

Schizophrenia

Its pharmacotherapy and backgrounds

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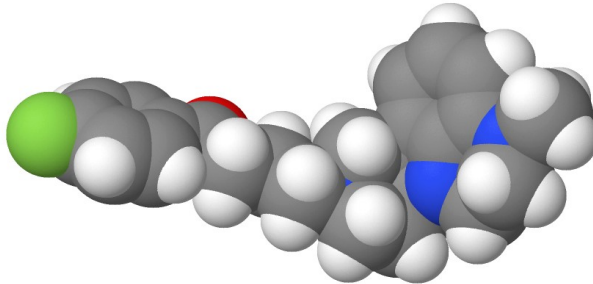
4th Scientific Edition

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Schizophrenia

Its Pharmacotherapy and Backgrounds



The molecule shown above represents a 3D model of the molecule lumateperone (a well-known new antipsychotic).

In brief terms, this book provides insight into the history of antipsychotics, the most important therapy for schizophrenia, the disease that is controversial because of its disease-laden name. Nowadays it is also called psychosis sensitivity syndrome. A different name does not change the suffering that accompanies it.

The development outlined and described has had an enormous impact on the lives of patients and family members over the past 7 decades.

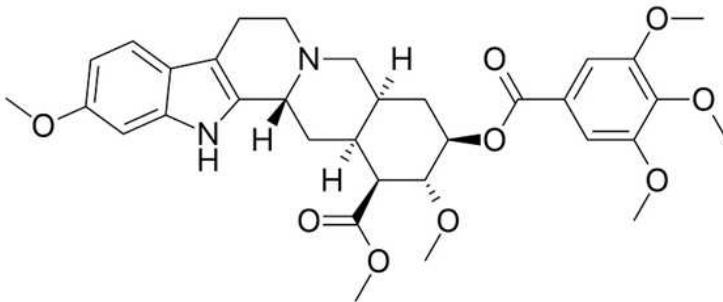
Where in earlier centuries an atmosphere of decay and putrefaction surrounded this disease, the image of this disease has changed enormously over the past 60

years due to the special medicines that are antipsychotics. Increasing knowledge about antipsychotics has been accompanied by an increase in knowledge about the nature and background of the disease schizophrenia.

This book aims to shed light on this and to have an illuminating effect. A number of recent developments can be mentioned. This book first describes the history and development processes of antipsychotics (early developments, conventional antipsychotics, atypical antipsychotics and future developments). Secondly, the development of adjuvant treatment options is described. Non-pharmacological treatment options are also briefly mentioned. Finally, the symptoms and backgrounds of schizophrenia are described. This book provides insight into the chemistry and pharmacology of antipsychotics and also into the backgrounds, causes and treatment of schizophrenia. In this Fourth Scientific edition, some new developments are discussed and new aspects are named.

1. Antipsychotics (early developments)

The first step towards antipsychotic drug therapy was around 1950. After the Second World War, many well-known drugs had been developed for well-known diseases. Development took off. Around 1950, signs appeared that perhaps even drug therapies for mental disorders (including schizophrenia) might be a real possibility.



Reserpine

Reserpine (Serpasil) is a Rauwolfia alkaloid, a nitrogenous substance of plant origin from *Rauwolfia Serpentina* that had some antipsychotic properties, but is far from safe (it can cause severe depression). It works by depleting neurotransmitters, dopamine, but also serotonin and noradrenaline via the Vesicular Monoamine Transporter 2 (VMAT2). In the period before the arrival of antipsychotics it was sometimes used, but with the arrival of antipsychotics it became obsolete.

However, this substance showed that it could be possible to develop a pharmacological treatment for schizophrenia. Previously it was hardly treatable, resulting in overcrowded psychiatric institutions with inhumane treatments and conditions. Schizophrenia is a serious illness and affects as much as 1% of the total population. The remainder of this book shows how, over time (especially in recent decades), more and more light has been shed on what was for centuries an obscure phenomenon, but is now seen as a syndrome that is in many cases treatable.

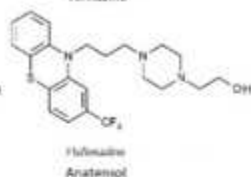
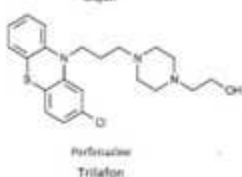
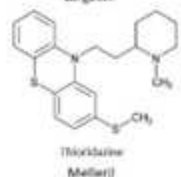
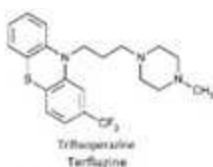
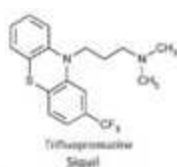
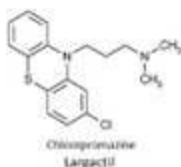
2. Antipsychotics (conventional, typical)

Conventional antipsychotics are the first generation of antipsychotics that were introduced from the 1950s onwards.

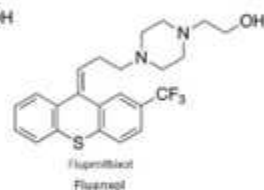
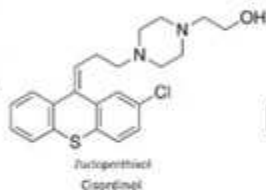
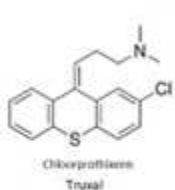
They are effective against positive symptoms, where the occurrence of extrapyramidal side effects can be a serious problem. They are called conventional or typical antipsychotics or classical neuroleptics. They can be roughly divided into the phenothiazines, the thioxanthenes, the butyrophenones, the diphenylbutylpiperidines and the benzamides. These conventional agents block the dopamine receptors in each of the four dopaminergic systems in the brain [the mesocortical system (which causes secondary negative and neurocognitive symptoms), the mesolimbic system (which combats positive symptoms), the nigrostriatal system (which causes psycholepsy and extrapyramidal effects) and the tuberoinfundibular system (which causes hyperprolactinemia and sexual side effects)].

The action on the nigrostriatal dopamine system increases the risk of serious side effects such as tardive dyskinesia (a late serious movement disorder) and neuroleptic malignant syndrome compared to a less prominent action on the nigrostriatal system, such as with the later atypical antipsychotics.

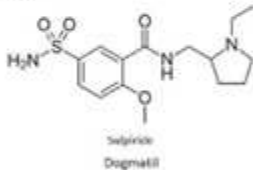
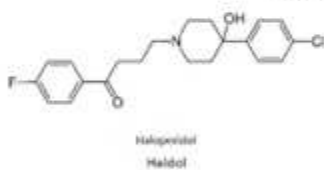
Chemical structures of classical/typical antipsychotics:



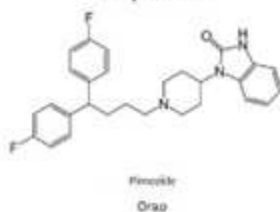
Fenothiazines



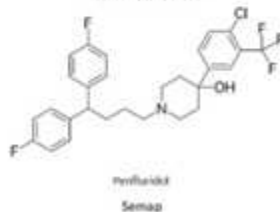
Thioxanthenen



Butyrofenon



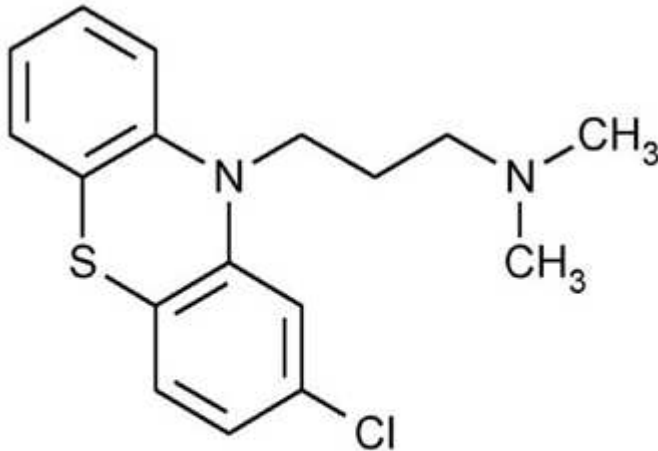
Benzamide



Difenylbutylpiperidines

Typical antipsychotics

Phenothiazines:

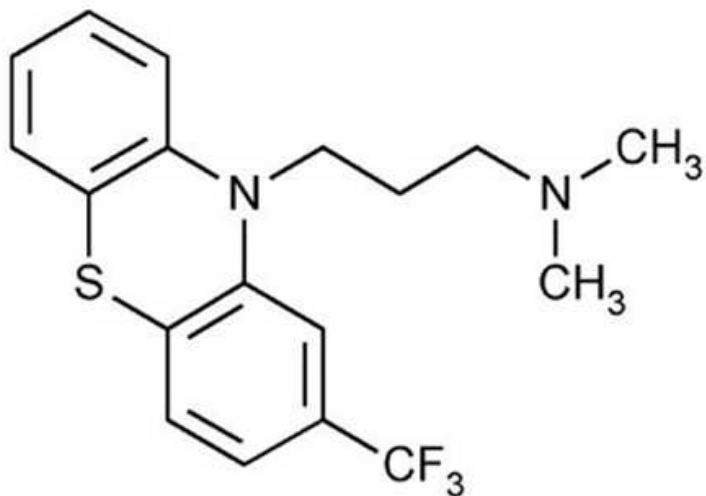


Chlorpromazine

Chlorpromazine (Largactil, Thorazine) was the first phenothiazine antipsychotic, which revolutionized the treatment of schizophrenia patients in 1952. The substance has structural similarities with the neurotransmitter dopamine.

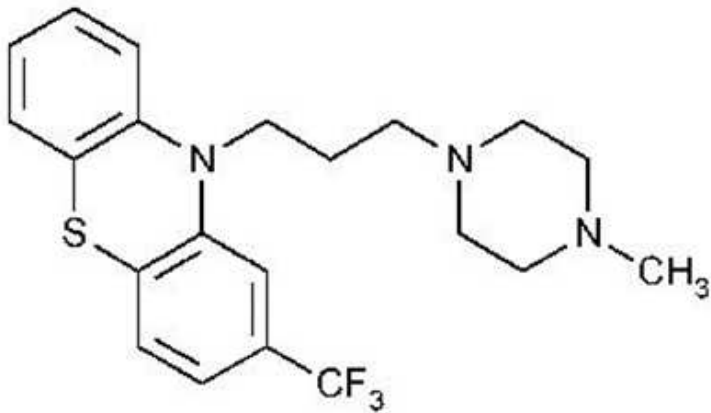
It works by blocking dopaminergic neurotransmission postsynaptically. The effect of chlorpromazine was discovered by chance (this is called serendipity). Some time ago, this drug was withdrawn from various markets, because there are now better alternatives. Over time, various side effects were discovered. After the introduction of this drug, large psychiatric institutions

literally emptied. A reverse trend had set in. The most striking and most disturbing symptoms of the disease, the positive symptoms, could now be addressed, albeit at the cost of adverse effects.



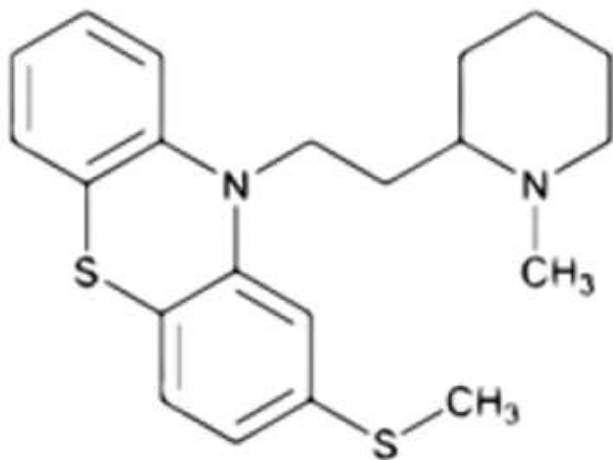
Trifluopromazine

By changing ligands on the structure, better and more potent antipsychotics were obtained, such as trifluopromazine (Siquil, Psyquil), in which the chlorine atom was replaced by a trifluoromethyl group. This study of varying the structure is called structure-activity relationship (SAR) studies.



Trifluoperazine

The use of a piperidine or piperazine ring in the side chain yielded even more potent antipsychotics, such as the piperazine ring in trifluoperazine (Terfluzine).



Thioridazine

An example of an alternative ligand and a piperidine ring in the side chain was thioridazine (Melleril, Mellaril). This drug used to be very well known, but is now no longer available in many countries.