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SCHIZOPHRENIA: A REVIEW

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Abstract

Schizophrenia is a chronic as well as severe mental disorder that gradually impairs a person's ability to think, feel, and behave in a normal way. The patient may with time lose his/her contact with the reality and often experiences a series of hallucinations and delusions. Their way of thinking is unusual or dysfunctional and sometimes they also experience movement disorders. The common symptoms observed are false beliefs, thinking disorders, lack of socialization, emotional expression and above all motivation. A complex interaction between the genetic and environmental factors is known to play a pivotal role in the development of schizophrenia, but the exact cause of this disease is still a matter of debate. As a result, the treatment options most of the time aims at eliminating the symptoms and helping the patient lead a normal life rather than eradicating the disease itself. The primary treatment in case of schizophrenia is antipsychotic medication. Some of these antipsychotics are Amisulpride, Aripiprazole, Risperidone, Sulpiride, Ziprasidone, Lamotrigine, Valproate and Topiramate. The conventional antipsychotics are effective in controlling the positive symptoms such as hallucinations, delusions, and confusion of schizophrenia. On the other hand, the new generation or atypical antipsychotics can treat both the positive and negative symptoms of schizophrenia, often with fewer side effects. Apart from the already available medications, many other drugs are being developed around the world for providing an efficient means of treatment for schizophrenia and they are in the various phases of their developmental study.

Keywords: Schizophrenia, hallucinations, delusions, negative symptoms, antipsychotics.

Introduction

Schizophrenia is a devastating illness that gradually impairs the mental and social functioning of an individual and often leads to the development of comorbid diseases. It affects both men and women equally, but the onset is often later in women than in men. This disease is characterized by a set of symptoms which can be grouped into positive and negative symptoms respectively. Positive symptoms include hallucinations, voices that converse with or about the patient, and delusions that are often paranoid. Negative symptoms include flattened affect, loss of will or drive, and social withdrawal. Schizophrenia is also characterized by disorganized thought which is reflected in speech and behaviour of the patient. The "disorganization" syndrome comprises a variety of abnormalities in the organization of thought, speech, and attention. This includes tangentiality and derailment, incoherence and pressure of speech, poverty of content of speech, and distractibility. There are basically five types of schizophrenia: paranoid, disorganised, catatonic, undifferentiated, and residual. Paranoid type is characterized by a preoccupation with one or more delusions or frequent auditory hallucinations. In this type the cognitive functions remains relatively unaffected and preserved. Disorganized type is characterized by disorganized speech as well as behaviour. Catatonic type has at least two of the following features: immobility (as evidenced by stupor or catalepsy); excessive, purposeless motor activity; extreme negativism (e.g., resistance to all instructions, maintenance of rigid posture, mutism); or peculiarities of voluntary movement (e.g., posturing, prominent mannerisms, grimacing).[1] If none of the criteria for paranoid, disorganized, or catatonic types are met, then the patient is said to be suffering from undifferentiated schizophrenia. Residual type is characterized by the continued presence of negative symptoms and at least two attenuated positive symptoms. . Inspite of all these symptoms the clinical heterogeneity of schizophrenia cannot be ignored. Virtually no two people show the same set of symptoms. Even the same patient may show different arrays of symptoms from time to time as the disease gradually gets intensified.[2] The proper and satisfactory treatment of schizophrenia has always been a matter of great concern since earlier days. At present, the treatment mainly consists of antipsychotic therapies, social support, and rehabilitation, but the need for more promising treatments and delivery of services still exists. But it is unclear whether typical or atypical antipsychotics are better. Each class of antipsychotics possess its characteristic advantages as well as disadvantages. As a result, no particular treatment can be considered as fully efficient. Hence the choice of which antipsychotic to use is a crucial step in the treatment of the disease and this decision is entirely based upon various considerations regarding the benefits, risks, and costs associated with it. Amisulpride, Olanzapine, Risperidone, and Clozapine are relatively more effective than other drugs but are associated with greater side effects. The side effects of Amisulpride include insomnia, hyperprolactinaemia, hypersalivation, vomiting, and nausea. Sometimes bradycardia, urticaria, oculogyric crisis, and tardive dyskinesis are also observed in patients undergoing treatment with Amisulpride. Clozapine is mainly used for the treatment of schizophrenia that does not improve following the use of other antipsychotic medications. It is possibly more effective than typical antipsychotics. Clozapine is associated with relatively high risk of low white blood cells (WBC's) which may result in death. Study of Risperidone began in late 1980's but was approved for sale in the United States in 1993. Risperidone is

mainly used for the treatment of schizophrenia, and bipolar disorders. Its side effects include movement problems, sleepiness, and tardive dyskinesia. The drug is also found to increase the risk of suicide which is regarded as a dangerous side effect associated with the use of Risperidone. Apart from this treatments there exist a number of psychosocial interventions which may be useful in the treatment of schizophrenia. This includes family therapy, assertive community treatment, supported employment, cognitive remediation, skills training and psychosocial interventions for substance use and weight management. Reviews of treatments focused on medication adherence, cognitive remediation, psychosocial treatments for recent onset schizophrenia, and peer support and peer-delivered services revealed that none of these treatment areas yet have enough evidence to merit a treatment recommendation, though each is an emerging area of interest.[3] A combination of carefully chosen antipsychotic medications along with suitable psychosocial interventions may prove to be successful enough to provide a much better as well as promising treatment to the patients suffering from this disease. But to ensure this completely and for its proper application, there still exist an immense need of researches and citation of convincing evidences.

Causes

The exact cause of schizophrenia is still a matter of debate. Several studies have been carried out in the past for the identification of the most responsible factor. Some factors have been proposed, some discarded and some were altered. These studies indicate that the possible causes of schizophrenia include genetics, prenatal development, early environment, neurobiology and psychological and social processes. Genetic epidemiological studies suggest that individual variation in susceptibility to schizophrenia is largely genetic, reflecting alleles of moderate to small effect in multiple genes. Recent studies have shown that inspite of many limitations which prevails, a number of regions of the human genome provide a consistent support for linkage, which is unlikely to occur by chance. A series of studies combining linkage and association analysis in the same family sets have identified promising candidate genes such as DTNBP1, NRG1, G72/G30, TRAR4.[4] Among these genes the evidences for Dystrobrevin Binding Protein 1(DTNBP1) and NRG1 are strong and promising. Another set of studies combining association with functional investigation of changes in associated genes in schizophrenia have also identified several candidate genes such as COMT, RGS4, PPP3CC, ZDHHC8, AKT1. Many identified positional candidate genes are now being replicated in independent samples. The major focus on this area of multiple research groups throughout the world indicates that within several years these or other loci might emerge as widely replicated susceptibility genes for schizophrenia. This may gradually enhance the impact of genetic factors on the development of this disease. Studies also reveal that obstetric complications or obstetric events increase the risk for schizophrenia in an individual. This is a small effect –the pooled odds ratio of the effect of exposure to obstetric complications on the subsequent development of schizophrenia has been estimated to be about 2.0(95% confidence interval, 1.6-2.4).[5] The term "obstetric complications" covers a wide range of events. The meta-analytic synthesis of the prospective population based studies revealed that three groups of complications were mainly responsible for causing schizophrenia. These includes pregnancy complications such as bleeding, diabetes, rhesus

incompatibility, and preedampsia, abnormal fetal growth and development such as low birth weight, congenital malformations, reduced head circumference, and complications of delivery such as uterine atony, asphyxia, and emergency caesarean section.[6] A significant association has been established through various studies between the age at which the onset of schizophrenia takes place and the history of obstetric complications. Subjects with onset of schizophrenia before age 22 were 2.7 times more likely than those with onset at a later age to have had a history of abnormal presentation at birth and 10 times more likely to have had a history of complicated caesarean birth.[7] This in turn indicates that the pathophysiology of early onset schizophrenia involves neurodevelopmental impairment. Research is being carried out to establish the link between schizophrenia and neurodevelopmental impairment. If the results are positive then there is an immense scope of new developments in the prevention and cure of this disease. Often it has been seen that schizophrenia is also associated with the use of certain substances such as drugs. The use of various drugs such as cannabis, amphetamines and other stimulants make the diagnosis of schizophrenia difficult because a person cannot be diagnosed without symptoms persisting after the use of the drug has completely ended.[8]

Signs and symptoms

Several studies have revealed that patients with schizophrenia show impaired performance in various aspects of social cognition which includes theory of mind, emotion processing, and agency judgement.[9] The common symptoms of schizophrenia can be categorized into three groups, namely, positive symptoms, negative symptoms, and cognitive symptoms. The positive symptoms include hallucinations where the patient might hear, see, smell or feel things which may in fact have no real existence, delusions or false beliefs, confused thoughts and speech where the patient's thoughts and speech are usually disorganized and he/she may take a long time to organize his/her thoughts. Positive symptoms generally respond well to medications. Negative symptoms of schizophrenia include the normal traits which are usually absent or reduced in the person who is ill. The negative symptoms are the deficiency of normal emotional responses or of other thought processes, and are less responsive to medication. This include flat expressions, poverty of speech, lack of desire to form relationships, lack of motivation, lack of initiative (avolition), and anhedonia where the patient may fail to experience or express pleasure in things that they once found enjoyable. Research suggests that the negative symptoms of schizophrenia, including problems with motivation, social withdrawal, and diminished affective responsiveness, speech, and movement, contribute more to poor functional outcomes and quality of life for individuals with schizophrenia than do positive symptoms.[10,11] Negative symptoms usually persist longer than the positive symptoms and are difficult to treat.[12] Although cognitive deficits are recognised as a core feature in schizophrenia, their evolution over the course of the illness is still debated. Cognitive functioning is moderately to severely impaired in patients with schizophrenia. This impairment is the main cause behind the significant disabilities in occupation, social, and economic functioning in patients with schizophrenia and these are also an important treatment target. The profile of deficits in schizophrenia includes many of the most important aspects of human cognition such as attention, memory, reasoning as well

as processing speed. Recent researches have shown that disturbance in social and occupational functioning in individuals with schizophrenia may be more influenced by the severity of cognitive deficits than by the severity of other symptoms such as hallucinations and delusions.[13] Working Memory (WM) is one of the most affected cognitive processes in schizophrenia. The Working Memory can be defined as the ability to hold a certain limited amount of information in consciousness, for use in guiding the behaviour after the information has been removed from the environment.[14] Studies suggest that WM capacity is reached sooner in patients suffering from schizophrenia. The Working Memory impairment is considered as a fundamental feature of schizophrenia and can be reflected throughout the course of the illness.

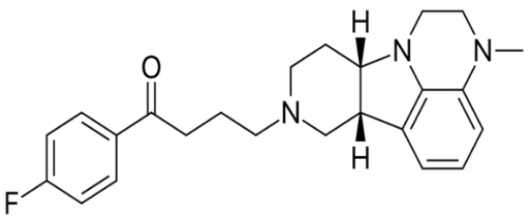
Diagnosis and treatment

The diagnosis of schizophrenia is associated with certain specific and demonstrable alterations in the structure of the brain and changes in dopamine neurotransmission. The dopamine neurotransmission changes are directly linked to the positive symptoms such as hallucinations and delusions. Certain pharmacological treatments which block the dopamine system are effective for delusions and hallucinations but they are less effective in disabling cognitive and motivational impairment.[15] The diagnosis of schizophrenia is based upon the criteria provided either in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, version DSM-IV-TR, or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. The ICD-10 criteria are typically used in European countries. The DSM-IV-TR criteria on the other hand are used in the rest of the world and are also used in various research studies which are prevailing. Studies have revealed that both of these systems are equally effective and reliable in diagnosis of the disease and show a perfect agreement between each other.[16] The metabolic studies represent an efficient tool for early diagnosis of schizophrenia. The main objective behind this study is to determine the differences in the steroid spectrum in patients and controls, and to assess the diagnosis of schizophrenia by building a predictive model based on steroid data. Studies suggest that this process of diagnosis of schizophrenia shows 100% sensitivity and may become a valid laboratory test in psychiatry in near future.[17] Techniques such as Magnetic resonance imaging-based markers of schizophrenia have been repeatedly shown to separate patients from healthy controls at the single-subject level, but it remains unclear whether these markers reliably distinguish schizophrenia from mood disorders across the life span and generalize to new patients as well as to early stages of these illnesses. However findings suggest that neuroanatomical informations may provide generalizable diagnostic tools distinguishing schizophrenia from mood disorders early in the course of psychosis. The psychiatric treatment of schizophrenia usually begins with antipsychotic medication. The antipsychotics are of two types – typical antipsychotics and atypical antipsychotics. Maintenance treatment with antipsychotic drugs benefits patients with schizophrenia. In fact the antipsychotic medications are regarded as the cornerstones for both the short-term and long-term treatment of schizophrenia. However evidence on long-term efficacy of antipsychotics is not entirely satisfactory though they are found to be extremely useful in improving a number of outcomes which are regarded as important to

patients including positive, acute, and psychotic symptoms. They can reduce the positive symptoms of schizophrenia but are found to be less useful in treating the negative symptoms as well as the dysfunctions associated with cognition.[18] Atypical antipsychotic drugs such as Clozapine, Amisulpride, Olanzapine, and Risperidone have been proved to be the most effective medication available for the treatment of schizophrenia. The atypical antipsychotics are also referred as Second Generation Antipsychotics (SGAs). The typical antipsychotics or First Generation Antipsychotics (FGAs) such as Chlorpromazine, Haloperidol, and Trifluoperazine are different from atypical antipsychotics in that they are likely to cause extra pyramidal motor control disabilities in patients which may include unsteady Parkinson's disease type movements, body rigidity and involuntary tremors.[19] However this does not mean that the atypical antipsychotics are devoid of any side-effects and can be used efficiently to battle the disease. The side-effects observed in patients undergoing treatment with atypical antipsychotics include considerable weight gain, diabetes as well as risk of developing metabolic syndrome. Patients are exposed to the risk of metabolic syndromes mainly when they are being treated with Olanzapine. However weight gain has been associated with the intake of drugs such as Quetiapine and Risperidone. Long-term studies have shown that when a new generation of antipsychotic drugs with additional benefits are developed, a fewer adverse effects are also introduced.[20]Thus there is an urgent need for the development of new treatments of schizophrenia which are effective against a broad spectrum of symptoms and at the same time are free of limiting safety issues.

Recent drugs, currently under investigation for the treatment of Schizophrenia

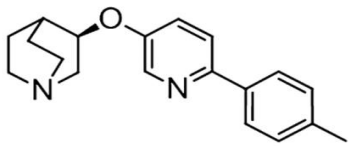
ITI-007



IUPAC Name: 1-(4-Fluorophenyl)-4-(3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-butanone

ITI-007 is an investigational drug which is being developed for schizophrenia as well as for other neuropsychiatric and neurodegenerative diseases like bipolar disorder, depression, and sleep and behavioural disturbances which occurs in case of dementia and autism. The drug was found to possess a unique pharmacological profile, combining potent 5-HT2a receptor antagonism with cell type specific dopamine and glutamate receptor modulation along with serotonin reuptake inhibition. This drug is associated with minimal safety risk and its antipsychotic efficacy has been confirmed in a recently completed Phase-III study.[21] This drug may hence prove to be an efficient treatment option for schizophrenic patients.

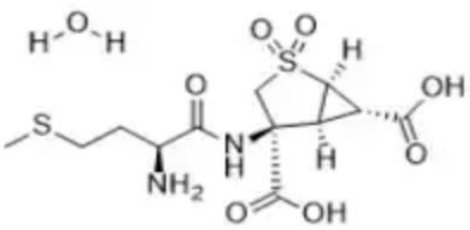
AQW051



IUPAC Name: (3R)-3-{[6-(4-methylphenyl)pyridin-3-yl]oxy}-1-azabicyclo[2.2.2]octane

The drug AQW051 is currently on clinical trial and may assist in the treatment of Schizophrenia in future. The activation of the a7 nicotinic ACh receptor is regarded as an important target treatment of cognitive impairment in neurological disorders. Hence, the novel a7-nACh receptor agonist AQW051 could be a promising drug for the treatment of schizophrenia.[22]

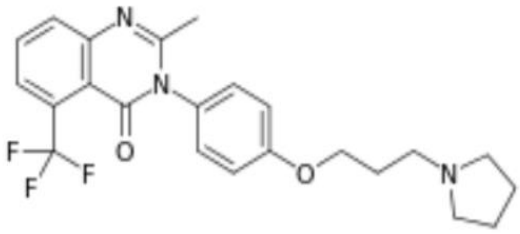
LY2140023



IUPAC Name: (1R,4S,5S,6S)-4-((S)-2-amino-4-(methylthio)butanamido)-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid 2,2-dioxide hydrate

Another drug LY2140023 has completed Phase-II of the trial and has been found to be effective for schizophrenia treatment. It is a prodrug of the orthosteric agonist, LY-404039, which operates at the metabotropic glutamate receptor 2/3(mGluR2/3) and is active as long as it is bound to the receptor.[23] An important advantage of LY2140023 is that there was no weight gain, which is usually associated with other drugs such as Olanzapine. It actually showed modest weight loss in patients.[24]

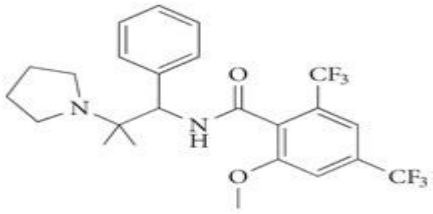
MK0249



IUPAC Name: 2-Methyl-3-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-5-(trifluoromethyl)quinazolin-4-one

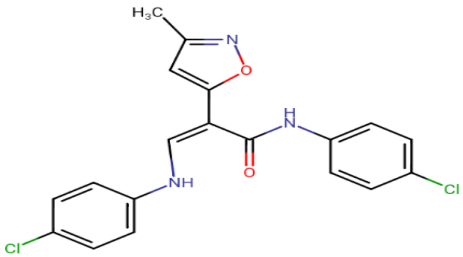
MK0249 is an investigational drug which has completed Phase-II of clinical trial. This drug is an H3R antagonist or inverse agonist and is capable of improving cognitive and perhaps negative symptoms but is not effective against the psychotic symptoms such as hallucinations and delusions.[25] Hence, MK0249 and other Histamine receptor 3 antagonists can be used for treating the cognitive dysfunctions associated with schizophrenia in future.

GSK1018921



GSK1018921 is a new drug which is under development for the treatment of schizophrenia. It has completed Phase-I of clinical trial and is believed to be effective against the positive symptoms such as hallucinations and the negative symptoms such as lack of drive.

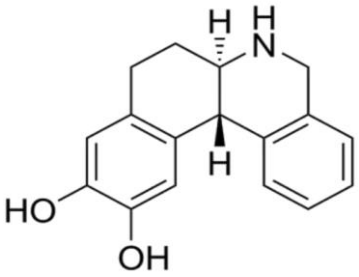
AVL-3288



IUPAC Name: (Z)-3-(4-Chloroanilino)-N-(4-chlorophenyl)-2-(3-methylisoxazol-5-yl)prop-2-enamide

The Phase-I study of AVL-3288 as a treatment option for schizophrenia will be undertaken in the near future. And there is an immense scope for the study to become successful, thus providing us with another efficient drug.

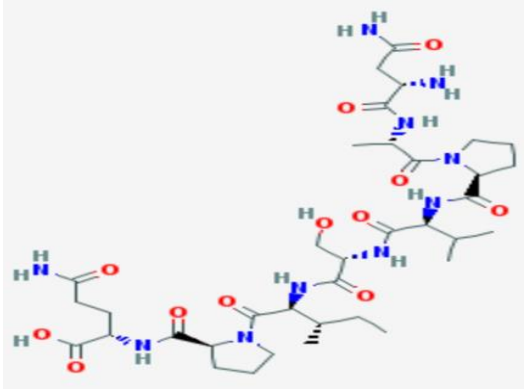
DAR O-100A



IUPAC Name: 5,6,6a,7,8,12b-hexahydro-benzo(a)phenanthridine-10,11-diol

DAR O-100A is a drug which was found to be immense helpful in the treatment of Parkinson's disease. It is going to undergo the Phase-II clinical trial to ensure whether it could be used in patients suffering from Schizophrenia. The drug functions by increasing the dopamine effects and the presence of the brain chemical, dopamine has been found to help people with schizophrenia. Hence, promising results could be expected from the studies.

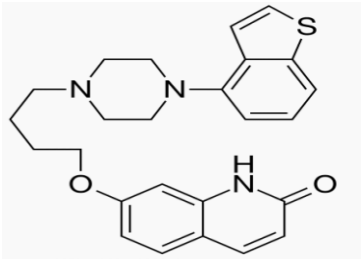
AL-108



IUPAC Name: (2S)-5-amino-2-[[(2S)-1-[(2S,3S)-2-[[(2S)-2-[[(2S)-2-[[(2S)-1-[(2S)-2-[[(2S)-2,4-diamino-4-oxobutanoyl]amino]propanoyl]pyrrolidine-2-carbonyl]amino]-3-methylbutanoyl]amino]-3-hydroxypropanoyl]amino]-3-methylpentanoyl]pyrrolidine-2-carbonyl]amino]-5-oxopentanoic acid

AL-108 is an intranasally administered peptide and it has completed the Phase-II clinical trial. It is found to improve cognition in schizophrenia and hence could be used for treating cognitive dysfunction associated with schizophrenia in the future.

OPC-34712



IUPAC Name: 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one

Brexpiprazole or OPC-34712 is a novel serotonin-dopamine activity modulator and displays a good safety as well as tolerability profile. It has been recently approved by the U.S Food and Drug Administration for the treatment of schizophrenia.[26]

Conclusion

As it is evident from the discussion, the disease schizophrenia is indeed a serious disorder which impairs a person's ability to distinguish between what is real and what is imaginary. The exact cause of schizophrenia is still unclear, the identification of which could enable the development of more efficient treatment methods that aims at treating the cause itself, rather than the symptoms. Currently, the medications available are used to diminish and eradicate the symptoms. These symptoms are different for everyone and may develop slowly over months or years, or may appear very abruptly. The disease may also come and go in cycles of relapse and remission. Though no complete cure for schizophrenia has been discovered yet, the symptom- oriented treatment available now-a-days significantly help people with schizophrenia to lead a productive and fulfilling lives. Apart from the already available remedies, many more drugs are being developed and investigated for the treatment of schizophrenia. These drugs have different mechanisms of action and aims at curing the disease efficiently with the least possible side effects. They are in the various phases of their investigational studies and once they get approved, the schizophrenic patients would have more efficient treatment options. Studies are also being carried out to determine the path of development of schizophrenia and thereby its exact cause. This would prove to be a significant milestone as this would modify the direction of development of drugs for the disease. And such drugs, if developed will be able to cure the disease entirely and provide a long term relief to the patient rather than providing a short term effect by curing the symptoms.

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