Episode 020: The History and Use of Antipsychotics

David Puder, M.D.

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There are no conflicts of interest for this episode.

In my last post, Dr. Cummings and I talked about what psychopharmacology is, how medicine works in our body, and what factors affect medicine absorption rates.

In the latest podcast, Dr. Cummings and I talked about antipsychotics, the particular branch of psychopharmacology that deals with medicines that treat psychotic experiences and other mental disorders, such as:

- Schizophrenia
- Severe depression
- Severe anxiety
- Bipolar disorder
- Psychosis exhibiting hallucinations and delusions

The History of First Generation Antipsychotics

The use of antipsychotics as medication began in 1933 in France. The research around developing antihistamines evolved into the introduction of promethazine. This drug produced sedative side effects, so doctors started prescribing it before surgeries as a calming agent.

Eventually, a doctor studied the derivatives of promethazine, altered it, and developed chlorpromazine. It was mostly used as a pre-surgery anti-anxiety pill, until psychiatrists took note of the calming effect of the drug and began prescribing it to their patients.

Prior to chlorpromazine, the options for treating psychotic patients were electroconvulsive therapy, hydrotherapy, and putting patients in an insulin coma. None of those are antipsychotic in nature.

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When two psychiatrists, Dr. Delay and Dr. Deniker, gave 38 psychotic patients a test round of chlorpromazine, they noticed the patients were calmer, and also less psychotic—they had less delusional thinking, fewer hallucinations, and fewer psychomotor-agitation symptoms. Deniker and Delay began giving talks on the benefits of the drug, and in 1955, chlorpromazine became available in the United States. Chlorpromazine is still used today as a treatment for different mental illnesses and mood disorders.

Once the government saw the positive effects of chlorpromazine, it began to shut down mental health facilities. There was no longer as large of a need to house psychotic patients, and they saw an opportunity to cut costs. However, they did not create adequate sources in the community for ongoing care. California alone is estimated to have 40-60% of homeless people that have a mental disorder.

Once chlorpromazine became a success, pharmaceutical companies rushed to create their own version of an antipsychotic drug. Because chlorpromazine was the grandfather of the first generation of antipsychotic drugs, the rest of that generation can be categorized by their ability to merely block dopamine D2 receptors in the brain.

In repeated studies, dopamine antagonism is responsible for 92% of their effectiveness. It also led to the thought that people were psychotic because they had too much dopamine. Since then we have found that their are much more complex psychopharmacological dynamics going on in psychosis.

Second Feneration Antipsychotics

The next set of antipsychotics that came on the market were clozapine, olanzapine, risperidone, and other related drugs. Those medications had less effects on motor movement than the first generation drugs.

Clozapine is a poor antagonist of dopamine- blocking 30-40% of dopamine receptors but also promotes the activation of glutamate through activation of NMDA receptor, which increases activity in the frontal lobe (which helps with schizophrenia's negative symptoms).

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Clozapine had more system-wide changes than just dopamine suppression, and it had more positive response from patients. It was more effective—40-60% of people who won't respond to a first generation antipsychotic, do respond to clozapine.

However, in Finland in 1975, 6 people taking clozapine died due to agranulocytosis (lowered white blood cell count, leading to a severe lack of immunity). A lowered neutrophil count (called agranulocytosis) can show potential problems with fighting off normal bacteria we live with all the time. When patients are on clozapine, initially they need weekly blood checks for this reason.

Despite the risks, clozapine can be an incredible drug—I have one patient who was schizophrenic and homeless, and she is now back in school and recently graduated with a perfect GPA! People who had been dysfunctional for decades, who are given clozapine, can become extremely high functioning. Key to success here was her willingness to work with me, despite having to try different things before something worked.

A trial run on a antipsychotic should be done at a minimum of 6 weeks, and blood tests must be conducted to make sure that the concentration of the medicine is at good therapeutic-dose levels. Dosage alone is sometimes not enough because we all metabolise drugs so differently. I have uploaded recommended levels in my resource page.

Third Generation Antipsychotics

What is deemed the third generation of antipsychotics, aripiprazole and brexpiprazole are **partial dopamine receptor agonists**. They keep dopamine at a max of 25% in the brain which due to the high affinity to the receptor it does not vary much based on dose.

The good thing about this generation of drugs is that they don't lower blood pressure, cause insulin resistance, and are not sedating in nature.

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It works for some people, it doesn't for others. But when it does work, it works really well.

Side Effects of Psychiatric Medicines

Akathisia is the inability to stay still, characterized by a feeling of inner busyness. It is a miserable side effect, exhausting to the patient.

If someone is experiencing this, they should immediately call their psychiatrist or go to an emergency room.

One of Dr. Cumming's patients described it as "ants running up and down the bones of his legs." It usually involves an anxious feeling, and a desire to move the lower extremities of the legs. Akathisia can be caused by any drug that lowers dopamine (including SSRIs).

This syndrome is so complex because it involves several compounds, including dopamine, norepinephrine, acetylcholine, and serotonin inputs. Options for treatment include: choosing a lower dosage, picking another dopamine antagonist that is less strong (quetiapine or clozaril), or prescribing a drug like amantadine, propranolol, mirtazapine or clonazepam (more nuance in the podcast on this).

It is a harmful disorder, and one to watch out for in patients. If a patient is sent home from the hospital experiencing these symptoms, but is not properly vetted for akathisia, a doctor could be subject to serious legal repercussions.

The questions to test a patient for akathisia are:

- Is the person moving? Can they not sit still?
- What is their internal sense of restlessness and anxiety?
- How much are they distressed by these feelings?

Acute dystonia involves muscle spasms and it affects movement, causing the posture to twist abnormally. It can be painful for patients to experience. This occurs because of too little dopamine in the basal ganglia part of the brain.

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Parkinsonism involves muscle stiffness and slower movements. It's usually uncomfortable, but not a miserable side effect. This also occurs because of too little dopamine in the basal ganglia part of the brain.

The Future of Antipsychotics

With each generation of new medicines, we've gotten closer to being able to help people stabilize their psychosis. We haven't been able to achieve complete wellness.

Dr. Cummings says he has hope that with further advances in the medical field, we will be able to identify who is at risk. There is hopeful data that we may be able to one day prevent the development of schizophrenia.

History of Antipsychotics (notes by Arvy Tj Wuysang).

- 1933, France
    - Initiative to develop antihistamine as treatment began
    - 1947
        - Promethazine
            - Produced sedation and calmness in animal models
            - Not highly effective in humans, but found to provide calmness in preoperative settings
    - 1950
        - Discovery of Promethazine Derivatives, especially Chlorpromazine
            - Initially tried in a surgical military hospital in France by Dr. Henri Laborit (1914-1995)
            - Successful in making people calm and indifferent to impending surgery
            - The medication was tried it in a volunteer
                - The individual reported favorable effects, until he stood up and promptly fainted
                - Determined as not safe in pre-operative setting because it was too effective as alpha-adrenergic antagonist in lowering blood pressure

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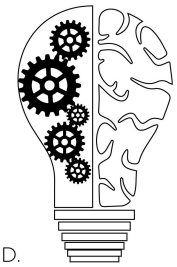

- 1952
  - Dr. Pierre Deniker (1917-1998), psychiatrist, with Dr. Jean Delay (1907-1987), his superintendent in Sainte-Anne's Hospital in Paris, led the Chlorpromazine introduction as a psychopharmacologic agent
    - They were interested in the calming effect of the drug
    - Tried the drug in psychotic agitated patients
      - Treatment options in those days were limited to:
        - Electroconvulsive Therapy
        - Hydrotherapy
        - Insulin coma
      - None of which were antipsychotic in nature
    - Tried it in 38 patients, made patients calmer, and less psychotic!
      - Especially effective for positive psychotic symptoms like hallucinations, delusional thinking, psychomotor agitation
    - Findings were impressive enough that Deniker began giving talks about the drug, including a conference in Montreal, that led to its introduction in North America
- 1955
  - Chlorpromazine was approved for usage as antipsychotic in the US
  - Subsequently used worldwide
  - Led to the deinstitutionalization of a lot of psychotic patients
    - Created a problem of lack of follow up of psychotic patients
      - I.e. California has around 357,000 homeless individuals, estimated 40-60% suffer from mental disorder with schizophrenia spectrum highly represented in that percentage
      - State spends about $200,000 per year per person to care for people committed to state hospitals. Funds committed to patients that are discharged from state hospitals are very minimal.
  - Led to development of a whole host of antipsychotic agents

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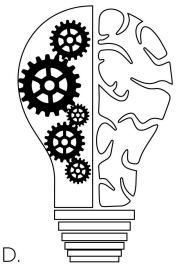
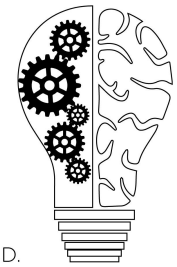
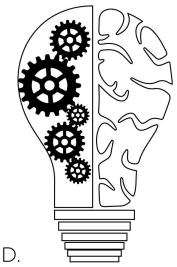


- 1960s
  - There was an explosion in the invention of antipsychotic drugs
  - US FDA took a stance, did not allow approval of antipsychotic drugs that are not clearly better than chlorpromazine or haloperidol
  - 1st generation antipsychotics all work by blocking Dopamine D2 receptors in the brain, counts for 92-23% of variance in mechanism
  - Led to the simplistic dopamine hypothesis of psychosis
- 1958
  - 2nd generation antipsychotic discovered by Eichenberger and Schmutz from the Swiss pharmaceutical company Wander AG, Clozapine
  - Created because 2 other -antadine antipsychotics have been successful, Loxitane (Loxapine) and Perlapine
  - Clozapine was initially thought of as a failure because it did not produce dystonia in white lab mice, as expected in 1st generation antipsychotics where it blocks dopamine effects in the brain
  - Clozapine found to be a poor antagonist to dopamine, only blocks **30-40% of dopamine receptors**. Although, it promotes release of **glutamate**, by binding to an allosteric site for glycine in the NMDA receptor, which in turn increases activity in the frontal lobe and suppresses dopamine release in the mesolimbic system.
  - A number of small studies in the 1960s found that patients that don't respond to 1st generation antipsychotics responded well to Clozapine treatment by showing better response of both positive and negative symptoms of schizophrenia.
- 1970s
  - 1972, Clozapine usage was introduced in Austria
  - 1974, Clozapine usage was introduced in Germany
  - 40-60% of people that did not respond well to 1st generation antipsychotics, responded well to Clozapine
  - 1975, 5 people in Finland died after Clozapine treatment due to agranulocytosis



        - Clozapine found to trigger formation of antibodies targeting bone marrow cells that make neutrophils and essentially shut down a person's immune system
        - Must monitor Absolute Neutrophil Count closely when prescribing Clozapine
            - Monitor weekly for 6 months, then every 2 weeks for another 6 months, and monthly for another year (in the USA)
            - Risk for agranulocytosis decreases with time: peaks at 4 months of exposure at about 1.3%, .38% after 1 year of exposure, .06% after 2 years of exposure
    - Clozapine usage in the US today
        - Siskind, D., McCartney, L., Goldschlager, R., & Kisely, S. (2016). Clozapine v. first-and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. The British Journal of Psychiatry, 209(5), 385-392.
        - 15-20% of patients in California State Hospitals are on Clozapine, 53% in New York State
        - Response rates to drugs other than Clozapine is pretty miserable in State Hospitals
        - Olanzapine response rate even at high plasma concentrations is only 9%, compared to 40-60% for Clozapine. Every other antipsychotics' response rate is between 0-5% for the severely psychotic, mentally ill patients.
        - If patients meet Kane criteria (after John M. Kane)---treatment failure after two clearly adequate trials of antipsychotic treatment with minimum of 6 weeks duration with therapeutic plasma concentration---odds that they will respond to anything other than Clozapine is fairly low.
        - Common mistake that clinicians make is to go by dosage as a measure of whether a person is receiving adequate medication
            - Dosages only weakly correlates with plasma concentration since the metabolism of antipsychotic drugs is so variable



        - Measuring plasma concentration to reach therapeutic levels is crucial in antipsychotic drugs administration, especially in patients who are seemingly refractory to treatment, to ensure adequate treatment
- Akathisia as side effect of antipsychotics
    - Very rarely happens with Clozapine use
    - Akathisia is a very miserable side effect of antipsychotics, described as “ants crawling up and down the bone of your legs” by a particular patient
    - Characterized both by internal sense of anxiety and a near irresistible urge to move
    - Barnes Akathisia Rating Scale, most commonly used to measure akathisia symptoms. Based on three main factors:
        - Objective movement
        - Internal sense of restlessness and anxiety
        - How much are they distressed by these feelings
    - Akathisia is a concerning and common reason for malpractice
    - Underlying pathophysiology of akathisia is distinct compared to other extrapyramidal symptoms, involves not only dopamine and acetylcholine. It also involves norepinephrine and serotonin inputs to basal ganglia, makes it a difficult syndrome to treat successfully.
    - Treatment options for akathisia:
        - Use a less robust dopamine antagonist, such as Quetiapine or Clozapine
        - Use lower dose of the antipsychotic
        - Use Amantadine, increases dopamine release in the basal ganglia
            - Was originally devised to treat influenza A

        - Discovered to be effective in treating extrapyramidal symptoms, also effective for tardive dyskinesias (15% respond to amantadine)
        - However, it is not as effective as B-blockers or Mirtazapine
        - Amantadine is not anticholinergic (no memory problems, no GI side effects, no blurred vision, no urinary retention)
    - Head-to-head trial between Propranolol versus Mirtazapine versus placebo, shows mirtazapine as more effective in treating akathisia
        - Poyurovsky, M., Pashinian, A., Weizman, R., Fuchs, C., & Weizman, A. (2006). Low-dose mirtazapine: a new option in the treatment of antipsychotic-induced akathisia. A randomized, double-blind, placebo-and propranolol-controlled trial. Biological psychiatry, 59(11), 1071-1077.
        - **Mirtazapine** at 15 mg at bedtime was effective in 43% of patients
        - Placebo was effective in 7% of patients
    - Akathisia may present as side effect in SSRIs and antiemetics (compazine)
- Expected or Therapeutic plasma concentration ranges for antipsychotics and mood stabilizers
    - DSH Psychotropic Medication Policy (see resource page)
- Aripiprazole (Abilify)
    - 3rd generation antipsychotics, partial dopamine agonist

- Has high affinity for dopamine receptors, higher than 1st and 2nd generation antipsychotics. If Aripiprazole is present at therapeutic concentrations, 1st and 2nd generation will have very little interaction with dopamine receptors.
- Keeps dopamine signaling at about 25% of dopamine's maximum signal transduction, tends to produce all or nothing response in terms of treating psychotics. Not much ability to vary where dopamine is blocked because of it's high affinity.
- Side effect profile is very favorable. Largely metabolically neutral, tend not to cause weight gain, glucose intolerance, and lipid abnormalities. Low affinity for alpha receptors or histamine receptors, is not very sedating and does not lower blood pressure.
- Use outside of schizophrenia
  - I.e. risperidone and olanzapine also exhibit utility as mood stabilizer and antidepressant.
  - 3rd generation antipsychotics also tend to improve mood, driven by quality of the molecules and in part by the desire of pharmaceutical companies to broaden their market
  - Use in dissociative state, such as Borderline Personality Disorder
    - Antipsychotics can help bring patients out of dissociative state in short period of time
    - Borderline patients was found to have a significant limbic dysfunction, hence antipsychotics may be helpful

- Future of Schizophrenia Spectrum Treatment
  - There is great need to identify individuals at risk for the disease and treat them with lower dose of antipsychotics. Hopeful data is currently present in support of this approach to lower the incidence and prevalence of schizophrenia.