Episode 019: How Psychiatric Medications Work with Dr. Cummings

David Puder, M.D.

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This week I interviewed Dr. Cummings, a psychopharmacologist, on the Psychiatry and Psychotherapy Podcast. Below is a brief introduction to the episode. For more detailed notes by Dr. Cummings, go to my resource page.

What is psychopharmacology?

Psychopharmacology is a branch of psychiatry that deals with medications that affect the way the brain works. The medicines used in psychopharmacology treat illnesses whose primary concerns and issues are mood, cognitive processes, behavioral control, and major mental disorders.

It is a unique branch of pharmacology because the illnesses are usually addressed by both medication and psychotherapy.

What makes a drug psychiatric in nature?

What makes a drug labeled as psychotherapeutic, is the intent behind the prescription. Some drugs will serve more than one purpose, so understanding why it was prescribed is important. For example, valproic acid is helpful in treating seizure disorders, and also bipolar disorder. For the seizure disorder, it would not be considered a psychotherapeutic drug. For the bipolar disorder, it would be considered a psychotherapeutic drug.

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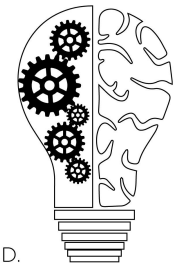

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How do medications work?

All medicines go through the same steps of digestion in our bodies. They are liquified in the stomach, and then absorbed. The drug travels through the liver, and then into the blood supply, which brings it to the organ it was designed to target.

Our bodies have receptor sites, made of protein, that sit on the surface of a neuron, or a nerve cell in the brain. The drug, when it reaches that receptor, either binds to it and blocks it, or it can help the neurotransmitter work to further what it does naturally.

For example, caffeine is an adenosine blocker. Adenosine is a naturally occurring molecule in our bodies that calms us down as the day wears on, preparing us for sleep. Caffeine, as a drug, blocks our natural adenosine from reaching its receptor; it keeps us awake.

Medicines work in the same way—inhibiting or helping certain molecules reach their targeted organs.

How absorption and dosage rates affect medicine

Many things can affect absorption rate, and medications absorb at different rates, and at different potencies.

Things like gastric bypass, (when they take out a part of the stomach and intestines) can affect absorption rate of drugs. One of my patients had a stomach surgery, and afterwards, their depression came back. I told them to start grinding their pills to help with absorption rate of their antidepressant, and their medication started working again.

Our livers play the main part in absorption. Sometimes they are gatekeepers, and they can hinder absorption rates dramatically. Animals and plants have been at war for thousands of years. Plants create toxins to try to discourage animals from eating them. Our livers develop different enzymes to break down those toxins in order to make the

plants safe for our bodies. Those same enzymes break down medications. Our bodies are constantly adapting and changing, adjusting to what we consume.

As a psychiatrist, it's important to pay attention to absorption rates to make sure our patients are getting maximum benefit. Maybe a patient has defected genes that limit absorption rate, or deficient enzymes to break down the medication. Or maybe other medications are interacting and changing absorption rates.

A few times in my practice I have seen patients come in on multiple medications which are interacting poorly. For example, they are on a medication called amitriptyline and also on something that blocks its breakdown like fluoxetine. In our session they complain that they are confused and disoriented. I figure out that the drugs they've been prescribed is either inhibiting, interacting with, or increasing the effect of another medication. Once we learn that, we can make changes to their prescriptions, and they return to feeling normal.

When you change the concentration of a medication, you can destroy the entire point of the prescription in the first place. There are numerous computer programs that can help us determine problems with drug interactions. Those programs can sometimes point out what could become a clinical problem, but often point out minor, irrelevant interactions.

Just prescribing medicines, without taking into account the individual ecosystems we each have, is often a practice of trial and error. With properly administered tests and observation, we can move towards an effective dose and effective treatment plan.

Because there are so many things that can change a drug level in the body, taking a plasma concentration may be the best way to assess if the dose is appropriate (check out my resource page for a list of appropriate levels). A high or low blood level might hint that the person is a rapid metabolizer, poor metabolizer, has GI issues with absorption, or has other medications or supplements that are increasing or decreasing the dose.

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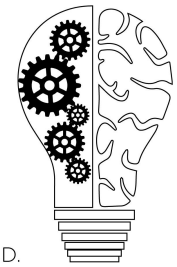

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How to reduce negative side effects

One of the reasons that people develop problems with psychiatric side effects to medications is because they are increased too fast. There is a balance between wanting to get someone to an appropriate dose, and minimizing side effects.

Too often, patients are prescribed a medication at full force and, due to sudden side effects patients will quit taking the medication.

If the medicines were administered in a slower onramp, giving time and attention to their perceived absorption rates and side effects, many problems with those medications would stop.

Is therapy or medication more helpful?

There are many trains of thought on psychotherapy and medication. Some people want a pill to fix everything. However, not everything is a chemical imbalance in the body and can be fixed with a pill.

If someone comes to me with a psychiatric problem, I almost always recommend psychotherapy, and often prescribe medication. Medications help, especially if someone has severe mental illness. If levels are mild to moderate, I find psychotherapy and lifestyle changes (like strength training and diet) are more effective for long term success.

Rates of prescribing medication has increased and use of psychotherapy has decreased. Too many patients are taking medication without psychotherapy or lifestyle changes. One study shows that 73% of antidepressants are prescribed by primary care physicians (Mojtabai, 2008). Antidepressant use has increased from 1996 to 2005 from 6% to 10% while rates of therapy have gone down from 31% to 20% for those on antidepressants (Olfson, 2009).

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Because of that, people are not being treated in the most effective way possible. This is especially the case when considering the treatment of psychological trauma, for which talk therapy can cure in ways medications can not.

Through both medications and psychotherapy, we can rewire the brain. In one study on obsessive compulsive disorder (OCD), two groups of people were studied—those who underwent cognitive behavioral therapy, and those that took medication. The therapy was found to be as helpful in eliminating OCD symptoms. However, the OCD symptoms returned when the medication was stopped. The symptoms did not return when the person had received cognitive behavioral therapy.

Dr. Cummings uses a simple guideline to see if someone would benefit from medicine or talk therapy. If what the person is depressed about is something in their lifestyle—their weight, their job, their relationship, lifestyle changes and talk therapy will probably be most effective.

If someone is experiencing neurovegetative symptoms of depression, such as: loss of appetite or increased appetite, severe energy loss, severe sleep disturbance with early morning awakening, physically slowed down, they are suffering from brain disturbances that are helped by medication.

For more notes by Dr. Cummings, go to my resource page.

Mojtabai, R., & Olfson, M. (2008). National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the national comorbidity survey replication. The Journal of clinical psychiatry.

Olfson, M., & Marcus, S. C. (2009). National patterns in antidepressant medication treatment. Archives of general psychiatry, 66(8), 848-856.

See below for notes on the episode writen by Arvy Tj Wuysang.

- **Defining Psychopharmacology and Psychopharmacologic Agents**

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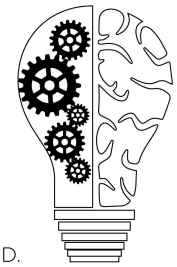

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- **Psychopharmacology: Study of medications and substances that affect how the brain works, both positively and negatively**
- **"Intent" in using versatile drug classes as psychotherapeutic agents**
  - **Valproic Acid usage as an anti-epileptic drug vs mood disorder drug**
  - **Caffeine usage as stimulant**

- **Metabolism and Physiologic Distribution of Psychopharmacologic Agents**
  - **Gastrointestinal surgeries and their effect on psychiatric drugs' absorption**
    - **Olanzapine will not be absorbed as effectively in individuals who had Gastric Bypass Surgery because of its slow absorption. Lorazepam, on the other hand, has a characteristically rapid absorption and will not have much disturbance in its absorption even in the context of post Gastric Bypass Surgery.**
  - **Properties of drug absorption within the liver**
    - **Cytochrome P450 enzymes**
      - **Evolutionary developed to metabolize plant toxins**
      - **Common classes that plays significant role in psychiatric drug metabolism**
        - **2D6, 2A4, 1A2**
    - **Interaction with other drugs**
      - **2D6 blockers (Fluoxetine, Paroxetine, Bupropion) will elevate plasma Amitriptyline levels.**
      - **Inducers will decrease plasma levels**
    - **Benefits of using drug-drug interaction applications/softwares**
    - **Importance of monitoring plasma levels versus genetic testing in determining effective/safe dosage**
    - **UCLA Imipramine Titration Study**

        - If receptors are given time to adapt to the medications, oftentimes side effects may be minimal
        - Imipramine titration goal of 150 mg
            - 1st group: increase of 25 mg increments per week
                - experienced significant side effects (sleepy, dry mouth, low BP)
            - 2nd group: increase of 10 mg increments per week
                - achieved the same blood levels as the first group but experienced minimal side effects
- How do psychiatric drugs work?
    - Most bind to receptor sites that typically sit on the surface of a neuron and initiate a variety of action related to a particular neurotransmitter
        - Agonists
        - Antagonists
        - Partial agonists
        - Reuptake inhibitors
    - Immediate vs Delayed Effect of different classes of psychiatric drugs are determined to their specific kinetic mechanisms
        - Benzodiazepine, ETOH has immediate effect
        - SSRI works through initiation and adaptation, produce downstream 2nd messenger effects, needs time and repetition to take effect, analogous to how psychotherapy works.
            - Baxter, L. R., Schwartz, J. M., Bergman, K. S., Szuba, M. P., Guze, B. H., Mazziotta, J. C., ... & Phelps, M. E. (1992). Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Archives of general psychiatry, 49(9), 681-689.

        - **Studied people with OCD, especially contamination obsession, for 6 weeks.**
            - **1st group: behavior response prevention**
            - **2nd group: fluoxetine**
            - **Both have similar biological effect in terms of their neurologic circuits as portrayed on PET scan imaging**
            - **At 6 months follow up, group with behavior response prevention has more permanent behavior change.**
            - **Follow up study of using combination of SSRI and behavior response prevention showed greater benefit than either treatment alone.**
- **How long should one stay on antidepressants?**
    - **Dependent on frequency and severity of depressive episodes**
        - **Single depressive episode**
            - **Treat to remission, keep in remission for 1 year, gradually taper the antidepressant**
        - **2-3 episodes of depression**
            - **Essentially, needs to stay on antidepressants permanently**
            - **Remains vulnerable to depression**
            - **Antidepressants ameliorates symptoms, but does not cure underlying pathophysiology**
            - **Each episode makes the next episode more likely!**
        - **Analogous to Diabetes Mellitus treatment**
            - **I.e., Blood sugar needs to be controlled for the rest of the patient's life**

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- **How do we determine between using medications versus lifestyle therapy in treating psychiatric conditions?**
    - **Depends on presentation**
        - **If merely dysphoric, can start by introducing lifestyle changes**
        - **If greater severity, showing neurovegetative signs, may start with medications right away**
            - **Neurovegetative signs: Loss/increase of appetite, significant weight changes, severe loss of energy, severe sleep disturbance, psychomotor agitation/reduction**
- **Pathophysiology of Depression**
    - **Multifactorial, not merely a single neurotransmitter deficiency**
        - **Core dysfunction of limbic system, influenced by disruption of multiple neurotransmitters**
        - **Inflammation may play a role through cytokine dysregulation**
    - **Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. Prevention & Treatment, 1(2), 2a.**
        - **Only ⅓ of patients studied had full remission of depression symptoms with antidepressants.**
    - **Variety of placebo effects in depression studies**

Dr. Cummings has recommended these articles to read along with this session (thank you Mona Mojtahedzadeh M.D. for organizing them and adding some notes):

1. Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: potential therapeutic targets. science, 338(6103), 68-72.

- Depression is associated with reduced brain size and decreased neuronal synapses in regions that regulate mood and cognition (the prefrontal cortex and the hippocampus).
- Antidepressants can block or reverse these deficits.

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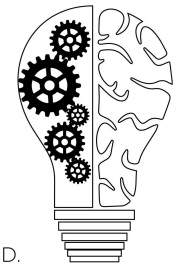

- Typical antidepressants have limited efficacy and delayed response times (weeks to months).
- Ketamine is a N-methyl-D-aspartate receptor antagonist that has been proven to produces antidepressant responses in patients who are resistant to typical antidepressants within hours.
- Ketamine has been shown to rapidly induce synaptogenesis.
- Ketamine can also reverse the synaptic deficits caused by chronic stress.
- Findings highlight the importance of a synaptogenic hypothesis of depression and treatment response.

2. Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E. K., ... & Ferrier, I. N. (1997). D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics, 7(6), 479-484.

3. Hyman, S. E., & Nestler, E. J. (1996). Initiation and adaptation: a paradigm for understanding psychotropic drug action. The American journal of psychiatry, 153(2), 151.

4. Tracy, T. S., Chaudhry, A. S., Prasad, B., Thummel, K. E., Schuetz, E. G., Zhong, X. B., ... & Tay-Sontheimer, J. (2016). Interindividual Variability in Cytochrome P450–Mediated Drug Metabolism. Drug Metabolism and Disposition, 44(3), 343-351.

5. Hunsberger, J., Austin, D. R., Henter, I. D., & Chen, G. (2009). The neurotrophic and neuroprotective effects of psychotropic agents. Dialogues in clinical neuroscience, 11(3), 333.

6. psychotropic medications: overview seminar core handout

7. McCutcheon, R., Beck, K., Bloomfield, M. A., Marques, T. R., Rogdaki, M., & Howes, O. D. (2015). Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms. Journal of Psychopharmacology, 29(8), 892-897.

- Big number of patients with schizophrenia have poor response to antipsychotics medications.

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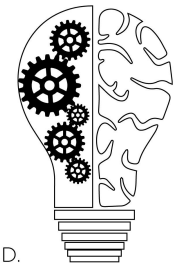

- Possible causes are subtherapeutic plasma levels of the medication or medication ineffectiveness.
- This study examines 36 patients with treatment resistant schizophrenia and assesses the extent of subtherapeutic antipsychotic plasma levels and the frequency of antipsychotic plasma level monitoring in standard clinical practice.
- Antipsychotic plasma levels were found to have been measured in only one patient in the year prior to our study.
- Over one-third of patients had subtherapeutic antipsychotic levels.
- In detail: sixteen (44%) patients showed either undetectable (19%) or subtherapeutic levels (25%), and 20 (56%) patients had levels in the therapeutic range.
- Black ethnicity, shorter duration of current treatment, and antipsychotics other than olanzapine and amisulpride were factors significantly associated with subtherapeutic plasma levels.
- This study indicates higher chances for under-treatment rather than treatment-resistance for those patients with poor response to antipsychotic medications.
- On another note, the measurement of antipsychotic levels may be under-utilised.