Schizophrenia & the Antipsychotics

- “splitting” of mind (cognition/emotion) from reality
  - 1% of population globally
  - shamans or mentally ill

- Several subtypes: paranoid / catatonic / disorganized / undifferentiated / residual

- positive (“exaggerated) / negative (“absence”) symptoms
  - perception (hallucinations)
  - delusions (false beliefs)
  - language (disorganized speech)
  - odd social behavior
  - motor (stereotyped and/or lack of movements)
  - avolition (lack of motivation / goal directed behaviors)
  - flattened affect / blunted emotional expression
  - anhedonia (lack of pleasure)
  - decreased memory, attention, executive function
Schizophrenia & the Antipsychotics

- Morphological / structural changes
  - disorganized neurons / larger ventricles
  - neurodevelopment problems induce susceptibility
- treatment is of the symptoms, not the underlying problem

This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).
Factors:
- genes that make one “susceptible”
- dysfunctional reward system
- environment - stress, infections (?)
- *in utero* - toxoplasmosis, flu (birth month effect)

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Schizophrenia & the Antipsychotics

- 1st signs generally appear after puberty / early 20’s in men, mid 20’s to early 30’s in women
  - ketamine / PCP

- “pre-morbid” signs sometimes seen in early childhood
- clinical deterioration tends to plateau after 5-10 years
- early treatment (pharmacological + talk therapy) provides pretty good prognosis
Schizophrenia & the Antipsychotics

- 10 years after 1st diagnosis:
  - ~25% are almost totally improved
  - ~25% “much” improved
  - ~25% improved but still need support
  - ~15% unimproved or worse
  - ~10% dead (often due to suicide)

- Among those with schizophrenia:
  - ~30% live independently
  - ~25% live with family
  - ~20% live in supervised housing
  - ~10% are institutionalized
  - ~8% are incarcerated
  - ~7% are homeless
Schizophrenia & the Antipsychotics

- Neurotransmitter abnormalities
  - DA, 5-HT, glu

  - Originally – “pure DA” hypothesis
    - too much
    - indistinguishable from an amphetamine / cocaine OD

  - “Typical” antipsychotics are DA antagonists

- 2 major receptor types
  - D\(_1\) (subtypes: D\(_1\), D\(_5\))
  - D\(_2\) (subtypes: D\(_2\), D\(_3\), D\(_4\))

  - Antipsychotics primarily antagonize / block D\(_2\) receptors
    - clinical efficacy highly correlated with degree of D\(_2\) binding
Schizophrenia & the Antipsychotics

The graph shows the relationship between the concentration of antipsychotic drugs and their dose in mg/day. The x-axis represents the antipsychotic dose in mg/day, ranging from 1 to 1000 mg/day. The y-axis represents the concentration of the drugs in nM, ranging from 0.01 to 100 nM. Various antipsychotic drugs are plotted on the graph, including Benperidol, Chlorpromazine, Thioridazine, Risperidone, Droperidol, Fluphenazine, Flupentixol-cis, Haloperidol, Molindone, Loxapine, Olanzapine, Ziprasidone, Clozapine, and Fluperlapine.
Glutamate receptors:

- NMDA receptor hypofunction
  - ketamine / PCP
- NMDA receptor knockout (NMDA−/−) mice:
  - behavioral symptoms similar to schizophrenia
  - no DA dysfunction
  - responded to antipsychotics (“dopaminergic”)

So...

- increased DA = “positive” symptoms?
  - particularly in the “limbic” areas
- decreased glu = “negative” symptoms?
Schizophrenia & the Antipsychotics

- Also 5-HT:
  - $5\text{HT}_2$ activity induces cognitive / motor abnormalities
  - lots of neurons with $5\text{HT}$ receptors release glu.....

- Psychedelics are generally $5\text{HT}_2$ agonists
  - possible treatment with $5\text{HT}_2$ antagonists
Schizophrenia & the Antipsychotics

- **Antipsychotics** (aka the “major tranquilizers”)
  - not pleasant / euphoric like the “minor tranquilizers” (benzodiazepines)

- **Typical / classical / traditional / neuroleptic**
  - generally, control “positive” symptoms
  - have some bad motor “extrapyramidal” effects
    - tardive dyskinesia (Parkinson’s-like)
    - Parkinson’s medicine (“dopamine”) causes schizophrenia-like psychosis
  - inseparable from antipsychotic effects
Schizophrenia & the Antipsychotics

- **Typical antipsychotics** - the Phenothiazines:
  - chlorpromazine ("Thorazine") – calming, detached effect
  - antidote for psychedelics (serotonergic ones like LSD)
- Medical model - started at Wash U (use of scientific method to study mental disorders)
- Thorazine developed in early 1950’s
  - in rats, induced indifference to aversive stimuli
  - quickly moved to use in humans
  - “woke” some schizophrenics ("lifted a blanket")
    - at higher doses ("institutionalization") can become a “chemical straight jacket”
- 1st drug used to treat a mental disorder - started “Golden Age of Psychotropic Drugs”
  - thorazine, lithium, imipramine, & prozac
    - almost everything else is based on these
Schizophrenia & the Antipsychotics

- **Pharmacokinetics:**
  - erratically absorbed orally, better by intramuscular injection
  - only a small % gets to brain
  - long half-lives (1-2 days)

- **Pharmacodynamics:**
  - block D$_2$ receptors - antipsychotic effects
    - about 60-80% of D$_2$ receptors must be blocked for clinical effects
    - higher blockage % leads to “extrapyramidal” motor effects
  - Also block:
    - ACh -> dry mouth, blurred vision, etc (scopolamine)
    - Histamine -> sedation
    - NE -> hypotension, sedation
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- IF increased sensitivity to DA is responsible for the “positive” symptoms...
- block receptors > reduce symptoms
- D₂ receptors in limbic system (target)
  - get DA from the axons neurons originating in the midbrain brainstem
  - involved with emotional expression
Schizophrenia & the Antipsychotics

- blocking $D_2$ receptors in the brainstem reticular formation:
  - reduces sensory inflow
  - induces indifference to external stimuli

- blocking $D_2$ receptors in the basal ganglia:
  - causes motor deficits:
    - extrapyramidal (early Parkinson’s-like) tardive dyskinesia

- blocking $D_2$ receptors in the hypothalamus:
  - causes deficits in eating, sleeping, sexual function

- side effects may be “prophylactically” treated with anti-Parkinson’s drugs
- other side effects – permanently impaired vision, cognitive deficits

- no tolerance or dependence issues
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- Newer ("atypical") drugs – also block multiple receptors, but primarily 5-HT
- control both positive and negative symptoms
- have fewer side effects:
  - weight gain, increased risk of diabetes, cardiac arrhythmia
  - "metabolic syndrome"
- may be less effective overall (?)
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- **Atypicals** generally defined as a drug that binds to and *blocks more than 80% of 5-HT_2 receptors and less than 80% of D_2 receptors*
- may improve, rather than impair, cognition
- by inducing release of ACh in cortex (positive memory effects)
**Schizophrenia & the Antipsychotics**

- **Clozapine** – 1st atypical (90s)
  - weak D<sub>2</sub> antagonist
  - strong 5-HT<sub>2</sub> antagonist
  - also blocks D<sub>4</sub>, 5-HT<sub>1c</sub>, adrenergic apha-1, plus others

- superior to typicals (?)
  - both + / - symptoms

- very few extrapyramidal effects
- fewer cognitive deficits than typicals
- sedation, extreme weight gain, white blood cell toxicity
- withdrawal syndrome - psychotic episodes
3rd generation antipsychotics

- Aripiprazole ("Abilify") 2003
  - partial AGONIST of D₂ receptors
    - stabilizes neuron:
      - increases activity at low dose, blocks activity at higher doses
      - "compressor" - reduces dynamic range of neural activity
  - 5-HT₂ antagonist
    - "antipsychotic"
  - 5-HT₁A agonist
    - "antidepressant"
  - no major side effects
  - also used for bipolar

CBD
Bipolar Disorder & Mood Stabilizers

- “manic depression” - recurring episodes of depression / mania
- usually more depression
- ~1-5% of population (2 episodes = long-term treatment)
- high incidence of substance abuse
- 10x more likely to commit suicide
Bipolar Disorder & Mood Stabilizers

- other causes must be ruled out:
  - thyroid hyperactivity
  - antidepressants, anti-Parkinson’s
  - corticosteroids, anabolic steroids
  - caffeine, (pseudo)ephedrine, other stimulants

- progressive neurodegenerative disease:
  - loss of neurons in the hippocampus and prefrontal cortex
  - altered function / plasticity

- medication used when it becomes disruptive to life
  - antidepressants (usually “1st line treatment”) can induce mania
**Bipolar Disorder & Mood Stabilizers**

- **Mood stabilizers** - “compress” dynamic range
  - major focus is reduction of mania
    - reduce / prevent “flipping” from depression to mania

- current 1st treatment - atypical antipsychotics

- Lithium (Li⁺) – the classic
- anticonvulsants / neuromodulators
- Lithium / anticonvulsant + antipsychotic

- omega-3s

- like the antidepressants, most newer drugs generally don’t work any *better*, but have fewer side effects
Bipolar Disorder & Mood Stabilizers

- **Lithium** (Li⁺) – the classic
  - chemically very similar to sodium
    - fluctuations in dietary sodium can mess with dosage
    - sodium used to treat lithium OD
  - very effective (~60-70%) at controlling mania / prevents relapse
  - at normal dosages, no effect in normal individuals

- bad side effects with narrow dosage range:
  - GI distress, tremor, lethargy, dizziness, slurred speech, ataxia, muscle weakness, muscle / eye twitches, massive weight gain, thyroid enlargement / goiter, cardiac arrhythmia, impaired concentration, memory, psychosis, stupor, death
  - teratogenic (harmful to developing fetus heart – especially 1st trimester)
  - relapse often result of non-compliance (almost 50%)

- also, patients can miss the “high” of manic phase
- when halted, increased risk of suicide
- relatively high % of patients resistant
Bipolar Disorder & Mood Stabilizers

● **Pharmacokinetics:**
  - rapidly absorbed orally, but crosses BBB slowly and erratically
  - long $\frac{1}{2}$ life (~1 day)
  - stored in cells: ~2 weeks for “steady state” blood levels
  - excreted **unchanged** by the kidneys

● **Pharmacodynamics:**
  - not well-understood (2nd messengers / intracellular enzymes)
  - upregulates expression of neurotrophic / neuroprotective proteins (CREB, bdnf, bcl-2)
    
    suggests early pharmacological treatment may reduce neuropathology

  - very narrow dosage range limits use (requires blood level checks)
  - starting to be used in combination with other drugs
Anticonvulsants / neuromodulators:
- used to control epilepsy
- typically augment GABA or decrease glu ("depressants")

Depressant-type drugs:
- GABAergic
  - barbiturates - bad side effects (like death)
  - benzodiazepines
  - GABA receptor upregulators
  - GABA breakdown and reuptake inhibitors
- Voltage-gated Na channel blockers

"Atypical" antipsychotics - antipsychotics have a long history of use in bipolar treatment (acute manic phase, prevention of relapse)