

**Biological treatments of CNS disorders**

**MALARIA**  
von Jauregg in 1917 in Vienna  
used malaria as a treatment for syphilis-induced paralysis  
this was the first biological treatment for a major CNS disorder

**SHOCK THERAPY**  
insulin shock therapy  
Manfred Sakel, a German physician in Vienna in 1933  
wanted to relieve morphine withdrawal by giving insulin  
decided it helped  
gave it to other patients  
said it helped schizophrenics

**ECT**  
employed in 1937 in Rome

**FRONTAL LOBOTOMY**  
developed by a Portuguese neurologist, Egas Moniz, in 1935  
noted that animals became more docile after cutting away the frontal lobes  
large number of operations performed in the 1940s  
but patients loose ambition and imagination

Thus, situation did not look very promising for patients  
in 1955 there were 560,000 patients in U.S. mental hospitals  
at least half of these were schizophrenic  
the number was increasing at the rate of 13,000/yr  
at this point drug therapy was introduced that started to reduce the hospital population
Current Drug Therapies

**PHENOTHIAZINES**
in the 1930s this class of compound was used for intestinal worms!
*promethazine* was found to be an antihistamine and a sedative
derivatives were made
one of these was *chlorpromazine* (cpz) (Thorazine)
sat on shelves of a French drug company for 10 years

Animal studies indicated it potentiated the effects of anesthetics and produced
“artificial hibernation”
a tendency to sleep and indifference to surroundings
Henri Laborit, a French surgeon, asked the drug company for their most sedating
antihistamine to use before surgical anesthesia. They gave him cpz. It calmed his
patients without putting them to sleep. He recommended its use in psychiatry.

In 1952 Jean Delay and Pierre Deniker reported the use of cpz for treating schizophrenic
patients. They reported that it calmed patients, but was not just a sedative. Some
withdrawn patients became more energetic, also reported that it did not help in treating
depression. They noted development of akinesia and coined the term “neuroleptic”
that which “seizes the neuron”

**RESERPINE**
Successful treatment for schizophrenia reported in 1954
actually had been reported in 1931 by Sen and Bose in India
The shrub is also known as pagla-ka-dawa (“insanity herb”)
but their report was ignored until reserpine treatment was “rediscovered” in 1954.

**HALOPERIDOL (HLP) (HALDOL)**
Success reported for hlp in 1958. A butyrophenone compound

**A COMMON PROPERTY OF CURRENT DRUGS**
Interfere with ability of *sensory stimuli to “get through.”*
Interfere with conditioned stimulus (bell) telling a rat to climb a pole to avoid a shock
without interfering with the shock-induced climbing itself. Implies that schizophrenia
associated with too many inputs coming in with insufficient screening? Similar to *LSD?*

implications: evidence for schizophrenia as a *biochemical disorder*. A chemical
agent can relieve symptoms (cpz, hlp, etc.). Chemical agents can produce symptoms
(amphetamine, LSD, PCP, etc.).
**NMDA theory of schizophrenia:**
a hypoactive NMDA system contributes to the symptoms of the disease
b. would suggest the use of activators of this system as

**GENETIC STUDIES**
average expectancy of schizophrenia in general population: @. 1%
   if one parent has it: @. 16%
   if one sibling or non-identical twin has it: @ 14%
   if one identical twin has it: @ 50%

Suggests that there is a strong genetic (i.e., biochemical) component, but that environment must also come into play

**DOPAMINE THEORY OF SCHIZOPHRENIA**
Main line of support is that neuroleptics block DA receptors
in common with reserpine, can produce extrapyramidal side effects.
   Produce a Parkinsonian symptomatology upon acute administration: slowing of volitional movement, rigidity, tremor at rest.
   Block turning behavior in rats with a unilateral lesion of the nigrostriatal pathway in response to either amphetamine or apomorphine.
   Increase rate of DA formation *in vivo*
   Increase rate of firing of nigrostriatal neurons *in vivo*
   Block DA-induced stimulation of adenylyl cyclase
although weaker in this regard, presumably because this is a D₁ response
   Block labeled DA binding to striatal membranes
   Increase prolactin blood levels (DA is inhibitory in this system)
   Ability to block DA receptors correlates with clinical efficacy in treating schizophrenia

**ANOTHER LINE OF EVIDENCE**
Production of symptoms resembling paranoid schizophrenia with amphetamine. Since amphetamine is an effective releaser of DA in the CNS.

**DIRECT EVIDENCE?**
Metabolite studies are not consistent: some studies on receptors have reported an increase in DA receptor number
but remember that neuroleptic treatment can produce this effect in animal studies could there be a transmitter imbalance, in which DA plays a part but is not necessarily the prime cause?

Other drugs can also produce some of the symptoms of schizophrenia:
   *phencyclidine* (PCP) can produce both type I and type II
symptoms, whereas amphetamine produces more of the type I symptoms. Since PCP is known to block the NMDA receptor, this suggests a possible role for *excitatory amino acids* in the etiology of schizophrenia.

LSD more of the type I symptoms. Since LSD is a *serotonin* receptor agonist, this suggests a possible role for serotonin in schizophrenia.

**Side effects of neuroleptic treatment**

*CPZ*
- CNS-mediated decrease in blood pressure
- alpha blockade
- both of above can contribute to hypotension and reflex tachycardia
- muscarinic blockade
- constipation
- decreased sweating

*HALOPERIDOL*
- Less muscarinic blockade than cpz

Short-term: *Parkinsonian symptoms*. Can treat with muscarinic blockers (e.g., benztropine: *Cogentin*)
- can potentiate CNS depressants such as alcohol and barbiturates

Longer-term: *tardive dyskinesia* (TD). No generally effective treatment. May be related to DA receptor blockade in the striatum.

Is it possible to block DA receptors in other brain areas without blocking in the striatum and still get clinical improvement? *Clozapine* (Clozaril) has a higher D₄/D₂ blocking ratio than classical neuroleptics. D₄ is high in the frontal cortex; D₂ is high in the striatum. D₃ is high in the accumbens and low in the striatum (also a target for clozapine?).
- Clozapine doesn’t produce as much TD as classical neuroleptics, and can treat about 35% of patients who don’t respond clinically to the classics. Clozapine also blocks 5-HT₂ receptors; could this also relate to clinical profile?

*Olanzapine* (Zyprexa) is related to clozapine, but doesn’t lower white blood cells

*Risperidone* (Risperdal) may also produce less TD: blocks 5-HT₂ₐ, D₂ and H₁ receptors