary neurons.

Haloperidol has been observed to decrease the viability of neurons and also to inhibit the autophagic process within the cell.[56]

2.3.Clozapine

Clozapine (Figure 7) is a second-generation antipsychotic drug which is the only antipsychotic agent available for treatment-resistant schizophrenia (TRS).[65;66]

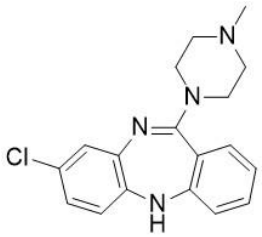
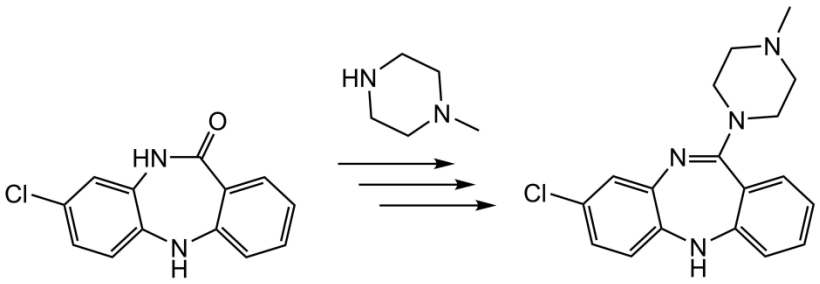


Figure 7. Molecular structure of clozapine.

Clozapine was synthesised in the 1960s and it was the first atypical antipsychotic drug to be discovered. Typical drugs have the ability to treat positive symptoms without causing EPSEs. It is proved to be effective in treating positive and negative symptoms and some cognitive deficits (memory, verbal learning and fluency, and psychomotor speed). Clozapine was withdrawn in 1975 due to the risk of serious adverse effects (as 0.7% of patients in a study in Finland developed agranulocytosis and 50% of them died) but it was reapproved by the Food and Drug Administration (FDA) in 1989 due to its unique feature to be effective in TRS.[66] However, due to the ability of clozapine to cause agranulocytosis, FDA and all regulatory agencies worldwide recommend regular full blood counts (FBCs) for all patients on clozapine.[65;66] Clozapine is only prescribed if the patient diagnosed with schizophrenia does not respond to two other antipsychotic agents, including an SGA.[67] Typically clozapine is reserved only for the most severe cases of schizophrenia.[68]

2.3.1. Synthesis

Clozapine is a tricyclic benzodiazepine derivative. It has a lone hydrogen bond donor and three hydrogen bond acceptors. The synthesis of clozapine (Scheme 3) was developed by Sandoz (nowadays Novartis).[66]



Scheme 3. Synthesis of clozapine **16** from main synthons.[66]

Several routes have been developed for the synthesis of clozapine, however all focus on the synthesis of the key intermediate 8-chloro-*5H*-benzo[*b*,*e*][1,4]diazepin-11-(10*H*)-one core (Scheme 3, left). Two more steps are then needed to afford clozapine.[66]

2.3.2. Mode of action and metabolism

Clozapine binds to a range of receptors, including the dopaminergic (D_1–D_5), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_6), cholinergic (M_1, M_2, M_4), histaminergic (H_1) and adrenergic (α_1) receptors.[68] It shows high affinity particularly for dopamine D_2 receptors and serotonin 5-HT_{2A} receptors. It is found to be effective when it occupies 40-60% of striatal D_2 receptors.[66] Clozapine does not saturate D_2 receptors even if it is given at high doses as compared to risperidone.[69] Among all SGAs, clozapine and olanzapine show the greatest affinity for 5-HT_{2C} and H_1 receptors which accounts for their major adverse effect – weight gain.[65] Clozapine is also found to be a modest inhibitor of the sodium-coupled neutral amino acid transporter, which activates NMDA receptors by increasing the synaptic glycine levels.[70]

The recommended dose of clozapine is between 200 to 450 mg/day and this is divided into small doses which patients take throughout the day.[66] Clozapine is 90-95% absorbed[66] when taken orally and it is subject to first-pass metabolism which results in moderate bioavailability of 50-60%.[66;68] It is metabolised by CYP450 enzymes and particularly by 1A2 and 3A4 enzymes. The metabolism of clozapine results in 80% of the dose discharged as metabolites both in the urine (50%) and faeces (30%).[66] Most of the metabolites of clozapine are inactive but *N*-desmethylclozapine (Figure 8) is an active metabolite which is believed to take part in the overall effectiveness of clozapine due to its activity on D_2 and 5-HT_{2A} receptors.[66;71]

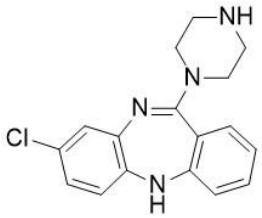


Figure 8. Molecular structure of *N*-desmethylclozapine.

Cigarette smoke and other compounds which induce the activity of 1A2 enzyme, increase the clearance of clozapine (by up to 50%)[67] and therefore smokers need higher doses of clozapine to maintain targeted plasma concentrations. Compounds such as ciprofloxacin inhibit 1A2 enzyme resulting in a decrease in the rate of metabolism of clozapine.[66]

2.3.3. Effectiveness

Treatment with clozapine leads to reductions in the number of hospitalised patients. Significant improvement in the life of patients diagnosed with the disorder was demonstrated as well as a decrease in hospital costs and overall treatment expenses.[68] Trials show that 50-60% of patients diagnosed with schizophrenia in the UK respond to clozapine.[65] Clozapine is also shown to reduce recurrent suicidal behaviour in schizophrenic patients by 88% compared

to other antipsychotic agents.[66] Clozapine shows a range of advantages and these are listed in Table 2.

Table 2: Clinical advantages of clozapine

Clinical Advantages of Clozapine
• The only antipsychotic agent available for TRS
• Highly effective for the treatment of positive symptoms
• More effective in reducing negative symptoms than the firstly approved typical antipsychotics
• Significant improvement in the life of patients diagnosed with schizophrenia
• Improved disorganised behaviour
• Treatment with clozapine leads to reductions in the number of hospitalised patients
• Decrease in hospital costs and overall treatment expenses
• Efficacy on depression
• Shown to reduce recurrent suicidal behaviour in subjects diagnosed with the disorder
• No extrapyramidal side effects (EPSEs)
• No tardive dyskinesia
• No elevation in prolactin levels
• Chance of relapse during clozapine therapy is less than with other antipsychotics

2.3.4. Limitations

Clozapine is associated with different adverse events including agranulocytosis (affects 0.8% of patients), sedation, elevation of liver enzymes (around 10%), constipation and hypersalivation ("wet pillow syndrome").[65;66] The increased risk of fatal agranulocytosis requires regular FBCs and strict monitoring protocol.[66;67] Clozapine is also associated with increased mortality in elderly patients diagnosed with dementia-related psychosis. Clozapine induces weight gain with ≥ 7% during the first six months of the treatment due to disruption of the metabolism of patients - body gains increased energy from fat and not carbohydrates, resulting in high levels of the latter thus leading to insulin resistance and diabetes. When compared to FGAs, clozapine shows low incidence of EPSEs and does not show effects on

prolactin levels. All these side effects become more apparent when the dose of clozapine exceeds 450 mg/day.[66]

2.4. Risperidone

Risperidone (Figure 9) is an atypical (2nd generation) antipsychotic which was approved in 1993 for the treatment of schizophrenia,[72] bipolar disorder, and irritability associated with autism. Risperidone is on the World Health Organisation's list of essential medicines and is available as a generic medication.[35] Risperidone combines the known antipsychotic effects of conventional D_2 antagonist antipsychotics with the clozapine-like 5-HT antagonists. Risperidone is the first antipsychotic to have been granted approval for use on children between the ages of 13 and 17.[73]

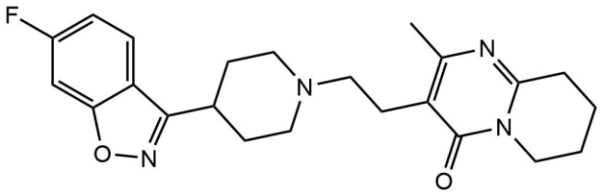
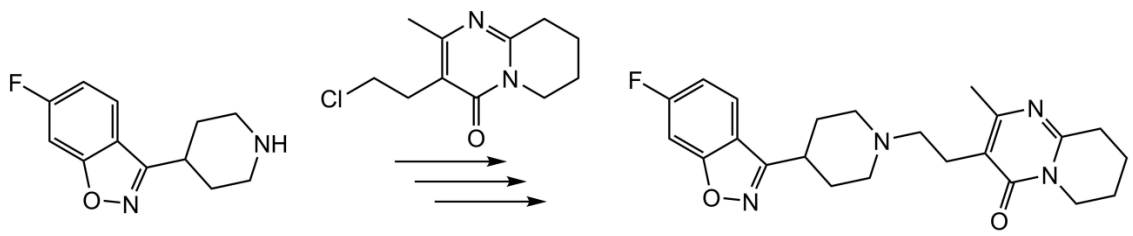


Figure 9. Molecular structure of risperidone.

2.4.1. Synthesis

Risperidone, was developed in the late 1980s by Janssen Pharmaceuticals, a division of Johnson & Johnson. It is usually synthesised *via* condensation of separately prepared 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,a]-pyrimidin-4-one with 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole in the presence of potassium iodide and sodium carbonate (Scheme 4).[74, 75]



Scheme 4. Synthesis of risperidone from the main building blocks.

The piperidine component is prepared by condensation of an acyl chloride with 1,3-difluorobenzene in the presence of aluminium chloride followed by hydrolysis, formation of an oxime, and dehydrohalogenation to create the five-membered ring. Cyclocondensation between 2-aminopyridine and a derivative of butyrolactone results in the formation of a pyridopyrimidine derivative. Hydrogenation on Pd/C gives the tetrahydroxypyridopyrimidine whose alcohol group is substituted by a chlorine to give the desired second component.

2.4.2. Mode of action and metabolism

Risperidone has significant affinity for D_2, 5-HT_{2A}, 5-HT_{2C}, H_2, α_1, and α_2 receptors, and a lower affinity for D_1, 5-HT_{1D}, 5-HT_{1C}, and 5-HT_{1A} receptor subtypes.[76] Risperidone occupies more D_2 receptors than the 48% needed to achieve a clinical response at the recommended therapeutic dose (6 mg/day).[77] This high affinity results in a long half-life.

The action of risperidone on serotonin receptors (5-HT_{2A} and 5-HT_{2C}) is expected to be responsible for its lower extrapyramidal side effect liability.[78]

Risperidone is mainly metabolised by alicyclic hydroxylation to give the enantiomeric 9-hydroxyrisperidone which is also an antipsychotic agent.[79] Its racemate, paliperidone, is commercially available for the treatment of schizophrenia as well.[80] *N*-dealkylation can occur at the piperidine nitrogen. Most of the metabolised and non-metabolised risperidone is excreted in the urine.[81]

2.4.3. Effectiveness

Risperidone, based on the benzisoxazole skeleton, ameliorates both positive and negative symptoms of schizophrenia, based mainly on its potent serotonin 5-HT_{2A} and dopamine D_2 receptor-blocking properties. Depending on studies, better therapeutic effects have been

observed either with risperidone or haloperidol in the treatment of negative symptoms of schizophrenia.[82] However risperidone, as a 2nd-generation antipsychotic drug has lower extrapyramidal side effects compared to haloperidol (1st-generation antipsychotic drug).

The effectiveness of risperidone has also been studied on children.[83, 84] Symptoms of adolescent-onset psychosis are usually similar to those developed by adults and diagnosis is therefore performed using the same criteria. However some other symptoms such as the negative symptoms are more pronounced for children. Trials on adolescent population are sometimes conducted without placebo and therefore dose-response studies can be conducted. Higher efficacy was observed for higher doses of Risperidone.

2.4.4. Limitations

Commonly reported side effects of risperidone include agitation, akathisia, constipation, dizziness, drowsiness, dystonia, extrapyramidal reaction, nausea, rhinitis, and weight gain. Risperidone can be associated with higher levels of prolactin secretion than other antipsychotic drugs.[85] These limitations have also been reported for children. Extrapyramidal symptoms are sometimes treated by benzatropine (Figure 10).

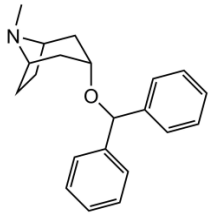


Figure 10. Molecular structure of benzatropine.

Prolactin is secreted by the anterior pituitary. An elevation of prolactin inhibits the hypothalamic-pituitary axis, suppresses gonadotropin-releasing hormone release from the hypothalamus and also reduces estrogen and testosterone both in males and females. Modest elevations of prolactin are associated with amenorrhea, galactorrhea, hirsutism, decreased

libido, and hypogonadism for women; decreased libido and reduced spermatogenesis for men.[86]

2.5.Quetiapine

Quetiapine (Figure 11) is an atypical (or 2nd generation) antipsychotic which is approved for the treatment of schizophrenia and some other illness (bipolar disorder, major depressive disorder). It is formulated as tablets and used to treat both positive and negative symptoms. Quetiapine was first approved by the FDA in 1997 for the treatment of schizophrenia.[87] A sustained-release version was approved by the FDA in 2007 for use as maintenance treatment for schizophrenia in addition to acute treatment.[88] Several generic versions are now available on the market.

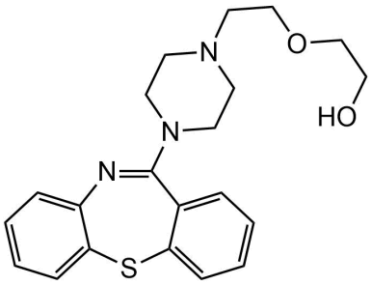
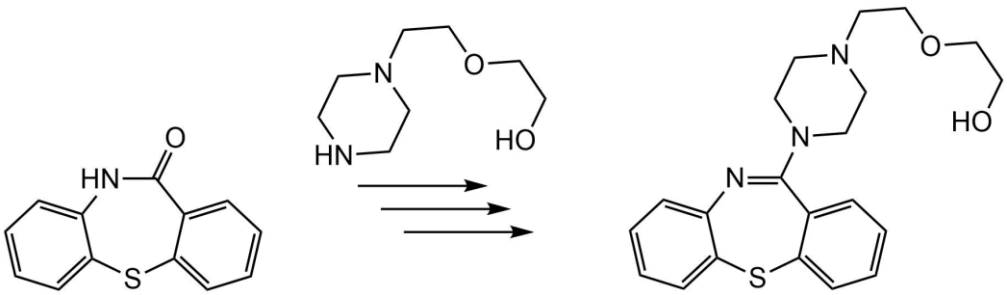


Figure 11. Molecular structure of quetiapine.

2.5.1. Synthesis

Quetiapine is a tetracyclic compound which structure is close to those of clozapine and other tetracylic antipsychotics. AstraZeneca developed this compound from 1992. It belongs to the chemical class of dibenzothiazepine derivatives, with fumarate used for the formation of the salt. The synthesis was first described in a patent publication, starting from dibenzo[b,f][1,4]thiazepin-11-[10H]one which is first halogenated phosphorous oxychloride, then condensed with 1-(2-hydroxyethoxy)ethyl piperazine (Scheme 5).[89]



Scheme 5. Synthesis of quetiapine, as reported in the initial patent.[89]

Several other patents filed by the same company describe slightly different pathways to obtain quetiapine with different aims: generation of less hazardous waste, replacement of hazardous reagent by less hazardous ones, higher purity obtained, pathway involving a one-pot process. The synthesis of the starting material has also been reported in the literature using different routes.[90] Other patents describe the sustained release formulations of quetiapine using different polymers[91] to either form gels[92] or micro matrix particles.[93]

2.5.2. Mode of action and metabolism

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: dopamine D_1 and D_2, serotonin 5-HT_{1A} and 5-HT_2, histamine H_1, and adrenergic α_1 and α_2 receptors.[94]

The mechanism of action of quetiapine is not fully elucidated; however it has been proposed that its efficacy is mediated through a combination of D_2 and 5-HT_2 antagonism. Quetiapine has been shown to occupy around 30% of D_2 receptors at therapeutic doses, which is lower than the 60-75% range associated with antipsychotic efficacy; such a low percentage can be explained by the fast dissociation from the D_2 receptor.[95]

Quetiapine is mainly eliminated *via* the hepatic metabolism with a mean terminal half-life of about six hours.[96] Quetiapine is highly metabolised in the body as less than 1% of the administered dose is excreted as unchanged drug. The major metabolic pathways are sulfoxidations and oxidations, with both metabolites being pharmacologically inactive.

Another important metabolite is norquetiapine (*N*-desalkyl quetiapine, Figure 12) which is pharmaceutically active: it has a moderate affinity for the 5-HT_{2C} receptor antagonist and is a partial agonist for the 5-HT_{1H} receptor, which may be associated with cognitive and mood enhancing/stabilising properties.[96]

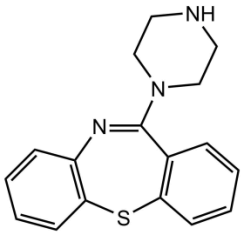


Figure 12. Molecular structure of norquetiapine.

Quetiapine has low affinity for muscarinic receptors while norquetiapine acts as an antagonist at the M1, M3, and M5 muscarinic receptors. The side-effect profile of quetiapine may come from such interactions.[97]

2.5.3. Effectiveness

Quetiapine has been shown to be efficacious for patients diagnosed with schizophrenia across a broad range of symptoms including depression, anxiety, and hostility.[98] The positive symptoms were also improved. Greater improvements were observed with patients receiving a slightly higher dose than the average dose of 300 mg/day. Quetiapine is generally well-tolerated by patients. Studies have also been conducted by comparing quetiapine with other 2nd generation antipsychotic drugs, focusing on their differential neurocognitive effectiveness. The hypothesis that an increase in neurocognitive performance could be a reflection of psychotic symptoms was not confirmed however the authors stipulate that such a link exists,[99] especially as a better response has been observed for patients taking quetiapine compared to conventional antipsychotics.[100] Quetiapine does not induce extrapyramidal side

effects nor increase prolactin levels across the entire therapeutic range, similarly to clozapine.[99]

2.5.4. Limitations

Quetiapine has been associated with higher risk for somnolence, dizziness, asthenia, and dry mouth compared to conventional antipsychotics or risperidone. Constipation, tachycardia, orthostatic hypotension, dyspepsia, and weight gain have also been reported. Sporadically reported side-effects include syncopal episodes, leucopenias, neutropenias, and peripheral angioedema.[101]

The extended-release formulation of quetiapine has been developed to allow a once-daily dosage regimen, hence improving the patient quality of life and ensuring medication is more likely to be taken as prescribed by physicians. However adverse effects were found to be significantly more likely compared with placebo or the immediate-release formulation.[102]

2.6. Aripiprazole

Aripiprazole (Figure 13) is an atypical antipsychotic drug which is approved worldwide for the treatment of adult patients diagnosed with schizophrenia.

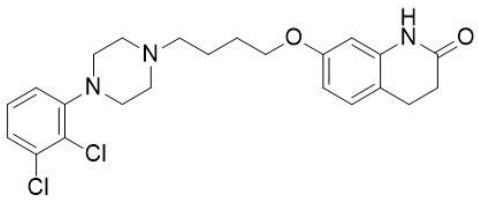


Figure 13. Molecular structure of aripiprazole.

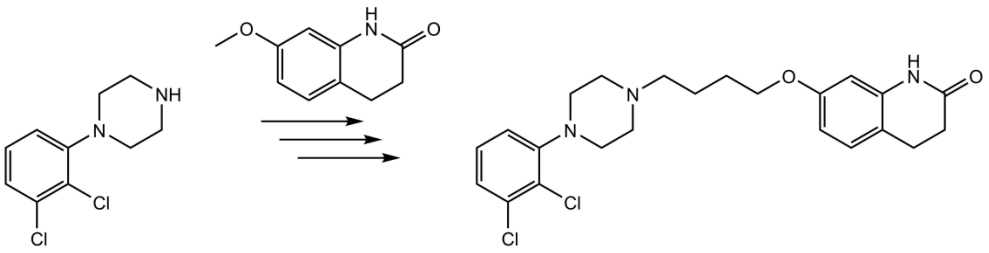
It can be used both as an oral formulation for long-term treatment or as an intramuscular formulation (injection) for the control of acute agitation seen in schizophrenic patients. The oral formulation of the drug is effective in treating the positive and negative symptoms of schizophrenia.[103] Aripiprazole was approved by the FDA for treatment of the disorder in

2002.[4] It possesses a unique receptor binding profile as all other SGAs are dopamine-receptor antagonists and it exhibits partial agonist activity as well as antagonist activity.[103] Therefore, it is considered to be a dopamine-serotonin system stabiliser which cannot be observed in the activity of any other antipsychotic drug.[104]

The FDA has recently approved (late 2017) the first drug in the USA with a digital ingestion tracking system, with the active ingredient being aripiprazole. Such a device allows a recording on when the medication is taken. While the product is not intended to improve patient compliance with their treatment regimen, it is expected to be useful for some patients to be able to track ingestion of medications.[105]

2.6.1. Synthesis

Aripiprazole is a quinoline derivative. It was developed by Otsuka in Japan in the mid-1990s.[106]



Scheme 6. Synthesis of aripiprazole. Adapted from reference[107]

Aripiprazole is composed of three different fragments: phenylpiperazine, a four-carbon aliphatic chain, and a modified quinoline moiety (Scheme 6). Its synthesis is based on the reductive alkylation of amine, with the phenylpiperazine acting as the amine moiety. The four-carbon aliphatic chain can be added first on both remaining fragments.[107]

2.6.2. Mode of action and metabolism

Aripiprazole is different from all others antipsychotics owing to its unique receptor binding profile. Multiple studies *in vivo* demonstrated that it acts as a partial agonist at dopamine D_2 and D_3 receptors, and serotonin 5-HT_{1A} receptors. It also exhibits antagonism activity at 5-HT_{2A} receptors.[103] Therefore, where neurotransmitter levels are high, aripiprazole will act as an antagonist and where the levels are low it will function as an agonist, stabilising the dysregulated dopamine and serotonin systems.[103;104] Treatment with aripiprazole results in a reduction of extracellular levels of dopamine in the frontal cortex and striatum, which is indicative of decreased release of dopamine in these brain regions.[104] Aripiprazole displays only minor affinity for α_2 adrenergic receptors, muscarinic cholinergic receptors and histamine H_1 receptors which accounts for its ability not to cause sedation, weight gain, postural hypotension and cognitive impairment.[108]

In addition to partial D_2 agonism, it has been recently suggested that aripiprazole also displays functionally selective properties, which leads to a unique pharmacological profile for this drug.[109] Functional selectivity (the ability of a drug to trigger different signalling pathways through a single receptor) has been shown to be of significant importance for the understanding of the mechanism of action of some anti-schizophrenia drugs.[110] In 2006, Mailman and co-workers reported clear evidence that aripiprazole affects D_{2L} signalling pathways in a differential way and therefore not only acts as a partial agonist but also as a functionally selective D_2 ligand.[111]

The recommended initial and target dose of aripiprazole (oral formulation) is between 10 to 15 mg/day which is taken at once. The approved dose of intramuscular aripiprazole is 9.75 mg single injection. When aripiprazole is administered orally, it is absorbed with peak plasma concentrations reached in three hours, resulting in 87% absolute bioavailability. It is

metabolised in the liver by CYP450 enzymes (mainly $3A_4$ and $2D_6$ enzymes), *via* *N*~~N~~-dealkylation, hydroxylation or dehydrogenation.[103]

2.6.3. Effectiveness

The oral formulation of aripiprazole is known to be effective in both minimising the symptoms of the disorder and preventing the relapsing episodes in patients with chronic schizophrenia.[103] Aripiprazole is less effective than olanzapine for controlling the symptoms of schizophrenia but aripiprazole demonstrated lower incidence of weight gain as compared to olanzapine and other SGAs.[108;112] It is also associated with a lower incidence of EPSEs than haloperidol and a reduced risk of metabolic syndrome compared to olanzapine. Several pharmacoeconomic analyses demonstrated that aripiprazole can provide more cost-effective treatment than other antipsychotic agents.[103]

2.6.4. Limitations

Aripiprazole is associated with different adverse events but the most frequent side effect is insomnia, affecting 22 to 42% of the patients.[103] Other adverse events include headache, anxiety, nausea and sedation.[4, 103] All these are seen more often in patients taking aripiprazole than in patients on other antipsychotic drugs.[4]

2.7. Lurasidone

Lurasidone (Figure 14) is a recently developed atypical antipsychotic drug, first approved in 2010 by the FDA, used for the treatment of schizophrenia in the USA, Puerto Rico and Canada.[113]

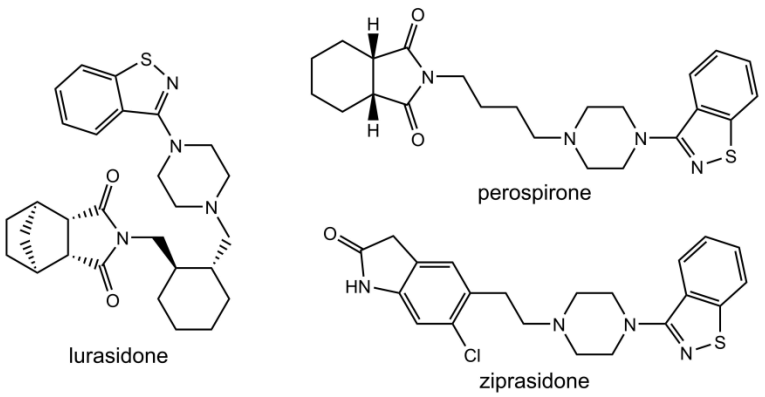


Figure 14. Molecular structures of lurasidone, perospirone, and ziprasidone.

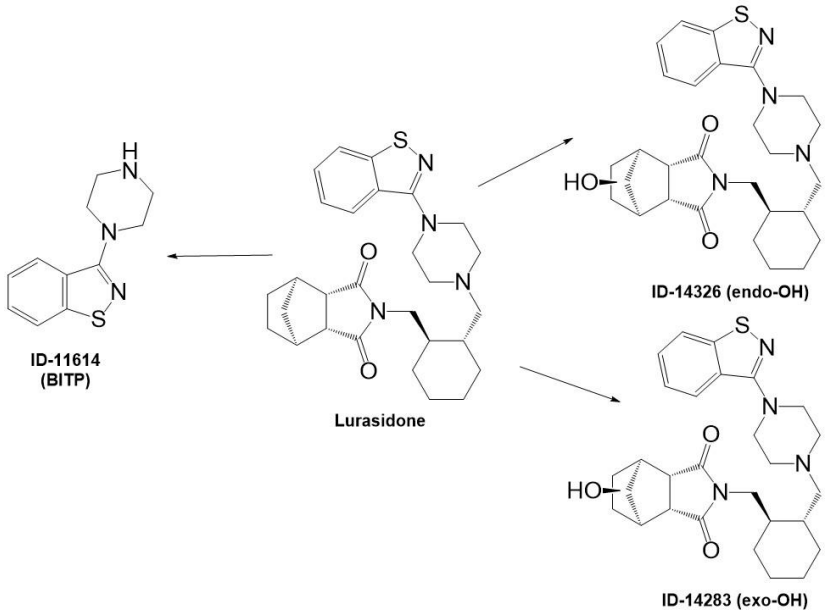
Lurasidone is structurally related to ziprasidone and perospirone.[114] It is proved to be effective for both positive and negative symptoms of the disorder, as well as the cognitive deficits and mood symptoms seen in schizophrenic patients.[115] It shows high affinity for a range of receptors, resulting in its powerful antipsychotic activity as well as antidepressant-like effects.[116] Lurasidone is poorly soluble in water, which results in low bioavailability. Therefore, lurasidone is administered with food which complicates the treatment and leads to poor effectiveness among patients diagnosed with schizophrenia. The formulation of lurasidone has been explored in the last years to overcome such issues; the use of nanosuspensions has been shown to enhance its bioavailability.[117;118]

2.7.1. Mode of action and metabolism

Lurasidone acts as a full antagonist at dopamine D_2 and serotonin 5-HT_{2A} receptors.[116] It is also a partial agonist at serotonin 5-HT_{1A} which helps stabilizing the frontal cortex function. Stimulation of the 5-HT_{1A} receptors reduces EPSEs such as epilepsy, dystonia and dyskinesia, which are all a result of the full blockage of dopamine D_2 receptors. Lurasidone demonstrates high affinity for serotonin 5-HT_7 receptors unlike other atypical antipsychotic drugs. The great effect of 5-HT_7 antagonism on cognitive deficits, mood symptoms and memory problems associated with schizophrenia was demonstrated.[114] Lurasidone shows low

affinity for 5-HT_{2C} receptors which accounts for its low ability to cause weight gain. As for the adrenergic receptors, lurasidone demonstrates high affinity for α_{2C} receptors (thus improving cognitive function) but low affinity for α_1 and α_{2A} receptors.[116] It has minimal effect on histamine H_1 and muscarinic M_1 receptors but antagonism of these receptors is associated with weight gain, sedation and unfavourable cognitive effects.[114]

The recommended dose of lurasidone is 40 to 120 mg/day which is administered once daily with food that contains at least 350 calories.[113] After absorption, lurasidone is distributed in tissues, followed by rapid penetration in the CNS showing approximately 80% occupancy of dopamine D_2 receptors. It is metabolised in the liver by CYP450 enzymes, mainly through CYP3A4 pathway. This process includes *N*-dealkylation, hydroxylation, *S*-oxidation, reductive cleavage, *S*-methylation, followed by a combination of some or all of these reactions. The active metabolites of lurasidone are shown in Scheme 7 and these possess pharmacological activity, contributing to the antipsychotic action of the main drug.[114]



Scheme 7. The active metabolites of lurasidone. BITP = 1-(1,2-benzisothiazol-3-yl)-piperazine (adapted from reference[114]).

BITP (ID-11614) is one of the active metabolites of lurasidone and it is similar to perospirone and ziprasidone. *In vivo* studies show that BITP possesses some of the pharmacodynamic properties of lurasidone in rodent and non-rodent species.[114] Both hydroxy-derivatives of lurasidone (ID-14326 and ID-14283) demonstrate similar binding profiles to the main drug – affinity for dopamine D_2 and serotonin 5-HT_{2A}, 5-HT_{1A} and 5-HT_7 receptors. After lurasidone is being metabolised it is excreted as 80% in faeces and 9% in urine.[114]

2.7.2. Effectiveness and limitations

Lurasidone can be used for both short and long term treatment of schizophrenia.[113] Short term clinical trials show that lurasidone is effective in acute schizophrenia.[114] Its pharmacological properties to improve cognitive processes and help with anxiety and depression for patients diagnosed with schizophrenia.[113;114] One of the greatest advantages of lurasidone is thought to be its low potential to cause weight gain and metabolic disorders.[115]

Lurasidone is associated with different adverse events including nausea, vomiting, insomnia, dizziness, sedation and somnolence.[113;114] Doses above 80 mg/day are associated with akathisia (psychomotor restlessness).[115] Lurasidone is shown to increase prolactin levels but to a lesser degree than other antipsychotic agents such as risperidone and paliperidone.[115] The major disadvantage of lurasidone hydrochloride is its low solubility and bioavailability when administered orally without food (only 9 to 19% is being absorbed).[117] Therefore, the recommendation for lurasidone is to be taken with food with at least 350 calories and no fat. This results in two-fold increase of the absorption rate of lurasidone. Such treatment compliance has been reported to be quite poor, hence the formulation of lurasidone has recently been studied to solve this issue. Lu *et al.* and Yu *et al.* demonstrated preparation of nanosuspensions by antisolvent precipitation-ultrasonication method and used these to enhance the dissolution and bioavailability of lurasidone.[117] An increased dissolution rate,

rapid absorption and enhanced oral bioavailability were reported for the nanosuspension compared to the original formula.[117;118]

2.8. Summary

It is clear that the activity profile on receptors of clinically-approved drugs is directly related to their biological mechanisms of action. A number of studies have unambiguously demonstrated the binding of these agents to various receptors (therefore shining light on their respective modes of action), whilst recent studies are still suggesting involvement of other receptors. The complexity of the interactions makes a comprehensive overview of clinically-approved drugs interactions with receptors difficult, but Table 3 summarises the main activity profiles of such drugs (when activity is written in bold, the drug acts as a full antagonist or agonist; otherwise the action is either partial or the affinity is relatively weak), along with chosen examples of recently reported studies.

Table 3. Summary of the activity profile on receptors of clinically-approved drugs discussed in section 1.

Drug		Chlorpromazine	Haloperidol	Clozapine	Risperidone	Quetiapine	Aripiprazole	Lurasidone
Generation		1st	1st	2nd	2nd	2nd	2nd	2nd
Dopamine	D1	**Antag**[119]	Antag[57]	Antag[68]	**Antag**[120]	**Antag**[94]	Ag + **Antag**[121]	-
	D2	**Antag**[122]	**Antag**[52]	Antag[66]	**Antag**[123]	**Antag**[95]	Ag + **Antag**[109, 111]	**Antag**[124]
	D3	Antag[125]	Inv Ag[57;58]	Antag[68]	Antag[126]	**Antag**[127]	Ag + **Antag**[103]	-
	D4	Antag[128]	-	Antag[68]	Antag[129]	Antag[127]	-	-
	D5	-	-	-	Antag[78]	Antag[127]	-	-
Serotonin	5-HT_1	**Antag**[130]	Ag[52]	Antag[65]	**Antag**[78]	Ag + **Antag**[131]	Ag + **Antag**[103]	Antag[116]

	5-HT_2	**Antag**[38]	Antag[52]	**Antag**[65]	**Antag**[78]	**Antag**[131]	Ag + **Antag**[103]	**Antag**[116]
	5-HT_7	-	-	-	-	-	**Antag**[103]	**Antag**[114]
α-adregenic	α_1	Antag[132]	**Antag**[52]	Antag[68]	**Antag**[133]	**Antag**[134]	Antag[108]	-
	α_2	Antag[135]	**Antag**[52]	Antag[68]	Antag[133]	**Antag**[134]	Antag[108]	**Antag**[116]
Histamine	H_1	Antag[136]	-	Antag[68]	Antag[137]	-	Antag[108]	Antag[114]
	H_2	Antag[136]	-	-	Antag[137]	-	-	-
	H_3	Antag[138]	-	-	-	-	-	-
Muscarinic acetylcholine	M1	Antag[139]	-	Antag[68]	-	-	-	-
	M2	Antag[139]	-	Antag[68]	-	-	-	-
NMDA		Antag[140]	**Antag**[59]	**Antag**[70]	-	-	-	-

Ag: Agonist; Antag: Antagonist; Inv Ag: Inverse agonist.

3. Emerging Approaches for the Treatment of Schizophrenia

3.1. Modulation of Glutamatergic Signalling

First- and second-generation antipsychotic agents have a profound effect on dopaminergic and serotonergic systems and therefore target positive symptoms of schizophrenia, and to a small extend negative symptoms and cognitive deficits. Schizophrenia includes complex alterations in the neurochemistry of key brain regions which are associated with cognition, neurodevelopment, memory, sensory processing and emotions. Dopamine and serotonin play a key role in the modulation of these brain regions but glutamate and GABA, which are the main excitatory and inhibitory transmitters, do regulate the signalling through these circuits.[141] Therefore, a new approach for the treatment of schizophrenia is to increase the activity of some glutamate receptors (such as NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and metabotropic glutamate (mGlu) receptors) so as to restore the signalling in the glutamatergic systems. Agents regulating the glutamatergic neurotransmission are reported to minimise all three groups of symptoms

associated with schizophrenia and could therefore provide a solution in the treatment of this illness.[141]

3.1.1. Glycine Transporter 1 (GlyT1) Inhibitors

The NMDA receptor is one of the glutamate receptors which is known to be involved in the mechanism of schizophrenia.[141;142] Studies have demonstrated a reduction in the function of the NMDA receptor in patients diagnosed with schizophrenia; therefore efforts are targeted towards enhancing the glutamatergic signalling.[16] Selective antagonists at the NMDA receptor have shown to induce positive, negative, and cognitive symptoms similar to those seen in patients diagnosed with the disorder.[141;142] Furthermore, agents such as glycine and serine have been shown to increase NMDA receptor responses to glutamate and thus to stabilise the dysregulated glutamatergic systems.[143] Glycine is a co-agonist for the activation of the NMDA receptor by glutamate and so increasing the synaptic glycine levels could improve the NMDA receptor function and enhance the glutamate neurotransmission.[144] Direct administration of glycine was a promising approach as this amino acid demonstrated a positive effect on the symptoms related to schizophrenia. However, glycine is not a suitable therapeutic agent as it is associated with a few serious limitations, including poor pharmacokinetic profile, low brain exposure.[141] The clearance of glycine is regulated by the GlyT1 and since glycine itself cannot be used as an agent for the treatment of schizophrenia, highly selective GlyT1 inhibitors have been developed to increase the concentration of glycine in the glutamatergic systems and facilitate NMDA receptor responses to glutamate.[141;142] One of the first GlyT1 inhibitors was structurally related to sarcosine which is an endogenous GlyT1 inhibitor.[141] These agents have shown efficacy in minimising the symptoms of schizophrenia but were also associated with serious adverse events such as compulsive walking, respiratory distress and in some occasions death.[145;146] Recent studies

have focused on GlyT1 inhibitors which are structurally distinct from sarcosine. RG1678 (Figure 15) is the first potent and selective GlyT1 inhibitor, developed by Roche.[147]

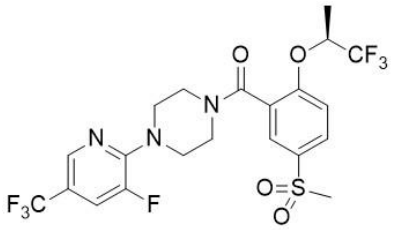


Figure 15. Molecular structure of RG1678.

A phase II clinical study demonstrated efficacy on the negative symptoms observed among patients diagnosed with schizophrenia when administered as an add-on treatment to atypical drugs.[148] In 2014, Roche has also designed a novel structural class of GlyT1 inhibitors – 3-amido-3-aryl-piperidines.[149] One of these compounds (Figure 16) demonstrated high GlyT1 potency and excellent brain penetration in animal models which resulted in its efficacy at very low plasma concentrations.[149]

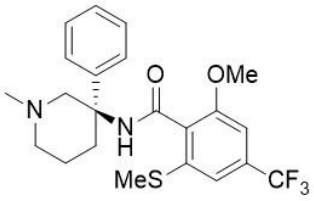


Figure 16. Molecular structure of (*R*)-2-methoxy-*N*-(1-methyl-3-phenylpiperidin-3-yl)-6-(methylthio)-4-(trifluoromethyl)benzamide.

ASP2535 (Figure 17) is another GlyT1 inhibitor identified by Harada *et al.* which is shown to be effective for the treatment of cognitive deficits in animal models of schizophrenia and Alzheimer's disease.[150]

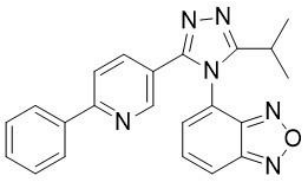


Figure 17. Molecular structure of ASP2535.

Its pharmacological profile indicates that it is an orally active, rapidly absorbed and blood-brain-barrier penetrable GlyT1 inhibitor.[150]

3.1.2. mGluR Positive Allosteric Modulators (PAMs)

Metabotropic glutamate receptors are G-protein coupled glutamate receptors which are thought to be involved in the mechanism of schizophrenia as they take part in modulating NMDA receptor-mediated neurotransmission.[142] Metabotropic glutamate receptor subtype 5 ($mGluR_5$) is of interest as it is known to be related to the NMDA receptor and more specifically, to physically interact with the NMDA receptor *via* binding to scaffolding proteins and also to potentiate NMDA receptor currents.[141] $mGluR_5$ PAMs have recently been developed and they act as modulators as they do not activate the receptor directly but they bind at an allosteric site and potentiate the responses to glutamate.[151] Janssen and the Vanderbilt Center for Neuroscience Drug Discovery discovered a potent, selective and orally bioavailable mGluR5 PAM - VU0409551/JNJ-46778212 (Figure 18).[152]

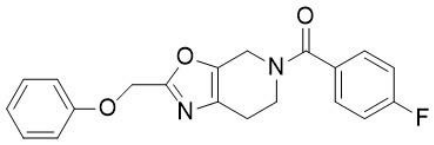


Figure 18. Molecular structure of VU0409551/JNJ-46778212.

VU0409551/JNJ-46778212 demonstrates an antipsychotic activity and cognition-enhancing efficacy without directly potentiating the NMDA receptor modulation.[152]

Recently, Yang *et al.* reported the robust *in vivo* efficacy in preclinical model of schizophrenia of BMS-955829 (Figure 19), a $mGluR_5$ PAM having the potential to treat cognitive abnormalities seen among patients.[153] It displays high functional PAM potency,

high selectivity for the $mGluR_5$ subtype, excellent $mGluR_5$ binding affinity and low glutamate fold shift.[153]

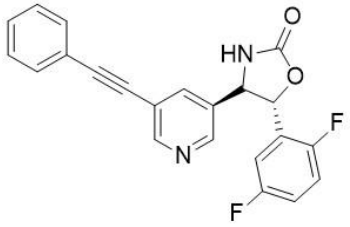


Figure 19. Molecular structure of BMS-955829.

3.1.3. AMPA Receptor PAMs

AMPA receptors are non-NMDA-type ionotropic glutamate receptors which mediate the majority of fast amino acid neurotransmission and are involved in the expression of long-term potentiation (LTP), a phenomenon associated with learning and memory.[154;155] AMPA receptors are also responsible for the fast excitatory postsynaptic potentials (EPSPs) and have recently been of high interest as glutamatergic neurotransmission could be regulated by activating this type of glutamate receptors.[142] Direct AMPA receptor agonists may cause severe neurotoxicity owing to their ability to interact with the glutamate receptor binding site and could therefore overstimulate the receptors. AMPA receptor PAMs (also known as potentiators) have no effect without the presence of the natural ligand at the synapse and therefore apply finer tuning and enhance the glutamatergic neurotransmission without causing excitotoxic effects.[154;155] AMPA receptor PAMs act by slowing the rate of key functional AMPA receptor properties such as desensitisation and deactivation.[154;155] Desensitisation is the process of ion channel closure with glutamate still bound to the receptor. Deactivation is the process of ion channel inactivation following the dissociation of the agonist.[154;155] Therefore, AMPA receptor PAMs can regulate the amplitude and duration of glutamate-stimulated EPSPs.[154] Recently, AMPA receptor potentiators have been used to enhance the glutamatergic neurotransmission, improve cognitive deficits and help with

various neurological disorders such as schizophrenia, depression and Parkinson's disease. Francotte *et al.* reported the synthesis of a benzothiadiazine dioxide compound (7-chloro-4-cyclopropyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide) (Figure 20). This compound is an AMPA receptor PAM which demonstrated favourable physiochemical properties and low *in vivo* acute toxicity observed in animal models.[155]

Figure 20. Molecular structure of 7-chloro-4-cyclopropyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide.

By measuring the cerebral and plasma concentrations after oral administration in animal models (3 mg/kg), benzothiadiazine dioxide was confirmed to be easily distributed into the brain. Carrying out an *ex vivo* electrophysiological test performed on rat hippocampal slices, it has been shown that the compound interacts with the postsynaptic AMPA receptors located on hippocampal neurons. Electrophysiological recordings of the postsynaptic response in the hippocampus in animal models demonstrated the *in vitro* effects of the benzothiadiazine dioxide on EPSPs on hippocampal slices, as well as its ability to increase the induction and the maintenance of LTP. As a result, this compound was found to considerably improve cognition processes at doses as low as 1 mg/kg.[155]

Citti *et al.* identified 7-chloro-5-(furan-3-yl)-3-methyl-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide which is the unsaturated derivative of 7-chloro-5-(furan-3-yl)-3-methyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (AMPA receptor PAM) when the latter is metabolised by hepatic CYP450 enzymes (Figure 21).[156]

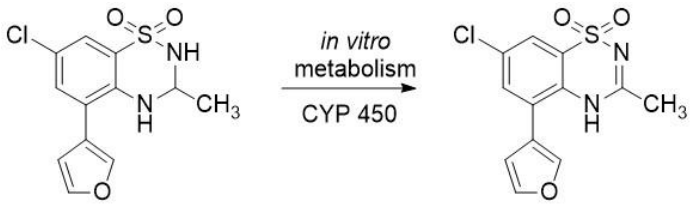


Figure 21. Molecular structures of the parent compound and its metabolite.

Animal microdialysis studies demonstrated that the metabolite is able to cross the blood-brain barrier, increasing the acetylcholine and serotonin levels in the hippocampus. Experimental data confirmed that the metabolite has the same pharmacological activity as its parent compound but it also displays enhanced chemical and stereochemical stability, as well as an enriched pharmacokinetic profile when compared to the parent compound.[156]

Recently, Ward *et al.* reported the synthesis of UoS12258 (Figure 22), a selective AMPA receptor PAM which has an excellent *in vivo* efficacy profile.[157]

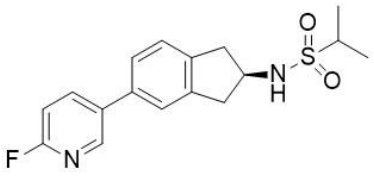


Figure 22. Molecular structure of UoS12258.

UoS12258 demonstrated an equivalent potency for all AMPA receptor subtypes and no measurable activity for other glutamate receptors. It has also been shown to enhance the AMPA receptor-mediated activity *in vivo* at low doses as well as to improve learning and memory processes in animal models when administered at higher doses. Preclinical studies confirmed that UoS12258 is expected to be a highly effective agent for treating the cognitive deficits seen among schizophrenic patients.[157]

3.2. Selective Agonists of alpha7 nicotinic acetylcholine receptor (α7 nAChR)

Neuronal nAChRs are ligand-gated ion channels permeable to cations such as Na^+, K^+ and Ca^{2+}.[158] nAChRs are spread in both the peripheral nervous system (PNS) and the CNS[158] and their function is to alter synaptic plasticity and to influence cell excitability and the release of other neurotransmitters such as dopamine, serotonin, glutamate and GABA.[159;160] These nAChRs are regulated by the endogenous agonist acetylcholine (ACh)[159] and are known to be related to cognitive and attentional processing.[160] Numerous nAChRs are known but α7 nAChR, which is one of the most commonly expressed subtypes of nicotinic receptors,[159] is of particular interest due to its role in reducing the cognitive deficits associated with schizophrenia. The homopentameric α7 nAChR consists of five α7 subunits and all of them provide an orthosteric binding site for the endogenous ligand ACh.[161] α7 nAChRs are located in the cerebral cortex, hippocampus and subcortical limbic regions and these receptors are associated with memory, sensory gating and neuronal plasticity.[162] Since α7 nAChRs have implications in the regulation of cognitive processes such as memory and attention, novel α7 nAChR agonists have been designed in order to improve the cognitive performance of patients diagnosed with different neurological disorders such as schizophrenia, Alzheimer's disease, depression and attention deficit hyperactivity disorder.[158] Abnormalities of α7 nAChRs function leads to deficits in sensory gating in patients diagnosed with schizophrenia and reduced expression of nAChRs in the hippocampus, reticular nucleus of the thalamus, dentate gyrus and frontal cortex of subjects diagnosed with the disorder.[160]

Nicotine has been shown to have a positive impact on attentional processing and cognitive functions in animal models, healthy volunteers and subjects diagnosed with schizophrenia.[163] Acute administration of nicotine has been found to enhance cognitive performance in schizophrenic patients and since nicotine acts as an agonist at nAChRs, this has linked nicotinic receptors to schizophrenia.[158;160] As a result, α7 nAChR agonists are currently

explored as novel agents to treat cognitive dysfunction seen in patients diagnosed with mental disorders such as schizophrenia.

O'Donnell *et al.* developed CP-810123 (Figure 23) as a potential agent for the treatment of cognitive deficits associated with neurological conditions including schizophrenia and Alzheimer's disease.[164]

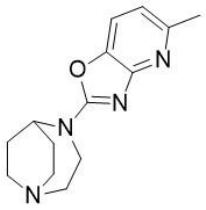


Figure 23. Molecular structure of CP-810123.

CP-810123 is a potent and selective α7 nAChR agonist with excellent pharmaceutical properties. In animal models, it demonstrated high oral bioavailability and good brain penetration which results in high levels of receptor occupancy. It has shown acceptable cardiovascular safety profile and genetic toxicology profile, as well as *in vivo* efficacy in auditory sensory gating and novel object recognition (NOR) models which are both indicative of improved cognitive function.[164]

Zanaletti *et al.* identified the compound SEN78702,WYE-308775 (Figure 24) as a potent and selective full agonist of the α7 nAChR.[165]

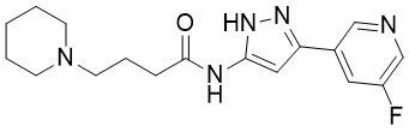


Figure 24. Molecular structure of SEN78702,WYE-308775

This α7 nAChR full agonist displayed rapid absorption, excellent bioavailability, good selectivity profile and moderate clearance. In a prepulse animal model, SEN78702, WYE-308775 demonstrated the ability to decrease pharmacologically induced deficits through the

glutamatergic system. It has also been subject to preliminary toxicology assessment and it indicated low toxicity risk.[165]

Recently, King *et al.* reported the synthesis of BMS-933043 (Figure 25) as a novel and potent α7 nAChR partial agonist.[166]

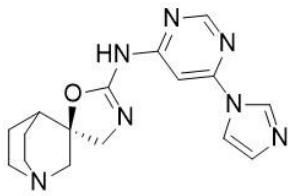


Figure 25. Molecular structure of BMS-933043

BMS-933043 demonstrated high selectivity for the α7 nAChR and against other nAChR subtypes, as well as against the 5-HT_{3A} receptor. Its effect on episodic memory was assessed in the animal NOR model where it displayed a robust increase in novel object exploration at doses of 0.1 – 10 mg/kg which is indicative of enhanced object recognition memory.[166] Bristow *et al.* reported the potent binding affinity of BMS-933043 to native animal and recombinant human α7 nAChRs and no agonist or antagonist activity at other nAChR subtypes.[167] It has been shown to considerably improve cognition and sensory processing in preclinical models of schizophrenia and it has also displayed favourable preclinical safety profile.[167] As a result of its favourable preclinical profile, BMS-933043 has been selected for further development to support clinical evaluation in humans.[167]

Hill *et al*. reported the synthesis of a series of quinuclidine-containing spiroimidates and their function as α7 nAChR partial agonists. Two of them – (1′S,3′R,4′S)-*N*-(7-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-4*H*-1′-azaspiro[oxazole-5,3′-bicyclo[2.2.2]octan]-2-amine and (1′S,3′R,4′S)-*N*-(7-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-4*H*-1′-azaspiro[oxazole-5,3′-bicyclo[2.2.2]octan]-2-amine (Figure 26) were identified as potent and selective α7 nAChR partial agonists.[168]

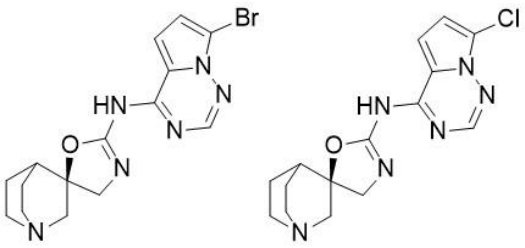


Figure 26. Molecular structures of the two quinuclidine-containing spiroimidate compounds developed by Hill *et al*.

In animal models, these two partial α7 nAChR agonists demonstrated an ability to enhance learning and memory function, to reverse memory and sensory gating deficits and also to reduce anxiety.[168]

Conclusions

Schizophrenia is a complex and unpredictable mental disorder which affects several domains of cognition and behaviour. It is a heterogeneous illness characterised by positive, negative, and cognitive symptoms, often accompanied by signs of depression. The disorder follows a complex route combining different anatomical changes in the brains of schizophrenic patients, as well as alterations of receptors and abnormalities in the concentrations of various neurotransmitters. Schizophrenia cannot be cured but suitable medications called 'antipsychotic drugs' are available to help with its severe symptoms. Second-generation atypical antipsychotic drugs are the current choice for most of the patients and these show different properties, receptor binding profiles, pharmacological features and adverse events. Here, we have tried to provide some basic information on the neurobiology and neurochemistry of schizophrenia, and surveyed the synthesis, mode of actions, and limitations of the different clinically antipsychotic agents used since the 1950s. It is however clear that the development of new molecules is crucially needed to overcome the major limitations of currently used drugs. A number of clinical trials are currently undergoing, and

we highlighted some of the most recent strategies used for the design of drugs that will achieve both efficiency and low level of side effects, in particular *via* modulation of glutamatergic signalling and selective agonists of α7 nAChR receptors.

Abbreviations

^{1}H-MRS	proton magnetic resonance spectroscopy
5-HT	serotonin
Ach	acetylcholine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BITP	1-(1,2-benzisothiazol-3-yl)-piperazine
CNS	central nervous system
CPZ	chlorpromazine
CYP450	cytochrome P450
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tension imaging
EPSEs	extrapyramidal side effects
EPSP	excitatory postsynaptic potential
FBCs	full blood counts
FDA	Food and Drug Administration
FGA	first-generation antipsychotics
GABA	γ-aminobutyric acid
GLX	glutamate and glutamine
GlyT1	glycine transporter 1
LTP	long-term potentiation
mGlu	metabotropic glutamate
$mGluR_5$	metabotropic glutamate receptor subtype 5
MRI	magnetic resonance imaging
nAChR	nicotinic acetylcholine receptor
NMDA	*N*-methyl-D-aspartic acid

NOR	novel object recognition
PAM	positive allosteric modulator
PET	positron emission tomography
PFC	prefrontal cortex
PNS	peripheral nervous system
SGA	second-generation antipsychotics
SPECT	single-photon emission computed tomography
STG	superior temporal gyrus
TRS	treatment-resistant schizophrenia
UGT	uridine 5'-diphospho-glucuronosyltransferase
WHO	World Health Organisation

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