# Schizophrenia

Its pharmacotherapy and backgrounds

3rd Updated Scientific Edition

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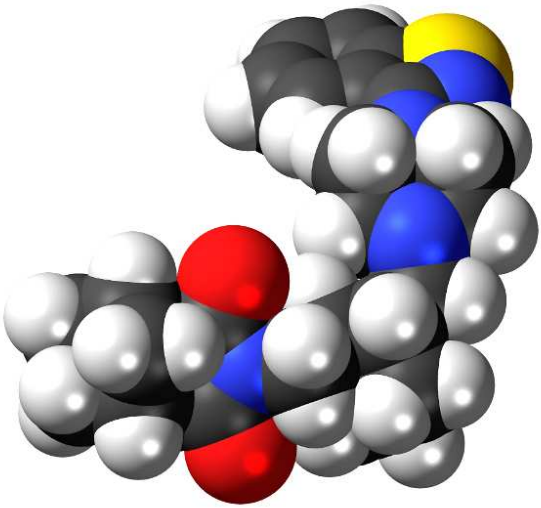


The molecule shown above represents a 3D model of the molecule lurasidone (a wellknown antipsychotic).

In concise terms it is attempted to provide an understanding in the history of the antipsychotic drugs, the main therapy for schizophrenia, the disease, which is at issue with the disease-laden name. Nowadays, it is also called psychosis sensitivity syndrome. Another name does not alter the suffering that goes with it. The development sketched and described, has had a huge impact in the lives of patients and family members over

the last 6 decades. Where hung in earlier centuries an air of decay about this disease, the picture of this disease has changed immensely over the past 60 years by the special drugs, which are antipsychotics. Increasing knowledge about antipsychotics went hand in hand with an increase in knowledge about the nature and background of the disease schizophrenia.

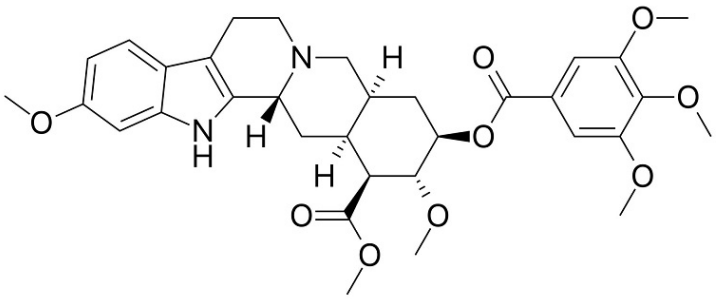
This book aims to shed a light and work clarifying. There are several recent developments to be mentioned.

In this book, in the first place, the development processes of the antipsychotics (early developments, conventional antipsychotics, atypical antipsychotics and future developments) are described. Secondly, the development of adjunctive treatment options is described, and finally, the symptomatology and backgrounds of schizophrenia are described. This book provides insights into the chemistry and pharmacology of antipsychotics and also into the backgrounds and causes of schizophrenia.

In this third Updated Scientific Edition some new developments have been discussed.

# 1. Antipsychotics (early developments)

The first step towards antipsychotic pharmacotherapy was around 1950. After World War II many known drugs had been developed for known diseases. The development took an enormous flight. Around 1950 there appeared signs that perhaps even drug therapies for mental disorders (including schizophrenia) could be a real possibility.



Reserpine

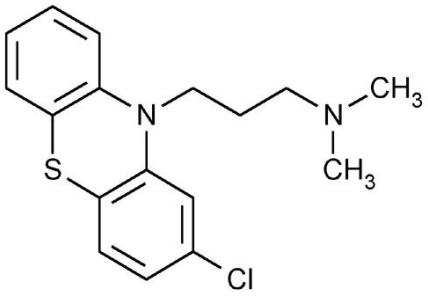
Reserpine (Serpasil) is a Rauwolfia alkaloid, a nitrogen-containing substance of plant origin from the Rauwolfia Serpentina that possessed some antipsychotic properties, but is far from safe (it can cause severe depression). It works by the depletion of neurotransmitters, dopamine, but also serotonin and noradrenalin. It was sometimes used in the period before the arrival of the antipsychotics, but with the advent of antipsychotic drugs it became obsolete (outdated). However, this substance showed that it could belong to the

possibilities that a pharmacological treatment of schizophrenia could be developed. Previously, it was hardly treatable resulting in overcrowded psychiatric institutions with inhuman treatments and conditions. Schizophrenia is a serious disease and affects as much as 1% of the total population. The remainder of this book shows how, in the course of time (especially in recent decades) more and more light has come into what for centuries was an obscure phenomenon, but nowadays seen as an in many cases treatable syndrome.

## 2. Antipsychotics (conventional, typical)

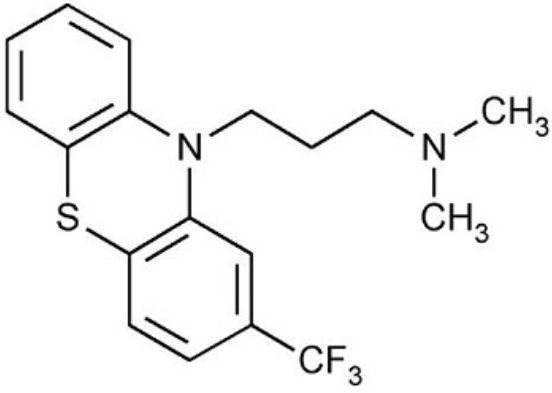
Conventional antipsychotics are the first generation antipsychotics which have been introduced from the 50s. They have activity against the positive symptoms, wherein the occurrence of extrapyramidal side effects may be a serious problem. They are called the conventional or typical antipsychotics, or classical neuroleptics. They can be grossly subdivided into the phenothiazines, the thioxanthenes, the butyrophenones, the diphenylbutylpiperidines and the benzamides. These conventional agents block dopamine receptors in each of the four dopaminergic systems in the brain [the mesocortical system (this causes secondary negative and neurocognitive symptoms), the mesolimbic system (this combats positive symptoms), the nigrostriatal system (this causes psycholepsy and extrapyramidal side effects) and the tuberoinfundibular system (this causes hyperprolactinemia and sexual side effects)]. By the action of the nigrostriatal dopamine system, the risk of serious side effects such as tardive dyskinesia (a late severe movement disorder) and malignant neuroleptic syndrome is greater than when there is a less prominent action on the nigrostriatal system, as with the subsequent atypical antipsychotics.

Phenothiazines:



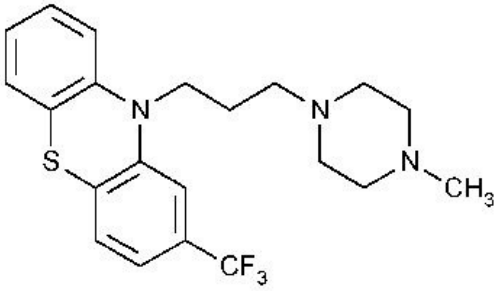

Chlorpromazine

Chlorpromazine (Largactil, Thorazine) was the first phenothiazine antipsychotic, that formed a revolution in the treatment of schizophrenia patients in 1952. The substance has structural similarities with the neurotransmitter dopamine. It works by blocking the dopaminergic neurotransmission. The action of chlorpromazine was discovered by chance (this is called serendipity). Recently, this drug has been withdrawn from several markets, because there are better alternatives today. Several side effects had been discovered after a period of time. After introduction of this drug, great psychiatric institutions literally ran empty. A reverse trend had been initiated. The most conspicuous and most distressing symptoms of the disease, the positive symptoms, could now be handled, albeit at the expense of adverse effects.



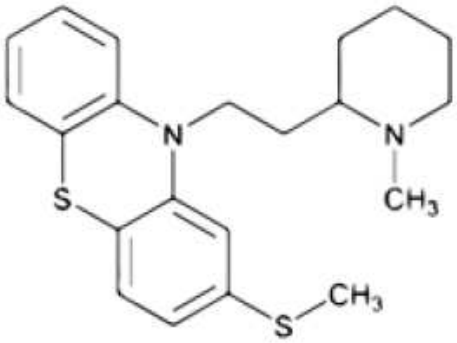

Trifluopromazine

By changing ligands to the structure, there were obtained better and more powerful antipsychotic drugs, such as triflupromazine (Siquil, Psyquil). This research into varying the structure is called structure-activity relationship (SAR) investigation.




Trifluoperazine

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




Thioridazine

An example of an alternative ligand, and a piperidine ring in