

THE TREATMENT OF THE SCHIZOPHRENIA: AN OVERVIEW

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Summary

The schizophrenia is a kind of psychiatric disease, characterized by a course longer than six months (usually chronic or relapsing), by the persistence of symptoms of alteration of mind, behaviour and emotion, with such a seriousness to limitate the normal activity of a person.

The terms *antipsychotic* and *neuroleptic* define a group of medicine principally used to treat schizophrenia, but they are also efficacious for other psychosis and in states of psychic agitation. The antipsychotics are divided into two classes: *classic or typical and atypical*.

The paliperidone, the major metabolite of risperidone, shares with the native drug the characteristics of receptoral bond and of antagonism of serotonin (5HT_{2A}) and dopamine (D₂). It's available in a prolonged release formulation and it allows the administration once daily.

Besides, the paliperidone has a pharmacological action independent of CYT P450 and in such way a lot of due pharmacological interactions would be avoided to interference with the activity of the CYP2D6, that is known to have involved in the metabolism of the 25% of the drugs of commune therapeutic employment.

Introduction

The schizophrenia has been a very hard disease to investigate by the research. This is not surprising because it involves the most mysterious aspects of human mind, as emotions and cognitive processes.

According to scientific conventions, the schizophrenia is a kind of psychiatric disease, characterized by a course longer than six months (usually chronic or relapsing), by the persistence of symptoms of alteration of mind, behaviour and emotion, with such a seriousness to limitate the normal activity of a person.



Today is not possible to prevent schizophrenia and the treatment is essentially symptomatic. Moreover the heterogeneity of reply, its variableness and relapses, (although the continuity of therapy), make the research about the mechanism of the medicines or the individual differences in fisiopathology very important.

Antipsychotics have in common an antagonistic effect on dopaminergic receptors but are very different in terms of selectivity for the different receptorial subpopulations, of receptorial bonds and of preferential affinity of limbic area in comparison with the striatal or of the other basal ganglions. Moreover antipsychotics of new generation act on different receptorial classes.

THE SCHIZOPHRENIA

The term, coined by the Swiss psychiatrist Eugen Bleuler in 1908, comes from Greek σχίζω (scission) and φρενός (brain): “divided mind”.

But “schizophrenia” is a quite generic term and it indicates a class of disorders characterized by a certain seriousness and by the compromising of the so called “exam of reality” on behalf of the subject. To this class belong very different symptomatic aspects and kinds of personalities that are extremely varying for seriousness and course.

In very serious cases the symptoms can be catatony, mutism, or total inabilitation. In the majority of cases there is some kind of apparent disorganization or incoherence of mind, but in some cases these symptoms don’t appear. On the contrary, rigid paranoic constructions can be manifested.

Positive symptoms and negative symptoms

According to the medical tradition, the schizophrenia is characterized by two kinds of symptoms:

- positive symptoms: they are behaviour or experiences of the subject that are something “more”, compared to the experience and the behaviour of a normal subject. These symptoms can be: fixed ideas, deliriums, hallucinations and disorders of mind.

Mind disorders

The mind of a schizophrenic subject is often afflicted with disorders. He can stay for hours incapable of “thinking correctly”. The thoughts go and come so quickly that it’s not possible “to seize them”. The person can be incapable of concentrating himself on a thought for a long time and he can be easily distracted because he is incapable of concentrating his attention.

The schizophrenic subject can be incapable of distinguishing, in a determinate situation, what is important from what is not. The subject can be incapable of putting his thoughts in order following a logic sequence and the thoughts can get muddled and fragmentary, with a continuous and confused passage from a subject to another. The lack of logic continuity, called illogical thought, can make a conversation very difficult and contribute to social loneliness. If someone can’t comprehend what another person is saying, it is possible that he felt himself ill at ease and he will tend to leave this person alone.

There are different kinds of formal disorders of mind:

- Acceleration: increase of associative speed, increase of verbal production and, in extreme cases, flight of ideas
- Slackening: opposite of acceleration, decrease of associative speed and of the ideatic content and, in extreme cases, stopping of thought
- Derailment: loss of the thread of what one is saying and continuous passage from a subject to another
- Tangentiality: answers joined to a question in an oblique way or completely unjoined
- Illogicality
- Procedural redundancy
- Neologisms: use of new-coined words to indicate personal concepts
- Concretism: inability to do abstractions or argue about abstract subjects as faith, family, religion, state. The schizophrenic subject tends to refer always to real things. Inability to understand proverbs and idiomatic phrases.

Disorders of the content of mind

Distortion of reality: as every normal person sees the world from one's point of view, as the schizophrenic subject has his own perception of reality. But his perception of the world is often completely different from the reality seen and shared by the people who surround him. Living in a world that may seem distorted, changeable, without datum-points that everyone use to anchor oneself to the reality, a schizophrenic subject can feel anxious and confused. This kind person may seem distant, worried and he can also stay seated, being as still as a statue, without moving for hours and without saying nothing or he can go around without stopping, always busy, awake, attentive and vigilant. A schizophrenic can show different behaviour in different times.

Affective disorders

Schizophrenic subjects often assume what is called an improper attitude. They show emotions that are in contrast with their own thought or speech. For example a schizophrenic can say to be persecuted by the devil and at the same time he can laugh. Some of them also show an euphoric or depressive mood and in these cases it's important to decide whether they are really schizophrenic or they are afflicted with bipolar diseases like depressive mania or with other depressive diseases. People who can't be exactly catalogued are sometime diagnosed as subjects with schizoaffective disorders.

In these cases the patient shows:

- apparent affective athymia, lack of affective resonance of the subject towards himself and others;
- affective instability, that is a sudden passage from joy to anger or sadness;
- affective incongruity: affective manifestations are not appropriate, so a schizophrenic can show **paratimia**, where affective manifestations are opposite to the ones that circumstances would justify (for example hilarity after tragic news);
- affective ambivalence that is the attribution of opposite feelings like love/hate towards another person, usually parents or other relatives.

Perception disorders

They are hallucinations, that is perceptions without an object and they can be:

- Auditory hallucinations: the patient hears voices. They are usually threatening and allusive towards the patient himself. Sometime these voices oblige the patient to do things (imperative hallucinations) until the patient can commit suicide. Sometime the patient hears different voices together (conversation of voices) that don't refer to him but that can talk about him.

- Visual hallucinations (rare), caused by abuse of drugs
- Olfactory hallucinations (even more rare) caused by cerebral cancer.

Delirium

A delirium is a conviction due to an abnormal error of judgement, often with a strange content, sometime with auditory hallucinations. It corresponds to a disadvantageous mental model of reality because decisions taken during a delirium leads to an inadequate behaviour and to an inferior level of adaptation. To be diagnosed, a delirium must be firmly supported by the delirious subject although the reality and the other subjects prove its falseness. It is not considered pathologic by the patient, because according to the idea of the subject, the delirium itself is alike the other ideas. The contents of a delirium are very different. We have deliriums of:

- Persecution
- Reference
- Jealousy
- Nihilist
- Control
- Hypochondriac
- Religious
- Bigness

Instincts diseases

- ✓ Action diseases

They can be classified in three categories:

- Inactivity-akinesia
- Perseveration
- Apathy

- ✓ Sexual diseases

It is also possible to find anomalies in the sexual sphere of adolescents and young adult people. In this sphere the schizophrenic subject has many troubles, so he will have problems to make friends with somebody, to find a partner with whom he can have a satisfactory sexual relation. For this reason many schizophrenic patients have a promiscuous sexual life and occasional relations with different partners. It often happens that the patient lives an adolescent sexuality, resorting to

masturbation. Sometime the patients complains a fall of sexual ability but this is caused mostly by the collateral effect of the antipsychotics.

- negative symptoms: decrease, decline or disappearance of some normal abilities or experiences of the subject like for example inadequacy in the behaviour of the person, emotive detachment or lack of emotions, poverty of speech and communicative functions, inability to concentrate himself, lack of pleasure (anhedonia) and lack of motivation.

The schizophrenia strikes more frequently late during the adolescence and in the first phase of the adult age but some kinds of schizophrenia strikes prevailingly adults or middle-aged persons. The symptoms generally manifest in men first and then in women although there is also a feminine incidence, for example the “post-partum” catatonic schizophrenia. [1]

The schizophrenia presents different phases:

PRODROMAL PHASE

This is the stadium where the subject doesn't get good results at school and at work, he starts to abandon social relationships. His ability to communicate impoverishes and his behaviour begins to be “strange” according to what the family says. All the symptoms of the prodromal phase are not enough to give a diagnosis of schizophrenia and they are often found after that the disease is in its acute phase.

ACUTE PHASE

It is characterized by the “positive symptoms”, that is deliriums and hallucinations. There are also speech alterations and negative symptoms, lack of personal care and health, scarce interests.

RESIDUAL PHASE

In this phase the symptoms of the acute phase are attenuated or absent, but as the schizophrenia is a chronic disease, it becomes acute periodically during the life of the patient.

Diagnosis and classification of different kinds of schizophrenia

There aren't pathognomonic tests for the schizophrenia. The diagnosis bases itself on a global evaluation of the clinic anamnesis, symptoms and signs. Information from family, friends and teachers are important to establish the chronology of the beginning of the disease. According to the *Diagnostic and Statistic Manual of Mental Diseases*, forth edition (DSM-IV), to make a diagnosis we need two or more typical symptoms, that manifest for a long time during a month.

Moreover they have to be evident some prodromal or attenuated signs of the disease with compromising of social and working life and lack of personal care for at least 6 months that includes 1 month of active symptoms. During the clinic exams and the anamnesis they must be included psychotic troubles caused by physical disease or combined with abuse of drugs and primary diseases of mood with psychotic characteristics. Moreover laboratory analysis can exclude medical, neurologic and endocrine diseases that are already present in the patient and that can appear as psychosis (for example lack of vitamins, uraemia, thyrotoxicosis, electrolytic unbalance).

The diagnosis of schizophrenia must satisfy the following principle:

A) (Typical symptoms). The persistent presence of two or more of the following symptoms, for at least a month (the duration can be inferior if the symptom recedes in consequence of a treatment):

- delirium
- hallucinations
- disorganization of verbal speech (for example loss of the thread of what one is saying, incoherence, digression and abstract expression)
- serious disorganization of behaviour (for example in the manner of dressing, in the daily habits, sleep troubles, frequent cry or laugh without a reason) or a serious catatonic state
- presence of negative symptoms that is symptoms that cause a strong sense of indifference, distance and absence of the subject (lack or decrease of emotional answers), **alogia** (absence of speech), avolition (lack of motivation), troubles of attention and of intellectual abilities, lack of visual contact.

NOTE: The principle A is the only one to be satisfied (the points B and C are not required for the diagnosis) just in case of eccentric and unrealistic fixed ideas or when the hallucinations make the patient hear one or more voices talking to each other and that can be identified as unreal, or in case of the presence of a voice that “comments” the actions and the perceptions of the patient.

B) Social and/or working deficit or trouble: for a significant period of time some of the main ambits in the life of the subject are seriously compromised (work, personal relationships, care of personal health, alimentation etc).

C) Duration: persistence of the symptoms “B” for at least six months, that include at least one month of symptoms “A”.

There are also other principles (D,E,F) that are used to make differential diagnosis, to exclude the schizophrenia in case of a diagnosis of a serious trouble of the mood (as the major depression), of a serious trouble of the evolutionary age or of neurologic troubles due to generic medical conditions or when the symptoms are the result of the use of drugs or medicine.

In patients with schizophrenia, serious cerebral anomalies can be found through RMN or TC, but they are not specific enough to make a diagnosis for every single patient. Generally the anomalies of the medial and superior temporal lobe are associated with positive symptoms: the frontal and cortical ventricular anomalies are associated with negative symptoms. In the functional studies about the regional cerebral glucose or oxygen utilization, the reduction of prefrontal cortex and mesolimbic region activation is associated with negative symptoms and cognitive troubles in patients with schizophrenia.

The most traditional classification considers four main kinds of schizophrenia: catatonic schizophrenia, hebephrenic schizophrenia, paranoiac schizophrenia, and simple schizophrenia.

- *Catatonic schizophrenia*: the most evident symptoms concern motory activity. In catatonic patients states of physical immobility and states of unbridled excitement alternate, but symptoms of the one or the other state can predominate. Catatonic patients resist to instructions and orders or repeat like a parrot a word or a phrase (echolalia) said by another person. The limbs of a catatonic patient in a state of immobility can be rigid and swollen; although the apparent state of total oblivion, the patient sometime is able to refer all has happened during the catatonic stupor. In the state of catatonic excitement he can shout and talk without stopping, incoherently and at the same time going to and fro with agitation.

This is the most difficult kind of schizophrenia.

- *Disorganized (or hebephrenic) schizophrenia*: it is possible to find both an affective involution (the patient becomes reserved, he lacks of interests etc) and disorganization of thought or disorders in behaviour (impulsive and unpredictable behaviour)

- *Paranoiac schizophrenia*: the most evident characteristic is the presence of deliriums. Deliriums of persecution are the most frequent, but also deliriums of greatness are common and the patient manifests a very high sense of importance, power, knowledges and identity. Some subjects are tormented by deliriums of jealousy and they have the unfounded conviction that their partner is unfaithful. Frequently, together with the deliriums there are vivid auditory hallucinations. Moreover these subjects often develop reference ideas: they put ordinary events inside a delirious system and read a personal interpretation in the common activities of other people. For example they think that fragments of conversation heard by chance refer to them or that the presence of a certain person on a street where they often walk means that they are followed. They think that what they read on newspapers or watch on TV refers to them. The paranoiac schizophrenics are upset, polemic, irritable and sometime violent. This form frequently appears after the age of 35 with a slow and insidious course in patients who already have some structured trouble.
- *Simple schizophrenia*: it is the most common. There aren't evident symptoms but it comes out from an affective impoverishment and detachment from reality; this is the so called "schizophrenic feeling". The disease appears when the person is between the 16 and 22 years old with a very slow evolution that become chronic ad a detachment from reality that becomes bigger and bigger.

There is also a kind of schizophrenia called *undifferentiated* with positive symptoms that are not structured according to the principles of the previous kinds [2].

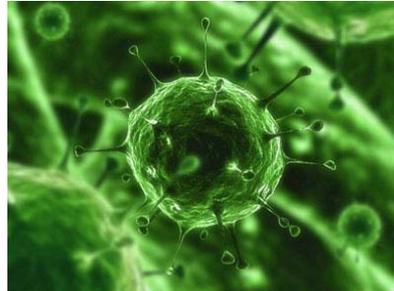
AETIOLOGY: THE PRINCIPAL THEORIES.

We are talking about a "multifactorial" pathogenesis where different associated factors contribute to the manifestation of the disease. The biological causes of schizophrenia are divided in four groups that can be associated together but in different subjects they assume a predominant role in a way or in another. It seems that the different causes are associated with different aspects of the disease that can appear with a majority of positive symptoms or negative symptoms.

The four groups of biological causes are the following.

- Genetic factors
- Alteration in brain chemistry
- Anomalies in the brain structure
- Alterations of the neurodevelopment

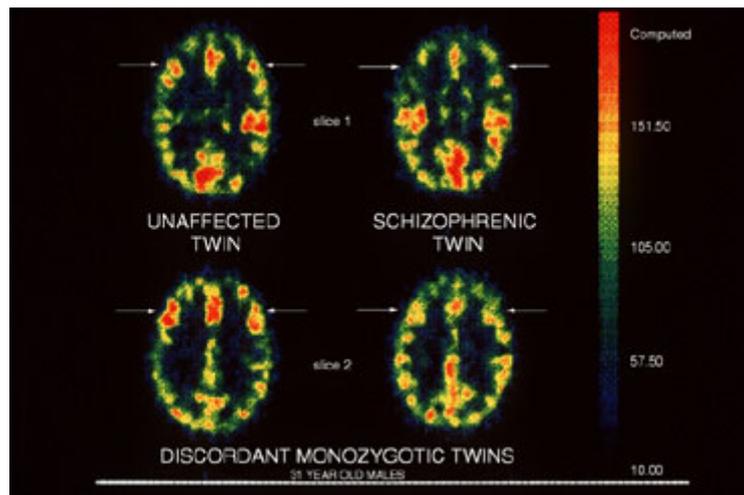
Further studies hypothesize also the role of some virus (especially **retrovirus**) that leave a cerebral “mark” that can cause the disease.



Moreover, studies done by a team of English biologists underline how people who have suffered from toxoplasmosis develop more easily the schizophrenia. According to these studies the toxoplasma, the parasite responsible of the toxoplasmosis increases the production of an enzyme that favours a stronger cerebral synthesis of dopamine. But the importance of the causes indicated above is primary.

Genetic factors

One of the oldest evidences in the study of the schizophrenia is that the risk to develop the disease increase if there is a relative who suffers from it. And the more the common genetic heritages are alike, the more the risk becomes stronger. Moreover, sharing a degree of relationship has also a great psychological and relational valency. For this reason some theories say that the disease is the result of pathologic and dysfunctional models of relationship. A relative of first degree of relationship has 10% of risk to fall ill. This possibility increases for the sons if both of the parents have this disease: the risk is 40%. Finally the relation between genetic heritage and risk to develop the disease has the most evident proof in the studies on twins. In fact if in heterozygotic twins (that is twins with a different genetic heritage) the risk that both can develop the disease is 10%, in homozygotic twins (that is identical twins), the risk is 40-50%. These are interesting data but they don't indicate a correlation between the presence of a genetic anomaly and the beginning of the schizophrenia. In fact the percentage of risk, in homozygotic twins too, is far from 100%. [3]



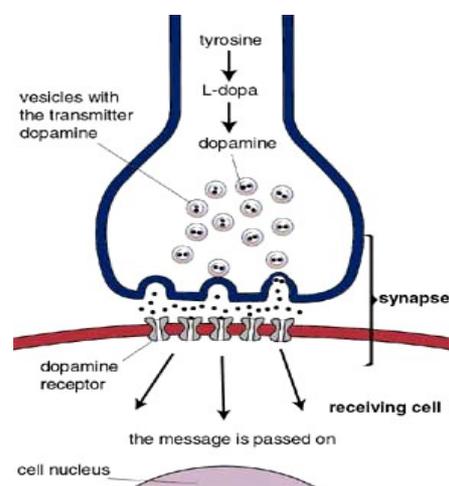
PET imaging showing areas of brain activity in twins - one schizophrenic, one not.

Alterations in brain chemistry

In the 50's of the past century one of the greatest discoveries of psychiatry was done: the chance of controlling and reducing the positive symptoms of schizophrenia through the administration of medicine called neuroleptics. At the beginning it was thought that this medicine could simply assuage the patients.

In the 70's it was proved that, on the contrary, this medicine had a more important therapeutic effect, specific on psychotic symptoms, mostly positive, of the schizophrenia. In fact if they were chronically administered they could control delirium and hallucination or make them disappear and in part, also the formal-logic dissociation of thought.

Later the action of this medicine called "antipsychotics of first generation", was found. It was connected to a drastic diminution in the brain of a particular neurotransmitter: the dopamine.



So, it was hypothesized, and the hypothesis was attested by many international studies, that in the schizophrenia it was present an anomalous quantity and cerebral circulation of dopamine, a neurotransmitter that makes two main actions: on one hand it regulates the behaviour of adaptation and the world of emotions that are associated with this behaviour; on the other the co-ordination of the movements. An abnormal increase of dopamine would cause a unbalance in the adaptive behaviour (eat, drink, search for gratification, avoid dangers etc.). On the contrary a diminution would compromise the movements (it was proved a deficit of dopamine in Parkinson disease. [4])

So the unbalance for excess of dopamine is one of the neurochemical causes of the schizophrenia. From antipsychotics medicine it was important to identify the dopaminergic receptors.

The D2 receptors are in the caudate and limbic system neurons, particularly in the nucleus accumbens, in the amygdala, in the hippocampus and in part of the cerebral cortex. They have a high affinity for the antipsychotics and they are considered the main place to explain the therapeutic action of this medicine. It is important to underline how the power of the typical antipsychotics in subjects with schizophrenia is strictly correlated to their affinity for the D2 receptors. The idea that an excessive dopaminergic transmission could have an important role in the pathogenesis of the schizophrenia was, in the past, supported by other proofs.

- Substances that increase the level of dopamine (DA) like cocaine and amfetamin, can cause the same psychotic symptoms of some forms of schizophrenia.
- Antipsychotics block the D2 receptors and forbid the psychotic manifestation caused by amfetamin.

Moreover a subtype of D2 receptors is still more interesting because it can be found in the same dopaminergic neurons, both in cell body e synaptic terminations.

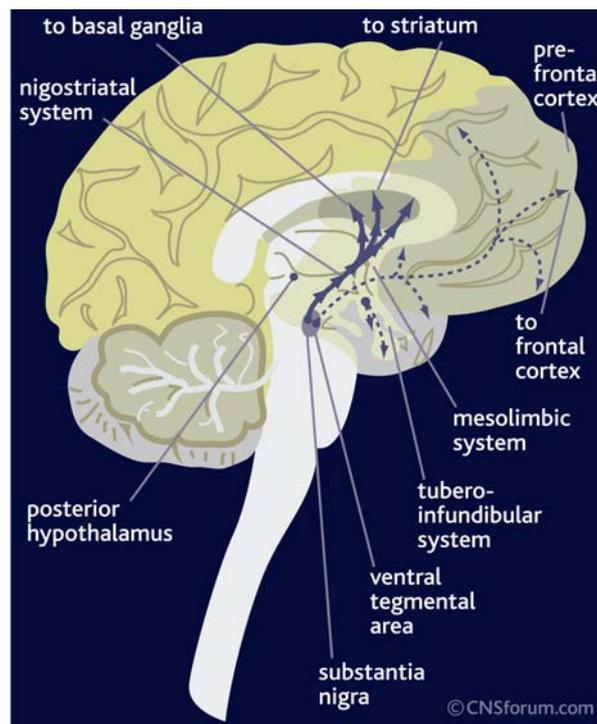
Its function is to act like inhibitor autoreceptor and to control both the electric activity of the dopaminergic neuron and the synthesis of DA and its releasing in the synaptic space. These dopaminergic autoreceptor, if stimulated, reduce the activity of the tyrosine hydroxylase and regulate the release of DA in the synaptic space, reducing the electric activity of the dopaminergic neuron.

Many research on animals show that the dopaminergic agonists like the apomorfina, if administered in low dosage, activate principally these autoinhibitor receptors, reducing the function of the dopaminergic system.

Today there are many convincing proofs that make us believe that in the schizophrenia there are two different alterations of the dopaminergic transmission and they suggest: an increasing activity

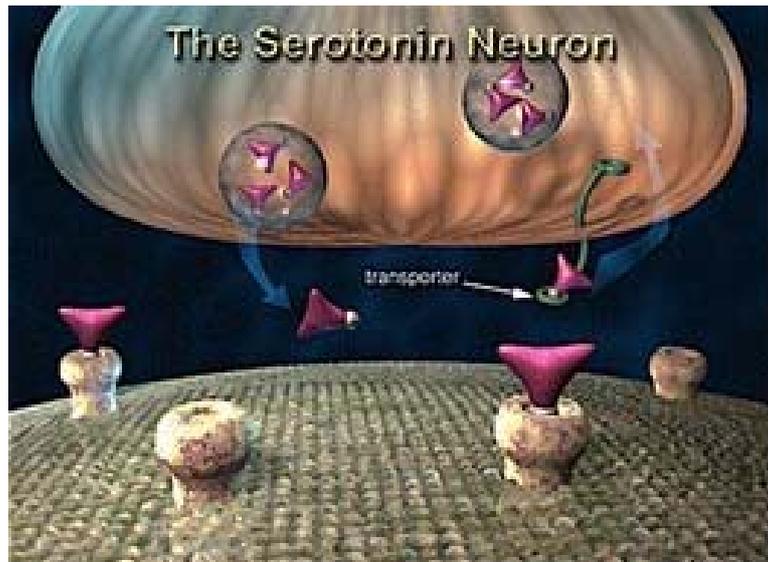
in the mesolimbic part of the dopaminergic system (involved in the control of emotions and memory) that can explain the positive

- symptoms and can be corrected by typical antipsychotics;
- a diminution of the dopaminergic activity in the pre-frontal area (involved in the motivation and ability to organize oneself, in the temporal organization of behaviour, in the attention and social behaviour) that can explain the negative symptoms and that is not modified by typical antipsychotics.



But as a high percentage of patients don't answer in a satisfactory way to the classic neuroleptics, we can say that the dopaminergic hyperactivity is not a common characteristic in all the patients. Because of the limitations of dopaminergic theory, it was supposed that other systems could contribute to the pathogenesis of schizophrenia. In fact other research proved that it's not only the dopaminergic system to have a role in the aetiopathogenesis of the disease.[5]

Through the experimentation of new medicine called "antipsychotics of second generation" that reduce the collateral effects of the first ones (mostly the compromise of movements) and act with efficacy both on positive and negative symptoms, it was proved that schizophrenia is caused also by the alterations in the production of another neurotransmitter, the serotonin that regulates sleep and dreams, body temperature and co-ordination of intestinal functions.



Different research pointed out that the serotonin has a chemistry structure similar to the LSD, one of the strongest hallucinogenic drugs, supposing that an excess of this neurotransmitter could be joined to the hallucinatory symptomatology of schizophrenia. In fact the block of 5-HT_{2A} is a common characteristic of the atypical antipsychotics.

Other biochemistry hypothesis for the schizophrenia are:

❖ GLUTAMATE HYPOTHESIS

- In the brain of schizophrenic patients there are structural and functional alterations in the cerebral cortex where the glutamate is the main neurotransmitter. There is a lower glutamatergic functionality.
- The phencyclidine, antagonist of NMDA receptors, induces psychotic symptoms, but it also produces the negative symptoms and the cognitive troubles of schizophrenia, that is, the most important peculiarities of the disease. In fact the abuse of phencyclidine, can cause hallucinations, deliriums, troubles of thought, cognitive troubles and less social interaction.

❖ ADRENERGIC HYPOTHESIS

- In schizophrenic patients there is a degeneration of the central noradrenergic neurons;
- In the brain of these patients the levels of dopamine beta-hydroxylase, that catalyzes the reaction that changes the dopamine into noradrenaline, gets lower.
- Moreover, the clozapine increases the plasmatic concentrations of NE in schizophrenic patients

❖ **CHOLINERGIC HYPOTHESIS**

- The anticholinergic (scopolamine) produce hallucinations
- The muscarinic receptor antagonists inhibit the answers in the test of active conditioned avoidment and reduce the climbing behaviour by apomorfina.

❖ **GABAERGIC HYPOTHESIS**

- deficit of inhibition on dopaminergic transmission
- Infusion of agonists GABA in some areas of the brain causes assuagement, catalexis (globus pallidus), aggressiveness and more appetite (VTA)

❖ **OPIOID HYPOTHESIS**

- The endorphine causes antipsychotic effects.
- The morphine inhibits the answers in the test of active conditioned avoidment.

To end, the latest news about the neurotransmittitorial alterations joined to the schizophrenia, point out the primary role of dopamine and serotonin, but above all of all the cerebral neurotransmittitorial system: it is the whole system that becomes (or it already is) dysfunctional and so the mechanism of action of the medicine involves more than one neurotransmitters so to balance the system and to avoid as much as possible the collateral effects due to a too much selective action on just one element.[6]

Anomalies of the brain structure



For some time it has been proved the presence of anomalies in the structure and working of the brain in people with schizophrenia (or it would be better to say in some of these people). Through more and more sophisticated research and techniques of cerebral visualization it has been possible to study the brain after death but also in living patients. In particular, various research done with T-Scan and RMI have pointed out structural anomalies in many patients, especially asymmetry of brain and in the ventricular apparatus of frontal lobes and left hemisphere, often correlated to a symptomatology of negative kind. According to some research, this symptomatology is associated with an alteration of the left temporal lobe (atrophy). In more than 80% of the patients, the SPECT, shows a diminution of blood-flux in frontal lobes.

Further research done with traditional techniques as the electroencephalogram (EEG), showed anomalies as an excessive cerebral answer to the stimulus (repeated sounds, intermittent lights) and difficulty in filtering stimulus: the brain of many schizophrenic patients seems to have a bad capacity to select information and to activate itself in a differential way according to the entity of the stimulus, "excluding" the undesired ones. In fact it seems that there is a deficit in specific cerebral cells, the inhibitor interneurons, that work like a filter for the stimulus coming from outside. This deficit cause an excessive exposure and vulnerability towards the stimulations that reach the brain. Anyway, the only structural and functional alterations don't cause necessarily schizophrenia.

Alterations of neurodevelopment

The brain is a plastic organ whose cells develop and organize themselves according to the genetic information and the relation to the environment. In some cases, a defect in the neurologic development, due to a premature trauma or to a disease, can cause schizophrenia. It was proved that in this process some alterations of the development during the pregnancy have an important role, especially in the second quarter: the complications during the pregnancy or the childbirth especially the perinatal hypoxia (that is the lack of oxygen in the foetus during the childbirth), that increase 2-3- times the probability of developing the disease; an eventual disease of the mother during the pregnancy, especially viral disease. Anyway, the precocious damage doesn't manifest immediately its effects but only after the following maturity of some systems of neurons, during the adolescence. Various environing stressing factors can favour the beginning or the relapse of the symptoms in weak people. Some examples are stressing events of life like the end of a relationship, leave home, find a job or study at university and factors like abuse of drugs. Family tensions can be caused by the frequent exacerbations of the disease. The beginning, the remission and the recurrence of the symptoms are the result of the interaction between "vulnerability" and environing stressing factors.

The “vulnerability-stress model”, points out that the schizophrenia manifests in people with a neurologic vulnerability. The vulnerability, as already said with regard to the theories that are at the basis of the development of the disease, can involve a genetic inclination, intra-uterine complications, during and after the childbirth, viral infections of the nervous system, the malnutrition of the pregnant woman, the influenza during the second quarter of pregnancy and the incompatibility of Rh in the second or in the following pregnancy.

Recently it has been proved that the use of cannabis is correlated to the risk of schizophrenia. According to a Danish research published on the British Journal of Psychiatry, about half of the patients treated for a mental disorder caused by the use of marijuana, develops a schizophrenic disease and one out of three of these patients is afflicted with paranoiac schizophrenia. Researchers gained information about 535 patients treated for psychotic symptoms due to cannabis. This information have been compared to the ones about 2.721 patients treated for schizophrenic disorders, but without health-problems caused by drugs. The researches discovered that the 44,5% of the patients of the first group were diagnosed with a schizophrenic disorder. Moreover these patients developed schizophrenia more precociously in comparison with the others: in men the disease manifested at 24,6 years old, against the 30,7 of the control group. The same was for women: the average was 28,9 against 33,1. But the team points out that the research doesn't consider the cannabis as the cause of the development of schizophrenia, but the use of this drug can increase the progression of the disease. It seems that the use of high quantity of cannabis during the adolescence (14-20 years old) could interfere with the neuronal development (that is still going on during that age) and so increase/cause the disease. [7]

RECENT DISCOVERIES ABOUT THE AETIOPATHOGENESIS OF SCHIZOPHRENIA

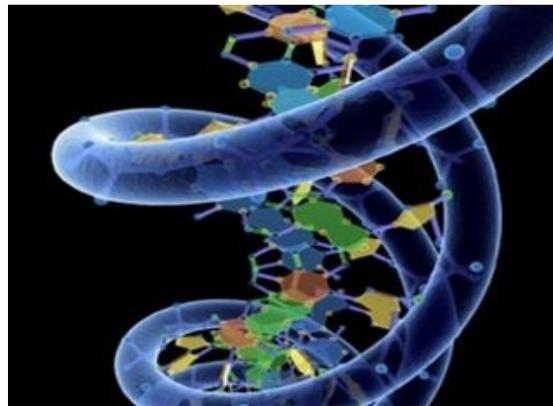
Deletion in the microRNA correlated to schizophrenia

At the basis of schizophrenia and other psychiatric and neurologic disease could be hidden anomalies of the micro RNA, molecules that regulate the expression of many genes. A group of researchers of the Columbia University Medical Center discovered in a murine model an alteration in the production of the micro RNA that was unknown till now. The scientists have developed a branch of rats that are carriers of a microdeletion (22q11.2) correlated to a high risk of developing schizophrenia and they observed the expression of more than 30.000 genes in specific areas of the brain. Analyzing the results, researchers hypothesize that the gene Dgcr8 could be responsible of the microdeletion 22q11.2. So they developed another branch of rats defective for this gene and they had a confirmation to their hypothesis.

In facts these last rats, studied with cognitive, behavioural and neuroanatomical tests, showed to be carriers of the typical deficit that strikes people afflicted with schizophrenia. People who are carriers of the microdeletion 22q11.2, have a high risk of developing schizophrenia. With a deep analysis of the chromosome it was observed that with regard to the genetic expression, this anomaly of the microRNA can be associated with behavioural and neuronal deficit, typical of the disease. This research shows the existence of a new group of genes that influence the predisposition to the disease. The micro RNA with altered functionality because of the microdeletion 22q11.2, acts on these genes.

It is also possible that other microdeletions could have the same effects. [8]

A gene, molecular sculptor, at the basis of schizophrenia



It has been discovered a variant of the gene that codify for the potassium pump, that can cause neuronal rigidity and increase of 2% the risk of developing the disease.

A research made at the University of Bari, in co-operation with the laboratory Gene Cognition and Psychosis Program del National Institutes of Mental Health (Nih) of Bethesda, Maryland, United States and published on Nature Medicine, discovered a gene that behaves like a “molecular sculptor”, changing the structure of some areas of the brain and this gene is supposed to be more present in the schizophrenic patients.

Analysing the variants of the gene that produces the potassium channel on 1.100 schizophrenic patients and 1.700 healthy subjects and investigating the brain of schizophrenic patients in comparison with healthy subjects, through magnetic resonance, the researchers concluded that the increase of the variant of the gene could cause an alteration in the brain structure, particularly a reduction of the volume at the level of the hippocampus and of the pre-frontal cortex.

With regard to the activity of the single neurons, the researchers discovered that in schizophrenic patients the protein of the potassium channels is modified and this would cause a “neuronal rigidity”, increasing of 2% the risk of developing schizophrenia.

It would be possible to develop more specific medicine with less collateral effects. [9]

Prognosis

The majority of the researchers consider that the course of the schizophrenia is generally chronic and that the worsening and remission of the symptoms alternate. They rarely observed the disappearance of symptoms. We have to say that the course of the disease is influenced by the scarce flexibility of therapeutic answers and by the hard relational and social integration due to the “stigma”. The prognosis of one year depends on the acceptance of the therapy. For longer times, the prognosis changes. One patient out of three gets a significative and lasting improvement; one patient out of three get a certain improvement but with intermittent relapses and a residual disability; one patient out of three has a serious and permanent disability. The factors associated with a favourable prognosis are: a quite good premorbid functioning, a tardy and/or acute beginning of the disease, a family anamnesis of mood troubles more than schizophrenia, a very little cognitive compromission and the belonging to the paranoid subtype or without deficit. The factors associated with a unfavourable prognosis are: a precocious beginning of the disease in young age, un inadequate premorbid functioning, a family anamnesis of schizophrenia and the belonging to the disorganized subtype with many negative symptoms. The mail sex has a more unfavourable prognosis than the female sex; women have a better answer to the treatment with antipsychotic medicine. We must remember that schizophrenia can be associated with other mental disorders. If it is associated with obsessive-compulsive symptoms it has a unfavourable prognosis; if it is associated to a borderline disorder of personality it has a better prognosis.

THE TREATMENT OF SCHIZOPHRENIA

Patients with schizophrenia tends to show psychotic symptoms for 12-24 months before asking for a medical care. The time between the beginning of the psychotic symptoms and the first treatment called “period of non-treated psychosis“ is correlated to the quickness of the answer to the initial treatment, to the quality of the answer and to the seriousness of negative symptoms. When the patients are immediately treated, they answer more quickly and in a more complete way. The general purposes of the treatment are: reduce the seriousness of psychotic symptoms, prevent the relapses of symptomatic episodes and the functional deterioration associated to them and help the patients to get a functional level as high as possible.

The interventions to do are:

- Admission to hospital. Subjects who had evident symptoms of schizophrenia can ask for an intensive treatment, that includes the admission to hospital. It is necessary to treat serious deliriums or hallucinations, serious suicidal intentions, inability to take care of oneself or serious problems with alcohol and drugs.
- Farmacological treatment. The principal medicine used for schizophrenia are called antipsychotics. They help to treat the positive symptoms and correct the chemistry unbalance that makes cerebral cells communicate. As it happens with the medical treatment used for other psychic troubles, many patients with serious mental disease must try different kinds of antipsychotics before finding the medicine or the combination of medicine that produce a positive effect.

The treatment of schizophrenic disorders is divided into three main phases:

- *acute phase*: it controls the symptoms of the acute psychotic episode (psychomotor agitation, hallucinations, deliriums) and it lasts about 6-8 weeks;
- *phase of stabilization*: it consists of the prosecution of the antipsychotic treatment with a full dosage for at least 6 months;
- *phase of maintenance*: it consists of the prophylaxis or prevention of the relapses.

This phase, especially in subject with an multiepisodic clinic history, should go on for at least 5 years and indefinitely in case of patients who have a family to support or a clinic state of health particularly serious.

- **Acute phase**

In the light of an acute psychotic episode, we should consider fundamental variables before choosing a medicine: the eventuality that the patient could develop extra-pyramidal collateral effects (or hypotensive reactions) and the risk of a iatrogenic deterioration of the global symptomatology. So, it is important to consider the symptomatologic characteristics of the acute psychotic episode to decide the correct medicine. It is usually good to start the therapy using one antipsychotic although in some cases (used as nocturnal soothing and to control aggressiveness and/or agitation) it seems to be better the association of neuroleptics with a different power of action or neuroleptics and new mixture.

- Phase of stabilization

The phase of stabilization of the neuroleptic treatment hasn't been considered yet in its specific and complex aspects and the data about it are not enough, principally with regard to the relation between this phase, the evolutive characteristic of the disease and the global management of the patient. Probably, after an acute episode, modifications of the cerebral neurochemical pattern might occur, partly due to the intrinsic evolution of the disease and partly secondary to the pharmacodynamic action of the neuroleptics that control dopaminergic hyperactivity.

This fact could explain the reason of a higher risk of mood depression and suicide during this phase and also the risk of psychotic relapses. In this context the "atypical" mixture have a privileged role. They are characterized by a high pharmacodynamic "eclecticity" and they easily adapt to the heterogeneity of the symptoms and symptomatologic seriousness of schizophrenic disease and to the evolution of the different psychopathologic cases after the remission of the acute episode, because they can stabilize the clinic situation better than others.

- Phase of maintenance

The main purpose on this phase is to prevent relapses, to reduce their number, frequency and the intensity and to try to stop or make the schizophrenic process slower. The medicine and the dosage must interfere as little as possible with the residual emotional and cognitive capacity of the patient, trying not to expose him to risks of serious collateral effects (as the tardy dyskinesia, whose incidence is between the 4% and the 5%) or to a negative syndrome, secondary to the neuroleptics themselves. The neuroleptics atypical are very interesting for a long-term therapy.

An aspect that can favour compliance and acceptance of the therapy is the positive influence that the atypical medicines seem to have on the cognitive side of schizophrenia. The alteration of the cognitive sphere is not only a characteristic of this disease but it is probably also the consequence of the strong and long dopaminergic block that the neuroleptics cause in the central nervous system. The atypical antipsychotics, produce a lower dopaminergic block and can increase through the block of receptors 5 HT₂, the dopaminergic release in the prefrontal cortex. They seem to improve the cognitive symptoms in patients who were treated with neuroleptics for a long time and they also could be able to prevent, in part, the neurocognitive deterioration if used from the beginning of the disease.

- Psychologic and social rehabilitation. The research shows that schizophrenic subjects who follow structured psychologic and social programmes of rehabilitation and keep on taking medicine, are able to control the disease better and obtain a better quality of life. The purpose of the therapy is to develop a collaborative relationship between, the patient, his family and the doctor, so that the patient can learn to understand and control his disease, can take the medicine according to the prescriptions and can control better the stress too.

Antipsychotics



The terms antipsychotic and neuroleptic define a group of medicine principally used to treat schizophrenia, but they are also efficacious for other psychosis and in states of psychic agitation. They have an anti-delirious and anti-hallucinatory action and they can be administered by mouth, with intramuscular and intravenous injections. A right dosage reduces delirium, hallucinations and diverting behaviour and favours the social integration. Taken by a healthy subject, this kind of medicine doesn't act as sedative but produces an extreme indifference to the environment stimulus and a very strong emotive apathy. It doesn't cause dependence and it isn't much toxic, but can produce important collateral effects. During the first years of the '900, it was discovered that a derivative of aniline, the promethazine, had important sedative and anti-allergic properties. From this substance derived the chlorpromazine, that at the beginning was used as sedative. Henry Laborit found out that this derivative could cause a particular indifference to the environment stimulus without altering the state of vigilance. Thanks to the great commercial success of the chlorpromazine, the research of new neuroleptic had begun by now and after about 10 years almost all the most important classes of antipsychotics that we have today were individuated and produced. They are: phenothiazines very similar to the chlorpromazine, but also thioxanthenes, dibenzoxazepine, butyrophenones, diphenylbutylpiperidine and more. There was also the introduction of new antipsychotics, with a great affinity for dopaminergic and serotonergic places as *risperidone, clozapine, olanzapine, quetiapine, aripiprazol*.

The antipsychotics are divided into two classes: *classic or typical and atypical*

“Typical” antipsychotics

They were introduced in the 50’s and all of them could treat the positive symptoms of schizophrenia.

This medicine block the dopamine receptor (type 2) and they can be classified “of high, medium and low power”. The specific medicine is chosen considering first of all the collateral effects, how to administer it and the previous answer of the patient to the medicine. Some of the classic antipsychotics are available as depot preparations with a long lasting action, useful principally to exclude a hidden pharmacologic non-compliance that could be the cause of symptomatologic exacerbations and lack of answer to the medicine. They can be useful also for patients who can’t take medicine everyday. Classic antipsychotics are associated with collateral effects as *sedation*, *acute dystonic reactions*, that include spasm of facial muscles and stiff neck, *syndromes similar to Parkinson*, characterized by a general slowing of voluntary movements, *akinesia* with facial mask, rigidity, trembling at the upper limbs, *akathisia*, that is the need to be always in motion, *tardive dyskinesia*, associated with long lasting treatment. They appear more frequently in elderly people and they are characterized by stereotyped and repeating movements orobuccal and choreiform movements the extremities, *raising of prolactin and weight*. The most serious complication that neuroleptics medicine could potentially cause is the “*neuroleptic malignant syndrome*”. A high parenteral dosage of *phenothiazine* or *haloperidol*, can cause this syndrome. The warning signs are: rigidity, rabbit syndrome, restriction of the throat, absolute akinesia or an incoercible agitation, deglutition troubles, profuse transpiration, tachycardia and mutism. The worrying signals are a persisting fever, during the 24 hours without an infectious cause.

The state of conscience is often perturbed, the patient is stupefying, obnubilated and he can easily evolve to coma; once the syndrome has begun it develops in 24-72 hours and the death can supervene suddenly with an isothermal pallor syndrome caused both for cardiovascular collapse and respiratory insufficiency. In particular the exams show a leucocytosis and an increase of muscular CPK that represents the best element to think of a malignant syndrome due to neuroleptics. It is necessary to suspend the administration of neuroleptics, to move the patient to an intensive care with a symptomatic treatment with a correction of metabolic deficit and cardiorespiratory treatment; it is also necessary to do a treatment with dopaminergic antagonists as *bromocriptine 15-30 mg/die (Parlodel)*. [10]

“Atypical” antipsychotics

The introduction in clinical practice of antipsychotics of new generation or “atypical antipsychotics”, has made it possible to make a great progress in the treatment of schizophrenia in comparison with the classic neuroleptics and it has also made available many molecules strictly associated with the physiopathology of this disease. They can be tolerated better than the other antipsychotics. In particular they cause extrapyramidal symptoms less often than the older antipsychotics. For most of the patients with schizophrenia, this medicine have more efficacy and less collateral effects than the conventional ones. From a pharmacodynamic point of view, the main characteristic of the atypical molecules is to link with less affinity the dopaminergic receptors D1 e D2, but to link with more affinity other receptors, as the serotonergic 5-HT_{2A}, adrenergic and histaminergic explaining the less incidence of extrapyramidal side effects (Extra-Pyramidal Symptoms, EPS) caused by the block of receptors D2 .

Moreover, the use of atypical molecules doesn't cause an increase of prolactin. In fact, this collateral effect, associated with the classic antipsychotics, cause a series of sexual and reproductive troubles; this can be related to the reduced block of dopaminergic receptors, that control in a inhibitory way the release of prolactin at the tubero-infundibolar level. It was also emphasized the importance of the constant of dissociation of these antagonists on the dopaminergic receptor, pointing out that, during the receptorial block, the more is the time spent to stimulate the receptor by the endogenous DA, the less is the risk of collateral effects.

But the less incidence of collateral effects is not the only advantage of this class of medicine. In fact it has been proved that, in part, these molecules are active in those patients who didn't respond to the therapy with classic antipsychotics and can oppose the cognitive deficit of schizophrenic patients. The atypical neuroleptics are characterized by a higher affinity towards the receptors 5-HT₂ in comparison with dopamine D₂ receptors and this affinity is very important to consider a medicine belonging to the class of the atypical.

Another characteristic of the atypical medicine is the multireceptorial profile: in fact, this medicine act together with serotonergic, cholinergic, adrenergic e histaminergic receptors although with different affinities. Moreover it is important to point out that beyond the similarities there are also differences among these molecules of new generation, principally in the interaction with the **serotonergic** receptors 5-HT_{1A}, 5-HT₆ e 5-HT₇ and the muscarinic cholinergic receptors.

Research in experimental neurobiology suggested that the efficacy of atypical antipsychotics is in part due to the capacity of this medicine to stimulate the neuronal trophism, to cause neurogenesis and in general to have protecting effects.

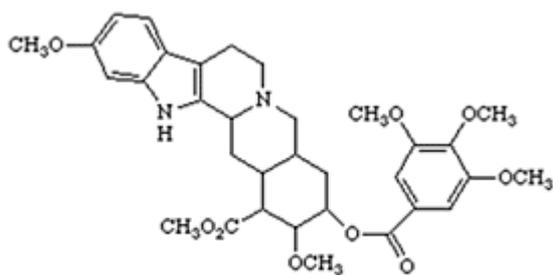
The improvement of global cognitive functions due to atypical antipsychotic could be secondary to the reduced collateral effects and to their higher efficacy on negative symptoms. Generally, the atypicals have showed a best efficacy in the tests of verbal production, fine motory control and executive functions in comparison with the classic neuroleptics.

A common characteristic of antipsychotics is the necessity of a long treatment for many weeks to have a therapeutic effect. This observation suggest that the effects of this kind of medicine is indirect and that its actions don't depend on the initial phase of the treatment but to a following phase of adaptation. Today the molecular mechanisms that characterize this phase of adaptation are not know yet but they probably involve changes in genetic transcription.

The atypical antipsychotics are:

- first quality medicine for schizophrenia of new diagnosis;
- an alternative in the treatment of acute episodes of schizophrenia;
- helpful in patients that don't tolerate the undesired effects of conventional medicine;
- advisable in case of relapses when the conventional therapy can't control adequately the symptoms

The first antipsychotic used in clinic: the reserpine.



Reserpine

It is an alkaloid obtained by the roots of *Rauwolfia Serpentina* and it was one of the first antipsychotics used in the 50's parallely with the phenothiazine and today it has a historical importance.

The sedative effect of reserpine

The reserpine, because of its lipophilicity, goes easily through the hematoencephalic barrier and it acts as sedative on the CNS causing depletion of noradrenaline .

Mechanism of action

It inhibits the peripheric sympathetic transmission blocking the cytoplasmatic transporter of amine, among them the noradrenaline, that takes these amine to the presynaptic vesicle. The noradrenaline accumulates outside and it is quickly degraded by the MAO.

Collateral effects

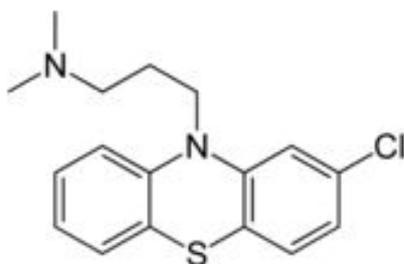
Extrapyramidal disorders, sleepiness, low blood pressure, vasodilatation, bradycardia, vertigo, ulcer, diarrhoea, psychic depression that can take to suicide, sleep disorders, impotence (in men), amenorrhoea (in women).

TYPICAL ANTIPSYCHOTICS

- **Phenothiazines:** aliphatic , piperidinic, piperazinic
- **Thioxanthenes:** thiothixene
- **Butyrophenones:** haloperidol
- **Diphenylbutylpiperidine:** pimozide
- **Dibenzoxazepine:** loxapina
- **Dihydroindolone:** molandone

Phenothiazine

There are many phenothiazine that differ among them for a certain elective nature action and for a greater or less incidence of collateral effects.



Chlorpromazine

The chlorpromazine is the prototype of the phenothiazines and the neuroleptics in general.

Its introduction in psychiatry in the 50's, opened the age of psycho-pharmacology in the treatment of psychic disorders, especially of psychosis. Thanks to it the condition of many psychiatric patients is notably improved so to favour a new integration of many of them and reduce admissions to hospital in mental hospitals (and today the abolition of them).

Mechanism of action

The phenothiazines act selectively on the reticulated substance, inhibiting the activating functions that this structure has especially on the cortical nerve centres. From a biochemical point of view, the phenothiazine interfere with the functioning of the chemical mediators of the CNS. In particular they block the dopaminergic receptors.

Classification

From a chemical point of view the phenothiazines can be divided in different groups; the most important are:

- a. **aliphatic:** chlorpromazine, promazine;
- b. **piperidinic:** tioridazine
- c. **piperazinic:** fluphenazine, tetilperazine, prochlorperazine, butirilperazine

Pharmacokinetic

The absorption of chlorpromazine orally administered depends on the kind of preparation, the peak of plasmatic level is generally reached 3 hours after the administration although there is a great variability among the subjects. The plasmatic levels can be reduced in a significant way by the presence of food in the stomach and by the contemporary administration of anticholinergic and antiparkinson.

Although plasmatic life is short, the metabolites of chlorpromazine are excreted with the urine during the two or six weeks after the end of the administration. More than 90% of the medicine is bound to the proteins. The chlorpromazine seems to concentrate in the CNS 4-6 times more than the plasma. This explains the persistence (for months) of its effects, even after the suspension of the treatment. The chlorpromazine is metabolized at the hepatic level and excreted both with urine and faeces. Some of the metabolites are inactive, others keep the pharmacologic properties of the chlorpromazine and contribute to its biological activity.

Effects on organic systems.

✓ Central nervous system

The chlorpromazine can act at different levels of the central nervous system. Its action at the cortical level is particularly interesting, because psychiatric disease treated with this medicine involve the high mental functions. Nevertheless, according to the present knowledge none of the experimental or clinic observations (electro-encephalogram, biochemical alterations) can be directly correlated to the therapeutic action of the medicine. Another place of action that could be important for the therapeutic effect of the chlorpromazine, is the limbic system, made of different cerebral nucleus inter-connected. It is very important for the control of emotiveness and the instinctive behaviour. The chlorpromazine has less important effects on the medulla oblongata, although a high dosage can depress breath centres. Such an action is modest and manifests just in case of intramuscular or intravenous injections. On the contrary the chlorpromazine has a strong action on vomit centres, it can prevent the vomit induced by apomorfina and by hydrogenated derived of ergot alkaloids. The antiemetic effect is already obtained with a very low dosage of medicine and it is of central nature. In fact substances or stimulus that cause vomit, acting at gastric level are not antagonized by chlorpromazine.

✓ Autonomic nervous system

The effects on the autonomic nervous system are complex, as expected by a drug with antidopaminergic, antiserotonergic, anticholinergic, antihistaminic, and antiadrenergic properties. Among the most common effects we remember the decrease of perspiration and salivation and the inhibition of ejaculation without interference on the erection.

✓ Cardiovascular system

The actions of chlorpromazine on the cardiovascular system are complex because the medicine has direct effects on heart and vascular system and indirect effects on the central nervous system and on autonomic reflexes. In a normal man the administration of chlorpromazine causes orthostatic hypotension and reflex tachycardia. Although one develops tolerance for the hypotensive effect, a certain orthostatic hypotension is always present. Few cardiotoxic effects have been observed principally in young patients.

✓ Kidney

The chlorpromazine can have a diuretic effect due both to the lower secretion of the anti-diuretic hormone and to inhibition of the reabsorption of water and electrolytics caused by the direct action on the renal tubule. The lowering of pressure observed often after the administration of chlorpromazine is not associated with a significative reduction of glomerular filtration. On the contrary there is a tendency to increase of renal flux.

✓ Liver

This medicine don't have particular hepatic effect except occasional reactions of hypersensibility (obstruent icterus). A certain caution is recommended only in patients with persistent hepatic troubles.

✓ Endocrine system

As said before, the effect of chlorpromazine on the hipothalamic activity results from important changes of the endocrine system. Frequently there are amenorrhoea, galactorrhoea, gynaecomastia. The chlorpromazine also reduces the secretion of the adrenocorticotropic hormone (ACTH) and so the circulating levels of adrenocorticosteroids decrease. The corporal growth is inhibited because of the inhibition of the growth hormone (GH); this effect is utilized in the treatment of the acromegaly. On the contrary weight and appetite are increased by the medicine.

✓ Metabolic effects

The chlorpromazine icreases significantly the plasmatic concentration of cholesterol.

✓ Cutaneous reactions

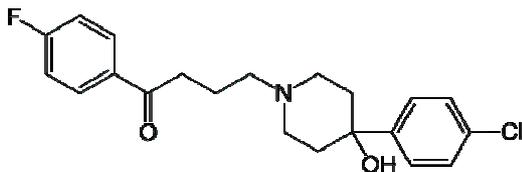
Skin reactions are frequent enough; urticaria and dermatitis occur in the 5% of the patients. The most frequent form is a photosensitization that appears like a sun burn and that can be prevented using sun creams with a high protective factor, avoiding the exposure to the sun light.

✓ Tolerance and physical dependence

The chlorpromazine gives a little tolerance and physical dependence; during the days following the suspension of the drug myalgia, troubles to get asleep, aspecific symptoms of malaise occur. The tolerance develops principally towards the sedative effects of the drug.

✓ Toxic actions

The phenothiazine have a therapeutic index that is high enough, so they are a kind of medicine relatively safe, although some rare cases of death caused by overdose have been reported. [15]

Butyrophenones**Haloperidol**

Prototype of this class: haloperidol. It was introduced in the treatment of psychosis in 1958 and it is a strong antipsychotic, efficacious in the treatment of schizophrenia and the maniacal phase of the maniacal-depressive disease; the mechanism of action is similar to the phenothiazines. The haloperidol calms the patient and induces sleep in agitated patients; the sedative effect is less strong compared to the chlorpromazine. They have in common many negative effects on the secretion of hypophysial hormones, caused to the same mechanism of action, that is the block of dopaminergic transmission. Another field of utilization of the haloperidol is the so-called *neuroleptoanalgesia*, a preanesthetic medication used in surgery administering the haloperidol associated with strong analgesics (generally morphine derivatives). Such kind of procedure make the general anaesthesia safer in cardiopaths patients and sometime make surgical operations possible on subjects in a conscious state. This is a very advantageous condition in different neurosurgical practices and in otorhinolaryngology. The haloperidol, compared to the other antipsychotics, has less strong effects on the autonomic nervous system because its antiadrenergic and anticholinergic properties are less marked. Consequently its secondary cardiovascular effects are inferior.

Collateral effects and toxicity

The haloperidol produces strong extrapyramidal reactions (tremors, agitation, muscular spasms), so the treatment must be decided with caution, especially in younger patients. Serious hematologic effects (leukopenia, agranulocytosis) are very rare like icterus as well.

Cardiac toxicity of Haloperidol

In the light of some proofs of serious cardiac toxicity, the profile of tolerability of this medicine has been recently revalued. Results of case report and the systematic analysis of literature have made it clear the seriousness and the nature of this toxic effect: the haloperidol cause a QT interval prolongation and it is associated with cases of sudden death.

This events occur both with oral administration and intravenous injections with dosages that are considered therapeutic, both in schizophrenic patients and not.

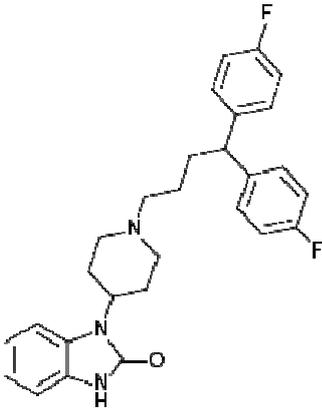
Among the molecular mechanism suggested to explain the effects of the haloperidol at the cardiac level, it was proposed the block of the K⁺ channels, responsible of the repolarization current IKR (inward rectifier) of the cardiac potential of action. In particular, it was observed that the haloperidol behaves like a strong blocker of this canal. A careful monitoring of the tract QT through the ECG is fundamental to control the cardiac toxicity of the haloperidol and decide a suspension of the medicine in case of alteration of the cardiac.

Even though we have many information about the cardiac toxicity of the haloperidol, this drug is still used in clinic practice, also in extra-hospital environment where to monitor carefully is not possible its effects on the QT and the possible appearance of arrhythmias associated to the prolongation of this interval.

Thioxanthenes

Clopentixolo and zucloptentixolo are strong and efficacious neuroleptics, with a pharmacologic profile similar to the phenotiazines, but with a longer action. In fact they are used for treatments of maintenance with a slow release. The clopentixolo is characterized by a block of the dopamine receptors D1 that is bigger than the block of the receptors D2 and a high affinity with the serotonergic receptors 5HT2. The medicine has a scarce adrenolytic, muscarinic and histaminic activity.

The clopentixolo is compounded of a third of Z-cloptentixolo, with a bigger antipsychotic activity and two third of E-cloptentixolo.

Diphenylbutylpiperidine*Pimozide*

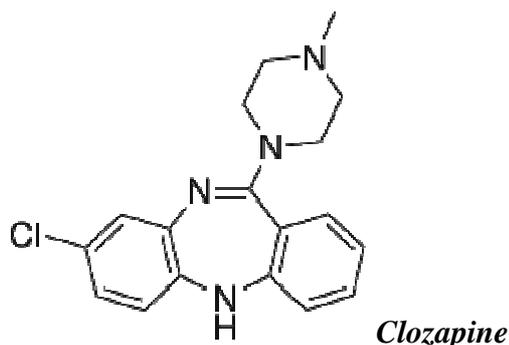
La pimozide is the prototype. It is an interesting medicine because it has a prolonged action (from a day to some weeks) after an oral administration. But the diphenylbutylpiperidine frequently causes extrapyramidal disorders, sleepiness, weakness, general malaise, spasms, galactorrhoea and it also has a sedative effect.

ATYPICAL ANTIPSYCHOTICS

- **Dibenzodiazepin:** clozapine
- **Benzamides:** sulpiride
- **benzisoaxazoles:** risperidone

Dibenzodiazepin

These drugs have more experimental than clinical interest because not always in the tests of laboratory they behave according to the established criterions for the drugs antipsychotics; they have scarce antidopaminergic properties. It's possible that these atypical actions are due to the fact that these drugs have a notable central antocolinergic activity.

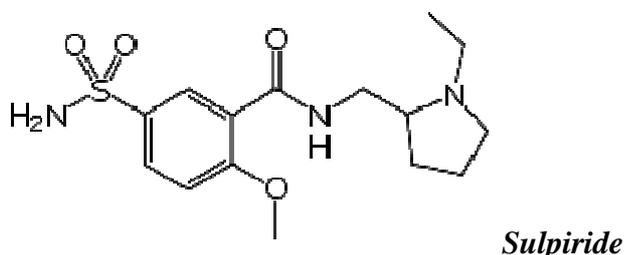


The clozapine, founder of the family and enough powerful antipsychotic, is effective in a percentage up to the 50% of the resistant patients to the conventional antipsychotics. The clozapine reduces the negative symptoms, it produces scarce or void motor adverse effects and are not the risk to cause tardive dyskinesia, but it produces other collateral effects as sedation, hypotension, tachycardia, increase of weight and increase of the salivation.

The clozapine can cause convulsions with a dose-dependent mechanism.

The more serious collateral effect is the agranulocytosis, that can be revealed in around 1% of the patients. This happens when thick doses of drug are used and it rise up within the first 8-12 weeks, the appearance can be sudden, for this to every symptom of infection (especially in the respiratory tract) it's necessary to perform an accurate hematological analysis. In fact for the first 18 weeks it's necessary to generally check the leucocyte counts and the clozapine it reserved to the patients that have unsatisfactory response to other drugs. [28]

Substituted benzamides



This is a recent therapeutic class of antipsychotics. The substituted benzamides represent a class of compounds characterized by analogous mechanism of action on the dopaminergic system, predominantly mediated by selective block of D2 receptors, but with a notable heterogeneity of clinical use.

The substituted benzamides currently in commerce in Italy are sulpiride (prototype of the class) amisulpride, levosulpiride, sultopride and tiapride, structurally analogous to metoclopramide (Plasil), drug with antiemetic and antidiarrheic action, had been using against nausea and vomiting and that, in sensitive patients (to es., children) or if used in prolonged times, it can cause extrapyramidal side effects. The substituted benzamides (particularly levosulpiride) maintain the antiemetic and antidiarrheic, procinetic characteristics of the metoclopramide, but, while to elevated dosing they involve as antipsychotics (through a block of the D2 post-synaptic receptors), to low dosing they show (particularly amisulpride) activating effect, that is attributed to a selective action on the D2 pre-synaptic receptor that determines an increase of dopamine release, involved in the antidepressant activity.

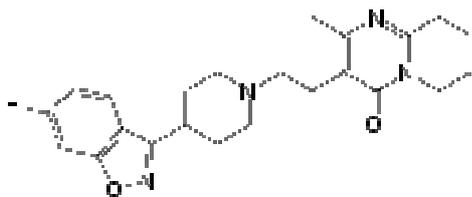
The substituted benzamides, as general class, show an elevated selectivity for the D2 receptors and few or nothing affinity for the D1 receptors and the serotonergic, noradrenergic, histaminergic and muscarinic receptors. In comparison to other antipsychotics the substituted benzamides have the advantage to cause smaller extrapyramidal effects, but more frequently they cause dyslexia and galattorrhea. The pharmacokinetics of the substituted benzamides results diversified: while the sulpiride and the levogire isomer, the levosulpiride, shows a very low (around 30%) bioavailability, the tiapride and the sultopride they have an almost complete absorption with great bioavailability.

The hepatic metabolism of the benzamides is very limited (to exception of the sultopride that suffers an elevated first pass hepatic metabolism) and such molecules are excreted, unmodified, by renal tract. Their elimination half-life is enough brief (around 4-7 hours) with exception of amisulpride, that reaches 17 hours. Notable differences of pharmacological (relatively to block of D2 receptors) power exist among various molecules. As regards the indications, also to forehead of the substantial described pharmacological homogeneity, the use of such drugs has peculiar clinical connotations. The sulpiride is used in numerous clinical indications, anxious and depressive disorders with visceral (to middle-low dosing) somatization, acute and chronic (to tall dosing) schizophrenia. The levosulpiride, that representing the active levogire isomer of the sulpiride can effectively be used to dosing around halves the sulpiride, is employed, to diversified dosing, in the dyspeptics syndromes, in the anxious or depressive somatizations, in the muscle-tensive cephalgia, in the control of the nausea and vomiting, as coadjuvant in the antidepressant therapies. The sultopride is primarily used as antipsychotic, exploiting the sedative action in the psychiatric urgencies, the states of psychomotor excitement, the acute delirious episodes and the confusional states, above all in the alcoholists. The tiapride finds indication in the choreic dyskinesias, in the cephalgic syndromes, in the behavioral disorders with nervousness and anxiety (to es., in the alcoholism and in the elderly), in the delirium tremens. The amisulpride is indicated in low dose in the treatment of the depressive disorders, especially in the dysthymic forms,

while, in high dose, it's used in the schizophrenia, showing effectiveness both on the positive and negative symptoms.

Benzisoxazoles

In this class there is Risperidone, that is a selective monoaminergic antagonist with unique ownership.



Risperidone

It derives from an extending search to focus on the drugs able to selectively stop the 5-HT₂ receptors, with the intention to discover a new classes of antipsychotics. A long series of these substances was discovered, between them the **ritanserin**, the **composed R41468**, the **ketanserin**.

These pharmacological agents opposed the action of the LSD and the mescaline, to in fact the effects of these psychomimetic depended on an interaction with the 5-HT₂ receptors. But the ritanserin and the ketanserin in the clinical trials mainly showed a strong action on the sleep, while the antipsychotic ownerships were scarce, in comparison to the haloperidol.

These two selective blockers of 5-HT₂ receptors improved the sleep in the neurotic depression, in the dysthymia and in the schizophrenia associated with depression, and so they contributed to improve the general state and the humor in the studied subjects. Although these two substances were not commercialized, they constituted the fundamental premise for the following development of the risperidone (Janssen 1998).

The **setoperone** was formulated, contemporarily to the ritanserin and the ketanserin, with the ability to block the D₂ receptors however too moderate, then the **pipamperone** was formulated and the compound **R64766** was synthesized in november 1984, a molecule that, in the rapes, it showed activity in all antagonism tests for the serotonergic 5-HT₂ receptors, and, equally of the haloperidol, it was active in all the antagonism tests for the dopaminergic D₂ receptors. The compound R64766 was baptized **risperidone**, the first serotonin-dopamine antagonist.

In comparison to the other antipsychotics, the initial studies showed that the risperidone had smaller neuroleptic effects: it induced catalexia to more elevated doses in comparison to the chlorpromazine, and already to clinically effective dosing it induced reduced extrapyramidal effects.

The risperidone has an elevated antipsychotic effectiveness combined with important abilities to improve the humor, the contact with the patient and to reduce contemporarily the existing extrapyramidal symptoms.

It became so the prototype of a new generation of drugs and it began to impose among the antipsychotics mostly prescribed. The risperidone also ties the adrenergic α_1 receptors and, with smaller affinity, the H₁- histaminergic and α_2 - adrenergic receptors, while it is not having affinity for the cholinergic receptors. The central antagonism balanced between serotonin and dopamine can reduce the risk of extrapyramidal side effects and to extend the therapeutic activity to the improvement of the negative and affective symptoms of the schizophrenia.

The risperidone is completely absorbed after oral administration reaching peak plasma concentration within 1 to 2 hours. The absorption is not influenced by food and thus risperidone can be given with or without meals. Risperidone is partly metabolized by the Cytochrome P-450 2D6 to 9-hydroxy-risperidone which has similar pharmacological activity to risperidone. Risperidone is submitted to N-dealkylation through another metabolic pathway.

After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is of 24 hours. In the greatest part of the patients. In plasma risperidone is bound to albumin and α_1 -acid-glycoprotein. The plasma protein binding of risperidone is 88%, while that of 9-hydroxy -risperidone is 77%. One week after administration, 70% of the dose is excreted in urine and 14% in feces. In urine, risperidone with 9-hydroxy-risperidone represents 35-45% of the dose. The remainder consists of inactive metabolites. [29]

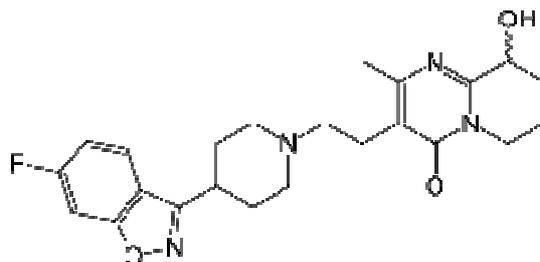
Aripiprazole

The pharmacology of aripiprazole is particular and innovative, it can be considered the first one of "new generation" of atypical antipsychotics, for the peculiarity of mechanism of action, that is unique in the typical and atypical class of antipsychotics. The preclinical study have shown that aripiprazole, quinolone-derived, acts as stabilizing of the dopaminergic and serotonergic systems, by partial agonist activity on the D₂ and 5HT_{1A} receptors and by 5-HT_{2A} receptor antagonist action.

The aripiprazole, as many antipsychotics, bound with high affinity to various dopaminergic receptors of family D₂, but, contrarily to other antipsychotics that acts as D₂ receptors antagonists, it is a receptor partial agonist. A partial agonist bound to dopaminergic receptors preventing the bond of the DA, but at the same time it cause a certain receptor activation, that is physiologically remarkable, however very more weak of that endogenous DA caused. Then, the postsynaptic receptor hyperactivity is modulated and stabilized, but not completely blocked.

The introduced clinical studies, which 1648 schizophrenic patients with acute episodes have participated, have shown that the therapy with aripiprazole allows a notable improvement both positive (hallucinations, deliriums) and negative (affective leveling, loss to like and of interest) symptoms, characteristic of this pathology. [32]

PALIPERIDONE



The risperidone is a very effective atypical antipsychotic in the delirious acute episodes, but that to tall dosing it behaves as typical antipsychotic. The risperidone is metabolized by the cytochrome P450, isoform CYP2D6, to the active metabolite paliperidone that, with the native drug, it shares the characteristics of antagonism on the receptors of the serotonin. (5HT_{2A}) and the dopamine (D₂), implicated in the schizophrenia. Inhibiting these receptors, the paliperidone contributes to the normalization of the cerebral activity and reduces the symptoms.

The dominant central antagonism of the serotonin can reduce the tendency of paliperidone to cause extra-pyramidal unwanted effects. The advantage of the use of the paliperidone, that has a pharmacological action independent of CYT P450, instead of the risperidone, it could be also due really to the fact that in such way a lot of due pharmacological interactions would be avoided to interference with the activity of the CYP2D6, that is known to have involved in the metabolism of the 25% of the drugs of commune therapeutic employment.

The paliperidone is available in a formulation to controlled release, able to increase the tolerability (demolition of the peak concentration) and to allow the once-daily administration, beginning the treatment with the effective dose, without necessity of titration, while the risperidone is administered twice a day.

Besides, the attainment of elevated hematic concentrations can be avoided, with consequent reduction of unwanted effects due to excessive block of the receptors D₂ (extra-piramydal effects, apathy, etc). The principal advantages of the paliperidone therefore they are represented by the reduction of the peak plasma concentrations and by the absence of metabolism by the CYP2D6.

This aspect can be particularly important for the psychotic patients that, on one side, being often strong smokers, they could manifest an increased metabolic activity for xenobiotics because of the induction of numerous isoforms of the CYP450 by some components of smoke, and from the other, being also often in treatment with drugs (to es. antidepressants) inhibiting of the CYP450, they could have a reduced metabolic activity. For these reasons, the paliperidone can be suitable for the elderly patients, also in presence liver insufficiency.

The drug that contains the active principle paliperidone is INVEGA, a racemic mixture of (+) and (-) paliperidone, whose pharmacology activity is qualitatively and quantitatively very similar. It is suitable for the treatment of schizophrenia, before approved in 2006 in the United States for the treatment of acute schizophrenia, then in the March 2007 for the maintenance treatment of schizophrenia. It is also approved for the schizophrenia's treatment in the European Union in June 2007. [33]

Osmotic-release oral system OROS

It is available in prolonged release tablets (3 mg, 6 mg, 9 mg, 12 mg), therefore it is released slowly by tablet.

INVEGA uses in fact a osmotic-release system, to slowly surrender the drug and to allow its administration once daily. The drug checks the symptoms of the schizophrenia through this system OROS (osmotic controlled oral delivery system), a system of oral osmotic pumps, composed by a special capsule that, through the osmotic pressure, it allows the gradual release of the drug within the 24 hours, avoiding the immediate release, that can reveal of difficult tolerability for the patient.

The system is composed of nucleus with 3 layers, surrounded by a polymeric membrane insoluble in water and semipermeable in comparison to it. The nucleus consists of two layers containing the drug and the excipients and a layer containing osmotically active components. On the layer containing the drug there are two orifices. In watery, in the gastrointestinal tract, the molecules of water spread inside the system through the semipermeable membrane. In this way, it produces a difference in concentration that to drain out the drug. In fact the absorbent polymers of the nucleus inflate and they form a gel containing paliperidone and then it's pushed out through the orifices. The biologically inactive components of the tablet they are intact during the gastrointestinal transit and they are eliminated in faeces with the insoluble components of the core.

Administration

The recommended initial dose of INVEGA is 6 mg, administered once daily to the morning. The tablet must be swallows whole with a liquid. INVEGA can be taken to fast or at breakfast, but it's necessary to take it always to fast or always at breakfast and not one day to fast and one day with food. The dose can be modified after the evaluation of the symptoms, up to an final dose inclusive between the 3 and the 12 mg once a day. INVEGA must be uses with caution in the subjects with serious troubles to the liver. The patients affections from light (creatinine clearance ≥ 50 to < 80 ml / min) or moderate (creatinine clearance ≥ 30 to < 50 ml / min) renal problems, inclusive some elderly patients, must begin with a smaller dose, while the use of the drug is not recommended in patient with serious renal problems (creatinine clearance ≥ 10 to < 30 ml / min). The dosing recommended for the elderly patients with normal renal functionality (≥ 80 ml / min) is the same recommended for the adults with normal renal functionality. Nevertheless, since in the elderly ones the renal functionality can be reduced, it can be necessary to repair the dosing.

In pregnancy and nursing suitable data regarding the use of paliperidone don't exist. In studies ducts on the animals, paliperidone is not shown teratogen, but other types of reproductive toxicity have been found. The use of antipsychotic during the last quarter of pregnancy has involved in the newborn neurological disturb for a long time, but reversing, of extra-pyramidal nature. However INVEGA must not be assume in pregnancy if not in case of absolute necessity and if it were necessary to interrupt the treatment during the pregnancy, the interruption must not be sudden.

Paliperidone is excreted in the maternal milk in such measure that in case of administration of therapeutics doses to women in nursing, the effects are probable on the newborn. INVEGA has not been studied in patient < 18 years of age .

Pharmacokinetic properties

The pharmacokinetics of paliperidone following the administration of INVEGA is proportional to the dose in the recommended clinical interval (3 to 12 mg).

Absorption

Following the administration of a single dose, INVEGA shows an ascending gradual release, allowing the plasmatic concentrations of paliperidone to constantly increase and to reach the maximum plasma concentration (C_{max}) 24 hours after the administration. With one daily administration, the concentrations to the steady state of paliperidone are reached within 4-5 days by the beginning of the treatment in the greatest part of the subjects. The characteristics of release are

translated in least fluctuations of the peak-valley concentrations of the active principle, if they are compared to those observed with risperidone to immediate release (fluctuation index 38% vs 125%). The absolute oral bioavailability of paliperidone following INVEGA administration is 28% (IC 90% of 23%-33%). The administration of paliperidone to release highly prolonged with a caloric / rich standard meal of fats increases the C_{max} and the AUC of paliperidone up to 50-60% in comparison to the administration in state of fast.

Distribution

Paliperidone is quickly distributed and the apparent volume of distribution is 487 l. The plasma protein binding of paliperidone is 74% and concerns the α 1-acid glycoprotein and the albumin.

Metabolism and elimination

One week following administration of a single oral dose of 1 mg immediate-release 14 C-paliperidone to healthy volunteers, 59% of the dose was excreted unchanged into urine, showing that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four primary metabolic pathways have been identified in vivo, none of which could be shown to account for more than 6,5 % of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission.

Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence in vivo that these isozymes play a significant role in the metabolism of paliperidone. The terminal elimination half-life of paliperidone is approximately 23 hours. In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No in vivo data are available and the clinical relevance is unknown. Elimination of paliperidone decreased with decreasing renal functionality. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = < 30 mL/min) renal impairment. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl \geq 80 mL/min). The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance between men and women.

Clinical trials

The effects of INVEGA have been analyzed in experimental models before studied on the human. INVEGA has been examined in three principal brief term studies, conducted on 1692 adult patient affections by schizophrenia. The effects of INVEGA have been analyzed in experimental models before studied on the human. INVEGA has been examined in three principal studies to brief term, conducted on 1692 adult patient affections by schizophrenia. In the three studies, the doses of INVEGA understood between 3 and 15 mg a day are been compared with placebo (fictitious treatment) and with olanzapina (another drug antipsychotic). Efficacy was evaluated through variation of the symptoms of the patients after 6 weeks, measured by standard scale for evaluation of the schizophrenia.

In a further study the effects a long term of INVEGA have been examined in the prevention of new symptoms; the study has been realized for a period up to 35 weeks in 207 patients that had been treated initially for symptoms of schizophrenia within 14 weeks.

INVEGA results more effective than the placebo and effectiveness as the olanzapina in to reduce the symptoms of the schizophrenia. In the first brief term study the patients essays with placebo have recorded a middle reduction of the symptoms score of 4,1 points in comparison to a middle reduction among 17,9 and 23,3 points, recorded in the subjects essays with INVEGA and 19,9 points in the patients in care with olanzapina. Analogous results have also emerged in the other two brief term studies. The three studies have shown that the greatest dosing of INVEGA are more effective in to reduce the symptoms in comparison to smaller dosing. In the long term study INVEGA results more effective than placebo in the prevention of new symptoms of the schizophrenia. [35]

Contraindications and undesirable effects***QT interval***

As with other antipsychotics, caution should be exercised when INVEGA is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other drugs thought to prolong the QT interval.

Neuroleptic malignant syndrome

As with other antipsychotics, has been reported the Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels.

Tardive dyskinesia

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face.

Hyperglycemia

Rare cases of glucose related adverse reactions, e.g., increase in blood glucose, have been reported in clinical trials with INVEGA. As with other antipsychotics, appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity.

Based on pooled data from the three, placebo-controlled, 6-week, fixed-dose trials with INVEGA (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with INVEGA compared with 0.8% of subjects treated with placebo. INVEGA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities),

cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

Seizures

INVEGA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Potential for gastrointestinal obstruction

Because the INVEGA tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, INVEGA should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable controlled-release formulations. Due to the controlled-release design of the dosage form, INVEGA should only be used in patients who are able to swallow the tablet whole.

Conditions with decreased gastro-intestinal transit time

Conditions leading to shorter gastrointestinal transit time, e.g., diseases associated with chronic severe diarrhoea, may result in a reduced absorption of paliperidone.

Elderly patients with dementia

INVEGA has not been studied in elderly patients with dementia. Hence, until data demonstrate otherwise the experience from risperidone is considered valid also for paliperidone.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotic medicinal products, including INVEGA, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA, paliperidone shares this pharmacologic activity and, therefore, may be associated with this risk.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing INVEGA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

In conclusion the most frequently reported adverse drug reactions (ADRs) reported in clinical trials were headache, tachycardia, akathisia, sinus tachycardia, extrapyramidal disorder, somnolence, dizziness, sedation, tremor, hypertonia, dystonia, orthostatic hypotension, and dry mouth.

The ADRs that appeared to be dose-related included weight increased, headache, salivary hypersecretion, vomiting, dyskinesia, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism.

The following are all ADRs that were reported in INVEGA-treated subjects in clinical trials. The following terms and frequencies are applied: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), and very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reaction		
	Very common	Common	Uncommon
Immune system disorders			anaphylactic reaction
Metabolism and nutrition disorders			increased appetite
Nervous system disorders			nightmare
Nervous system disorders	headache	extrapyramidal disorder, parkinsonism, tremor, hypertonia, dystonia, akathisia, dizziness, sedation, somnolence,	grand mal convulsion, syncope, dyskinesia, dizziness postural

Eye disorders			oculogyration
Cardiac disorders		tachycardia, sinus tachycardia, bundle branch block, atrioventricular block first degree, bradycardia	palpitations, sinus arrhythmia
Vascular disorders		orthostatic hypotension	ischaemia, hypotension
Gastrointestinal disorders		vomiting, abdominal pain upper, salivary hypersecretion, dry mouth	
Musculoskeletal, connective tissue and bone disorders			muscle rigidity
Reproductive system and breast disorders			amenorrhoea, galactorrhoea, erectile dysfunction, gynaecomastia, breast discharge, menstruation irregular

General disorders		asthenia, fatigue	oedema
Investigations		weight increased	electrocardiogram abnormal

Events of Particular interest to the class

Extrapyramidal Symptoms (EPS).

In clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of INVEGA. Dose dependence for EPS was seen with the two higher doses of INVEGA (9 and 12 mg).

Weight Gain.

In clinical trials, the proportions of subjects meeting a weight gain criterion of $\geq 7\%$ of body weight were compared, revealing a similar incidence of weight gain for INVEGA 3 mg and 6 mg compared with placebo, and a higher incidence of weight gain for INVEGA 9 mg and 12 mg compared with placebo.

Serum Prolactin.

In clinical trials, median increases in serum prolactin were observed with INVEGA in 67% of subjects. Adverse events that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, gynaecomastia) were reported overall in 2% of subjects. Maximum mean increases of serum prolactin concentrations were generally observed on day 15 of treatment, but remained above baseline levels at study endpoint.

Preclinical safety data

Paliperidone was not teratogenic in rat and rabbit and it was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

Interaction with other drugs

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450 isozymes.

Given the primary CNS effects of paliperidone, INVEGA should be used with caution in combination with other centrally acting medicines, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when INVEGA is administered with other therapeutic agents that have this potential, e.g., other antipsychotics, tricyclics. Caution is advised if paliperidone is combined with other medicines known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.).

In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications in vitro nor in vivo that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of INVEGA with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone. In vitro studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate.

Co-administration of INVEGA once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of INVEGA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA should be re-evaluated and decreased if necessary. It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer the effect wears off over a similar time period. Other medicinal products or herbals which are inducers, e.g. rifampicin and St John's wort (*Hypericum perforatum*) may have similar effects on paliperidone.

Medicinal products affecting gastrointestinal transit time may affect the absorption of paliperidone, e.g., metoclopramide.

Overdose

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. In the case of acute overdosage, the possibility of multiple medicinal product involvement should be considered.

Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. Gastric lavage (after intubation if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. [38]

Conclusion

The paliperidone, the major metabolite of risperidone, shares with the native drug the characteristics of receptor bond and of antagonism of serotonin (5HT_{2A}) and dopamine (D₂). It's available in a prolonged release formulation and it allows the administration once daily. The drug has a comparable cost to the olanzapine, inferior cost to the aripiprazole, but almost double in comparison to his "progenitor" risperidone, of which besides to could be a further reduction of cost being in patent expiration. Missing, therefore, studies of direct comparison with the atypical (the only studies vs olanzapine was not drawn for effecting a statistic comparison with the active comparator) antipsychotics and particularly vs risperidone, it is difficult to be able to define the role in therapy of the new drug, of forehead of a very great cost in comparison to the progenitor.

Experimental studies however are effecting on the *Paliperidone palmitate*, the palmitate ester of paliperidone, administered by injection and endowed with long duration of action. The last studies effected in San Francisco, in double blind on 681 patients, of which 408 included in the preventive phase of recidivist, have noticed that the paliperidone palmitate, administered by injection, it reduce the risk of recidivist in schizophrenic patients, submitted to the treatment with the drug or with the placebo for one month.

References

- 1) Tamminga CA, Holcomb HH. *Phenotype of schizophrenia: a review and formulation*. Mol Psychiatry 2005;10:27-39.
- 2) Pubblicazione, "Diagnosi & Terapia" n.10 - 20/12/98. Dott. Roberto Vincenzi.
- 3) Harrison PJ, Weinberger DR. *Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence*. Mol Psychiatry 2005;10:40-68.
- 4) Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Rev* 2000;31:251-69.
- 5) Carlsson A. *The dopamine theory revised*. In: Hirsch SR, Weinberger DR (Ed.). *Schizophrenia*. Oxford: Blackwell Science; 1995. p 379-400.
- 6) Massotti Marino, Racagni Giorgio, Laboratorio di Farmacologia, Istituto Superiore di Sanità, Roma, Dipartimento Scienze Farmacologiche, Università di Milano e Società Italiana di Neuropsicofarmacologia. *Gli antipsicotici*.
- 7) Terenius L. Schizophrenia: *pathophysiological mechanisms – a synthesis*. *Brain Res Rev* 2000;31: 401-404.
- 8) Redazione MolecularLab.it 30/06/2008.
- 9) Redazione MolecularLab.it 05/05/2009.
- 10) B.G. Katzung. *Farmacologia Generale e Clinica*. Piccin.
- 11) Glenthøj BY, Hemmingsen R. *Transmitter dysfunction during the process of schizophrenia*. Acta Psychiatr Scand 1999;99(suppl. 395):105-12.
- 12) David A. Williams, Thomas L. Lemke, Foye's *Principi di Chimica Farmaceutica*. Piccin.
- 13) T. Usala, L. Lecca, A. Zuddas Centro Terapie Farmacologiche in Neuropsichiatria dell'Infanzia e dell'Adolescenza, Dipartimento di Neuroscienze, Università di Cagliari.
- 14) Miyamoto S, Duncan GE, Marx CE, Lieberman JA. *Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs*. Mol Psychiatry 2005;10:79-104.
- 15) Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*. N Engl J Med 2005;353:1209-23.
- 16) Maria Del Zompo, Giovanni Severino *Sezione di Farmacologia Clinica, Centro di Psicofarmacologia Clinica, Dipartimento di Neuroscienze "B.B. Brodie", Università degli Studi di Cagliari*.
- 17) Peralta V, et al. Differentiating primary from secondary negative symptoms in schizophrenia: a study of neuroleptic-naïve patients before and after treatment. *Am J Psychiatry* 2000;157:1461-6.
- 18) Olney JW, Farber NB. *NMDA receptor hypofunction model of schizophrenia*. J Psychiatry Res 1999;33:523-33.
- 19) Meltzer HY. *Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin 2pKi values*. J Pharmacol Exp Ther 1989;251:238-46.
- 20) Wadenberg ML, et al. *Dopamine D2 receptor occupancy is a common mechanism underlying animal models of antipsychotics and their clinical effects*. Neuropsychopharmacology 2001;25: 633-41.
- 21) Svensson TH, et al. *Mode of action of atypical neuroleptics in relation to the phencyclidine model of schizophrenia: Role of 5-HT2 receptor and alfa-adrenoreceptor antagonism*. J Clin Psychopharmacol 1995;155:11-8.
- 22) Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypical *J Clin Psychiatry* 2000;61(suppl. 3):16-21.
- 23) Sekine Y, et al. Correlations between *in vitro* affinity of antipsychotics to various central neurotransmitter receptors and clinical incidence of their adverse drug reactions. *Eur J Clin Pharmacol* 1999;55:583-7

- 24) Bellantuono C, Balestrieri M. *Gli psicofarmaci. farmacologia e terapia*. Roma: Il Pensiero Scientifico Editore; 1997.
- 25) Keck PE, et al. *The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility and suicidality in patients with schizophrenia*. J Clin Psychiatry 2000;61 (suppl.3):4-9.
- 26) Woods SW, et al. Consistency of atypical antipsychotics superiority to placebo in recent clinical trials. *Biol Psychiatry* 2001;49:64-70.
- 27) Green MF, Braff DL. *Translating the basic and clinical cognitive neuroscience of schizophrenia to drug development and clinical trials of antipsychotic medications*. Biol Psychiatry 2001;49: 374-84.
- 28) Lieberman JA, et al. *Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome*. Am J Psychiatry 1994;151:1744-52.
- 29) Janssen PA. "From Haloperidol to Risperidone", in Healy (ed) *The Psychopharmacologists II*, Altman, London, 1998.
- 30) Cavallaro R. *Differential efficacy of risperidone vs haloperidol in psychopathological subtypes of subchronic schizophrenia*. Human Psychopharmacology 2001.
- 31) Harvey PD. *Long term cognitive effects of risperidone vs haloperidol*. Washington, DC, USA: American Psychiatric Association; 2000.
- 32) Mobascher A, Mobascher J, Shlemper V, Winterer G, Malevani J. *Aripiprazole pharmacotherapy of borderline personality disorder*. Pharmacopsychiatry 2006;39:111-2.
- 33) Nussbaum A and Stroup TS. *Paliperidone for schizophrenia*. Cochrane Database Syst Rev 2008; Apr 16; (2):CD006369.
- 34) Jehan Marino, Pharm.D.; Joshua Caballero, Pharm.D. *Paliperidone Extended-Release for the Treatment of Schizophrenia* 12/12/2008 From Pharmacotherapy.
- 35) Kane J et al. *Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial*. Schizopher Res 2007; 90:147-61.
- 36) Tzimos A et al. *Safety and tolerability of oral paliperidone extended-release tablets in elderly patients with schizophrenia: a double-blind, placebo-controlled study with six-month open-label extension*. Am J Geriatr Psychiatry 2008; 16:31-43.
- 37) Kramer M et al. *Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study*. J Clin Psychopharmacol 2007; 27:6-14.
- 38) *Paliperidone*. Riassunto delle Caratteristiche del Prodotto.
- 39) FDA *Issues Complete Response Letter for Paliperidone Palmitate for the Treatment of Schizophrenia* - August 27, 2008.