Antipsychotic Drugs: History, Pharmacology, and Synthesis

The Serendipity of Antipsychotics: Phenothiazines
“Luck, ingenuity, and a straightforward chemistry have made phenothiazine the most promiscuous lead structure of the 20th century”

1876 Heinrich Caro synthesizes methylene blue (MB)
1883 Heinrich August Bernthsen synthesizes phenothiazine
1885 Bernthsen determines MB structure
1891 Malaria treatment using MB pioneered by Paul Ehrlich “the first fully synthetic drug used in medicine” MB ultimately paved the way for aminoguanidine antibiotics
1930s-40s Phenothiazine used as an anthelmintic in animals and children, dubbed “worm chocolate”
1940s Paul Charpentier at Rhône-Poulence Laboratories begin synthesizing N-substituted phenothiazines
1950s Henri Laborit finds promethazine to have sedative and anxiolytic effects when administered as an anesthetic

Current Research
Interest in phenothiazines to treat cancer, Parkinson’s & Alzheimer’s diseases, tuberculosis
Other Uses of Phenothiazines
- Prevention of oxidation of jet-engine lubricants
- Lithium ion batteries & solar panels
See also: Ritter’s selective C-H functionalization using thianthrenes

Nature, 2019, 567, 223-228

Covered Topics
- Symptoms and diagnosis of schizophrenia
- Development and MOA of ASDs
- Select syntheses
- Future Directions

Not Covered
Diseases outside of schizophrenia which may be treated with antipsychotics, including bipolar disorder (type I&II), borderline personality disorder, and major depressive disorder

Chlorpromazine, fluphenazine, and haloperidol listed in 2021 World Health Organization List of Essential Medicines

Relevant Resources
Lundbeck Institute online slide library for overview of psychiatric disorders and neurobiology
Drug Discovery Today, 2011, 16, 119-131 for phenothiazines
**Schizophrenia Diagnosis**
Affects 1% of the world population; approximately half of individuals with schizophrenia have a co-occurring psychiatric or behavioral disorder. Marked by positive and negative symptoms:
- Positive: acute psychosis which may include hallucinations, disorganized thought patterns, delusions, incoherent speech.
  
- Negative: slowed motor function, depressed mood, flattened affect.

Severity of negative symptoms are correlated with long term outcomes, while that of positive symptoms are not.

**DSM-5 Criteria**
Continuous display of symptoms for six months paired with decline in function:
- Two or more positive symptoms must be observed within this time frame for at least 1 month.

*note: subtypes of schizophrenia in DSM-IV were dropped*

**Historic Treatment of Schizophrenia**
Primary plan of care based on institutionalization or keeping patients at home; keeping patients from living on the streets or being a harm to themselves/others.

Only medications used were sedatives, including barbituates; belief that the CNS could “settle down” and restore itself while a patient slept.

Use of electrotherapy.

**Chlorpromazine**
After synthesis in 1950, Laborit recognized its sedative and calming effects while testing it as a general anesthetic.

Jean Delay and Pierre Deniker discovered its antipsychotic effects.

Under the trade name Largactil, the drug was available in France by 1952, and quickly introduced worldwide before trials.

By 1955, ten clinical studies corroborated its efficacy.

Lasker Prize awarded in 1957 to Laborit, Deniker, and Heinz Lehmann for involvement of development of the drug.

Chlorpromazine emptied psychiatric hospitals and many patients who had lived decades in confinement were able to assimilate to life outside of an institution.

Institutionalization in U.S. dropped from 559,000 patients in 1970 to 107,000 in 1998.

Upon 3 weeks of chlorpromazine treatment, a patient who has auditory hallucinations of a “Mr. Knock who put filthy thought in her mind” reported that she “did not bother anymore with Mr. Knock.”

“The disappearance of the foul-smelling odor of paraldehyde from the wards.”

**Advent of Biological Psychiatry: Dopamine Hypothesis of Schizophrenia**
Physiological understanding of schizophrenia largely developed from understanding MOA of drugs.

Antipsychotics block D<sub>2</sub> receptors: schizophrenia linked to hyperdopaminergia.

- Chlorpromazine and haloperidol increased dopamine metabolites in the mouse brain, linking schizophrenia to dis regulates dopamine pathways.

- 1960s: reserpine, a natural product known to deplete biogenic amines (dopamine, norepinephrine, serotonin) by inhibiting vesicle formation, displays antipsychotic properties.

- Amphetamines, known to increase catecholamines in the brain, induce psychosis that can be reversed by ASDs.

No physiological or clinical differentiation between positive and negative symptoms.

G. Gründer & P. Cumming. 2016, *The Dopamine Hypothesis of Schizophrenia: Current Status*
Antipsychotic Drugs:  
History, Pharmacology, and Synthesis

Alex Rerick

Baran Group Meeting  
10/09/2021

Structure Activity Relationship of First Generation Antipsychotics

1. Phenothiazines
   a. aliphatics
      - chlorpromazine
      - triflupromazine

   b. piperidines
      - thioridazine
      - mesoridazine

   c. piperazines
      - fluphenazine
      - perphenazine
      - prochlorperazine
      - trifluoperazine

2. Thioxanthenes
   - thiothixene
   - chlorprothixene

3. Dihydroindoles
   - molidone

4. Diphenylbutylpiperidines
   - pimozide

piperidine phenothiazines compared to aliphatic phenothiazines:
- higher anticholinergic action
- lower prevalence of EPS
- rarely prescribed: addition of black box warning due to high risk of QTc prolongation

piperazine phenothiazines
- greater D₂ blockade
- lower affinity for muscarinic, adrenergic, histaminergic receptors
- FGAs in this class are frequently prescribed

- only FGA not associated with weight gain
- only FGA approved for Tourettes
- highest D₂ selectivity and potency of FGAs
- high risk of QTc prolongation, thus limited use
6. Butyrophenones

haloperidol
- considered best known FGA
- $K_i$ values (nM):
  - $D_2 = 0.89$
  - $5HT_{2A} = 130$
- 90% protein binding

droperidol
- prescribed as an antiemetic

7. Benzamides

sulpiride
- no benzamine class of FGA available in US
- commonly prescribed in Europe
- selective $D_2$ antagonist
- neglibile cholinergic, histaminergic, noradrenergic receptor activity
- low prevalence of EPS

Antipsychotic Drugs: History, Pharmacology, and Synthesis

Structure Activity Relationship of First Generation Antipsychotics

5. Dibenzoxazepines

loxapine ($R = \text{Me}$)
- pharmacological profile similar to SGAs
- $K_i$ values (nM):
  - $D_2 = 24$
  - $5HT_{2A} = 6.2$
- intermediate sedative and autonomic effects
- its metabolite, amoxapine ($R = \text{H}$), is an FDA approved antidepressant

6. Butyrophenones

haloperidol
- considered best known FGA
- $K_i$ values (nM):
  - $D_2 = 0.89$
  - $5HT_{2A} = 130$
- 90% protein binding

Advent of Second-Generation Antipsychotics

clozapine
- $K_i$ values (nM)
  - $5HT_{2A} = 9.6$
  - $D_2 = 190$

Developed by Wander AG (now Novartis)
Though highly efficacious with low prevalence of EPS, "neuroleptic dogma" severely hindered the acceptance of this drug
Janssen initially claimed it was "no neuroleptic," eventually relenting, calling it "at best, an atypical neuroleptic"

Cases of lethal agranulocytosis halted clinical trials and led to withdrawal of the drug in 1975
Brought back to market in 1989 due to efficacy in treatment-resistant schizophrenia not seen with FGAs

Relevant GM: for syntheses of phenothiazine antipsychotics, see: G-Protein-Coupled Receptor Drugs, Barton, 2019

The Problem with FGAs: Haloperidol

Paul Janssen used cataleptic activity (muscle rigidity) in animals as a model for antipsychotic efficacy, and in 1959 discovered haloperidol, a drug with a marked structural departure from the phenothiazines.

Haloperidol, as all other ASDs, had high prevalence of extra pyrimidal symptoms (EPS):
- acute dystonia (involuntary muscle contractions), akathisia (restlessness), tardive dyskinesia (contraction of face & neck muscles), Parkinsonism, neuroleptic malignant syndrome (NMS; fever, muscle rigidity, altered mental state, autonomic dysfunction)

“Neuroleptic dogma”: ASD efficacy and EPS were functionally linked
- EPS was used as a marker of an efficacious ASD

ASDs also had low efficacy for alleviating negative side effects

Neurological studies were limited at the time:
- Post mortem studies did not unanimously show increased dopamine in the brain, though a few found increased dopamine in the striatum
- Autoradiography (X-ray imaging of radiolabeled compounds) did not suggest altered dopamine receptors
- Studies obfuscated by convoluted ASD treatment history in patients

Brought back to market in 1989 due to efficacy in treatment-resistant schizophrenia not seen with FGAs

5-HT2A receptor antagonists increase dopaminergic transmission in the cortex, without affecting striatal transmission.

**Dopamine Hypothesis Two**
Published in 1991 by Davis and coworkers: “abnormal, although not necessarily excessive, dopamine activity is an important factor in schizophrenia”

Symptoms and side effects linked dopamine dysregulation to regionally specific pathways:
- Homovanillic acid (dopamine metabolite produced in frontal cortex) found to be higher in cerebral spinal fluid of schizophrenia patients
- PET imaging revealed antagonist occupancy of D2 in the striatum correlated with relief of positive symptoms AND prevalence of EPS

Positive symptoms arise from striatal hyperdopaminergia (mesolimbic pathway)  
EPS arises from striatal hypodopaminergia (nigrostriatal pathway)  
Negative symptoms arise from frontal hypodopaminergia (mesocortical pathway)

**Dopamine-Serotonin Antagonism Hypothesis: 5-HT2A Receptors**
Clozapine was found to treat patients with refractory schizophrenia, though it has low affinity for (1/10th of chlorpromazine) and <60% occupancy at striatal D2 receptors (FGAs require >75% occupancy for efficacy)

5-HT2A receptor antagonists increase dopaminergic transmission in the cortex, without affecting striatal transmission

SGAs are defined by low risk of elevated prolactin levels & EPS; believed to have a superior efficacy in treating negative symptoms.

- Preferential D2 binding in the mesolimbic system  
- Fast dissociation from D2 receptors  
- High ratio of 5-HT2A to D2 receptor binding

Life Sci. 1995, 56, 25, 2209-2222
**Antipsychotic Drugs: History, Pharmacology, and Synthesis**

**Other Neurotransmission Dysregulation Implicated in Schizophrenia**

- **N-methyl-D-aspartate (NMDA) Receptor Hypofunction**
  - Glutamate (Glu) excitatory
  - γ-aminobutyric acid (GABA) inhibitory
  - Acetylcholine (ACh) excitatory
  - Muscarinic (M₁) ACh receptor agonism potentiates NMDA receptors

- **Implication of frontal D₃ hypofunction?**
  - PET study of D₃ receptors show that haloperidol, olanzapine, and risperidone upregulate extrastriatal D₃ receptors

- **Second Generation Antipsychotics**
  - **Quetiapine**
    - Associated with abuse due to sedative effects
    - Often used in psychiatric facilities and prisons where there is no access to other intoxicants
    - “Q-ball”: mixture of quetiapine with cocaine
    - Low D₂ affinity and high dissociation rates, also 5-HT₁A partial agonist
    - Antihistamine activity: at low doses, primarily histamine and α₁-adrenergic receptor antagonist
  - **Aripiprazole**
    - D₂ binding nearly 100%, but a partial agonist: low EPS incidence
  - **Olanzapine**
    - 5-HT₂A = 9.6 nM
    - D₂ = 31 nM
    - Alkermes developed olanzapine/samidorphin combination, FDA approved in 2021
  - **Asenapine**
    - Kᵣ values (nM)
      - 5-HT₂A = 0.06
      - D₂ = 1.3 & 0.42
      - α₁ = 1.2
      - H₁ = 1.2
  - **Ziprasidone**
  - **Paliperidone (R = OH)**
    - Active metabolite of risperidone
  - **Risperidone (R = H)**
    - Fast D₂ dissociation rate (kₒff)

**References**
- Nat. Rev. Drug Discovery, 2009, 8, 197-202
- ACS Chem. Neurosci. 2013, 4 1018-1025
Antipsychotic Drugs: History, Pharmacology, and Synthesis

Alex Rerick

Baran Group Meeting
10/09/2021

N\_N\_O\_NMe\_2 Selective M\_1 and M\_4 receptor agonist in development

Abandoned in Phase III clinical trials due to gastrointestinal side effects

N\_Cl\_CN\_N\_Cl\_Cl\_N\_Cl\_CN \nKOH, DMSO THF, reflux
64% 73%


Selective M\_1 and M\_4 receptor agonist in development

L-glutamic acid

bicyclic amino acids as ASD motif glutamate group II and III (mGlu\_2/3) receptor agonists downstream mimicry of 5-HT\_2A antagonists?

pomaglumetad methionil
• active, hydrolyzed, drug: low oral bioavailability
• methionine amide prodrug: improved pharmacokinetics
Eli Lilly halted Phase III trials in 2012

The search for drugs with dampened \( D_2 \) antagonism

Lumateperone

\[ K_i \text{ values:} \]
\[ 5-HT_{2A} = 0.54 \text{ nM} \]
\[ D_2 = 32 \text{ nM} \]

- low affinity for \( \alpha_1 \) and histaminergic receptors
- low prevalence of EPS and adverse effects from metabolites

fast-track designation in 2017
FDA approved in 2019

Routes B & C: SAR of N-alkylsubstitution

\[ \text{Route A: SAR of aryl substitution} \]

\[ \text{Route B enabled process scale synthesis with chiral resolution using mandelic acid after silane reduction} \]

\[ \text{cis-enantiomers separated by HPLC after alkylation} \]
Antipsychotic Drugs: History, Pharmacology, and Synthesis

(+)-asenapine
 marketed as the racemate but (+)-isomer has favorable pharmacokinetics

Org. Biomol. Chem. 2016, 14, 1332-1337

Process route to racemate (similar to original synthesis in 1994)

J. Labelled Comp. Radiopharm. 1994, 34, 9, 845-869;
Antipsychotic Drugs: History, Pharmacology, and Synthesis

Alex Rerick

Long Term Outcomes
10 years after initial diagnosis:
• 50% are completely recovered, 25% are improved but require considerable continued support
• 15% remain unimproved
• 10% of those diagnosed commit suicide (~20% attempt)

Ending the Age of Serendipity in ASD Discovery
For rational, novel drug development:
• Is D2 too far downstream?
• How to find new targets when animal models are sparse for psychiatric disorders?

Is a Fix-All Drug Possible?
Pharmacological heterogeneity among patients:
• 34% of patients are treatment-resistant (persistent symptoms after >2 trials of ASDs)
• D2 receptor occupancy not significantly different between treatment-respondent and -resistant patients

Intervention in the Prodromal Stage?
Recognition of genetic and environmental risk factors

The Search for a Perfect the Me-Too Drug or a Rational Drug Design?
Does continuing to derivative the same scaffold provide a chance to perfect the current ASD motifs?

Revisiting the Second Generation Craze
Today, only 5% of ASDs prescribed are first generation

Some low-potency SGAs have similar occurrence of EPS and elevated prolactin levels as FGAs
The majority of SGAs don’t relieve negative symptoms to the extent originally proposed
• Clozapine remains the only SGA which has been proven to significantly treat negative symptoms compared to the FGAs
Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) have challenged superiority of SGAs

Does grouping by FGA and SGA serve anything more than a historical purpose?

Clozapine led to a search for ASDs with the ability to treat all physiological symptoms associated with schizophrenia

ASD efficacy appears to be effective due to its varied targets: not a “magic bullet” as Erlich described… but a “magic shotgun”

Nat. Rev. Drug Discovery, 2009, 8, 197-202
Npj Schizophr. 2020, 6, 1

Relevant GM: For mental health resources, see: Antidepressant and Anxiolytic Drugs, Eberle, 2020