Episode 024: The History, Mechanism and Use of Antidepressants

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There are no conflicts of interest for this episode.

In this week's episode of the podcast, Dr. Michael Cummings and I talk about the history of antidepressants, and their use in overcoming depression and anxiety disorders. Below is a short blog on the topic to complement the podcast and subsequently I you can find detailed notes on the topic further below.

What is Depression?

The overarching term "depression" is characterized by feelings of sadness and hopelessness, anxiety, and loss of pleasure.

But there are many different types of depression and depressive disorders:

- Psychotic depression
- Bipolar disorder with depression
- Seasonal affective disorder
- Major depression
- Chronic depression (dysthymia)
- Postpartum depression
- Premenstrual dysphoric disorder
- Atypical depression
- Melancholic depression
- Depression due to a medical illness or medication

Some symptoms of depression are:

- Weight gain or loss
- Sadness
- Anxiety

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- Agitation
- Social isolation
- Sleep problems
- Guilt
- Loss of pleasure
- Loss of interest in activities
- Mood swings

Major depression

Major depression is characterized by a continuous feeling of sadness—it does not lift for long periods of time. The average length of an episode of major depression, if not treated, last around 11 months. People with major depressive disorder often had an average of four to eight episodes during their lifetime.

Each episode of major depression usually makes the next episode more likely.

The annual prevalence rate for major depression estimated in the US and in Europe ranges from 2-7%. But, if somebody has an episode of major depression, the odds that they have a second episode at some point in their life rises to almost 50%. Then, for each episode they have after that, the probability of the next one becomes more likely.

For people who had recurrent episodes of major depression, by the time they were in their 50s, 60s, or 70s, they had often become chronically depressed or apathetic; their life had deteriorated significantly.

Melancholic depression

Melancholic depression is at the severe end of the depressive spectrum.

These people have a severe loss of enjoyment, and they usually lack energy. They often develop mood congruent psychotic symptoms, such as delusions that they are guilty for everything in the world.

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This tends to be the most resistant form of depression. When severe. people who suffer with melancholic depression sometimes require electroconvulsive therapy to snap them out of a depressive state.

Is depression a chemical imbalance?

People with recurring bouts of major depression can actually experience anatomical damage to the cortex and the spine, because depression is caused by, and can also cause further, chemical changes in the brain. How does this work?

- One main marker for major depressive occurence is a rise in the release of corticotropin from the pituitary, which eventually stimulates our adrenal glands to produce more cortisol.
- There is a 30-40% decline in the rate of metabolic activity among neurons. Lowered metabolic activity among neurons.
- There is a steep decline in the production of neurotrophic factors, proteins that promote neuron activity and cell growth in the brain. As a consequence, there is a thinning of the cortex, a loss of the dendritic spines on neurons.

The History of Antidepressants

Doctors used to believe depression was norepinephrine or serotonin deficiency. We now view depression as the inability of the limbic system to be modulated by the neurotransmitters.

Antidepressant medications target this problem by increasing the ability of these molecules that deal with our emotions, motivations and memory to do what they need to do.

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Before antidepressants

Prior to the discovery of antipsychotics and and antidepressants, depressed and anxious patients were sent to restful places, or asylums. In the late 19th century, the number of asylums surged.

They used psychoanalysis and psychotherapy to treat patients, but there was no medicinal treatment for psychiatric issues. They sometimes used chemically induced convulsive therapy to induce a grand mal seizure two to three times a week, and it was quite a brutal treatment.

Electrical induction of convulsive therapy came about in the 1940s. It was widely used in both mood disorders and psychosis.

As a result of these two treatments, people had broken bones and muscle damage. Because of that, electroconvulsive therapy developed a horrible reputation.

The treatment was later reformed in terms of paralyzing people and using anesthesia prior to treatment. These steps made electroconvulsive therapy much more humane than it originally was. Now people don't experience the side effects they would have back then. It still remains the most effective treatment there is for severe melancholic or catatonic depression.

As I discussed in a previous blog on psychopharmacology, in 1940 the original antipsychotic was originally an antihistamine. When doctors noticed the sedative effect it had, they started prescribing it for pre-surgery anxiety. It was the first time doctors prescribed a medication to treat mood.

In 1951, Dr. Roland Kuhn discovered that imipramine, a drug originally tried for psychosis, was not in fact effective in treating psychosis. He did found that imipramine was effective in improving mood and anxiety symptoms.

This led to to the discovery of other tricyclic antidepressants, such as amitriptyline, nortriptyline, and desipramine.

First generation antidepressants

After World War II, there was a surplus of hydrazine missile fuel leftover. People began experimenting with hydrazine as a base compound for development of drugs.

One of the first drugs that came out of that endeavor was Isocarboxazid, which was initially used to treat tuberculosis.

It turned out that a few people who were being treated for tuberculosis happened to be bipolar and became manic while taking isocarboxazid, which led to the discovery of monoamine oxidase inhibitors (MAOIs).

MAOIs stop the breakdown of serotonin, dopamine and norepinephrine in the brain. MAOIs stop that enzyme from removing those chemicals from the brain. The result is more balanced neurotransmitters—and a lack of depression.

Still, the possible side effects including incredibly high blood pressure when eating certain foods made scientists keep searching for better alternatives.

SSRI Antidepressants

Selective serotonin reuptake inhibitors were introduced to the market in 1987, with the introduction of Fluoxetine. The SSRIs were almost instantly popular because they were much safer.

These drugs increase the amount of serotonin available in the brain.

The SSRI became very widely used very quickly for treatment of depression.

They have even been found useful because the increased serotonin input to the limbic system they create (the part of our brain that deals with motivation, learning, emotions and memory) decreases the amount of anxiety and vigilance that the person has.

SSRI was also found to be effective for:

- Post traumatic stress disorder (PTSD)
- Obsessive compulsive disorder (OCD)
- Generalized anxiety disorder (GAD)
- Social phobias
- Impulse based disorders (like binge eating)

If someone was still resistant to SSRI medication and is still depressed, electroconvulsive therapy is still the best option available.

When do you Prescribe Antidepressants?

If the initial episode of depression is not severe to the point that it's inducing suicidal ideation or impairing their ability to engage in activities of daily living, then psychotherapy and exercise should be the first treatment.

If the following statements are true, antidepressants could be prescribed:

- The person doesn't respond to exercise positively with fewer depressive symptoms
- Psychotherapy does not seem to be helping
- The depression is becoming severe
- Their family is genetically tended towards depression

Overall, about 40% of the probability of becoming depressed is genetically determined, the other 60% arising from the environment.

There are also important gender differences, women during their reproductive years have about twice the rate of major depression compared to men.

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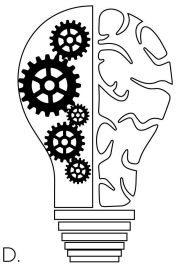
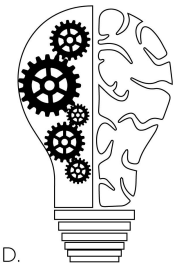
If somebody has recurrent episodes of depression, an antidepressant should be considered, and possibly continued indefinitely. However I often recommend for these patients a combination of treatments including exercise, diet, effective therapy, and over time can get them on lower doses or less medications.

Below is a detailed review of the episode, with most of the content. Thanks Arvy Wuysang (MS4) for your help with this!

- History of Antidepressants
    - The investigation of antihistamines leading to the discovery of promethazine, chlorpromazine brought on a decade of intensive discovery and investigation of different antipsychotic compounds.
    - Swiss Psychiatrist, Dr. Roland Kuhn (1912 - 2005) discovered the Tricyclic Antidepressant, Imipramine.
        - His experiments with Imipramine led him to the discovery that it was not effective in treating psychosis. However, he found that Imipramine was effective in improving mood and anxiety symptoms.
        - This led to to the discovery of other Tricyclic Antidepressants, both tertiary and secondary amines, such as amitriptyline, nortriptyline, and desipramine.
    - As an after effect of World War II, there was a great amount of hydrazine missile fuel leftover. People began experimenting with hydrazine as a base compound for development of drugs.
        - One of the first drugs that came out of that endeavor was Isocarboxazid, which was initially used to treat Tuberculosis.
        - It turned out that a few people who were being treated for TB happened to be Bipolar and became manic while taking Isocarboxazid, which led to the discovery of Monoamine Oxidase Inhibitors (MAOIs).
    - How were people treated for depression before the discovery of MAOIs?
        - Sent to restful places in the country, the asylum movement of the late 19th century.
        - Psychotherapy, psychoanalysis

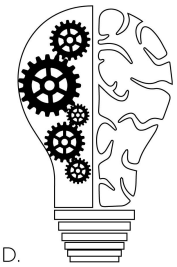


    - Convulsive therapy, discovered by the psychiatrist Von Meduna in Hungary.
        - Was not originally electrically induced, was chemically induced convulsive therapy instead, quite a brutal treatment.
        - Electrical induction of convulsive therapy came about in the 1940s. It became widely used in both mood disorders and psychosis.
        - The treatment was later reformed in terms of paralyzing people and using anesthesia prior to treatment. These steps made Electroconvulsive therapy a much more humane treatment. It still remains the most effective treatment there is for severe melancholic depression.
    - There were no effective pharmacological treatments for depression before the MAOIs.
    - Winston Churchill, was thought to have depression and was treated with Amphetamines, which was later known to be ineffective as an antidepressant.
        - Amphetamines or Methylphenidate are still occasionally used in anergic depressions, such as in HIV, or in the elderly depressed person who has a severe lack of energy as part of their depressive illness, but in combination with antidepressants.
- If someone with melancholic depression does not get treatment, how does the progression of their disease look like?
    - A fairly negative development. The average length of an episode of major depression, if not treated, last around 11 months. People often had an average of four to eight episodes during their lifetime.
    - Each episode of major depression makes the next episode more likely. The annual prevalence rate for major depression estimated in the US and in Europe ranges from 2-7%. But, if somebody has an episode of major depression, the odds that they have a second episode at some point in their life rises to almost 50%. Then, for each episode they have after that, the probability of the next one becomes more likely. For people who had



recurrent episodes of major depression, by the time they were in their 50s, 60s, or 70s, they had often become chronically depressed, apathetic; their life had deteriorated significantly.

- What physiological effects within the brain contributes to the greater likelihood of a subsequent episode of depression?
    - Major depression, aside from changing neurotransmitter signaling, reduces the metabolic rate of neurons in the brain. There is a 30-40% decline in the rate of metabolic activity among neurons. There is a steep decline in the production of neurotrophic factors, proteins that promote neuron activity and cell growth in the brain. As a consequence, there is a thinning of the cortex, a loss of the dendritic spines on neurons. There was evidence that although recovery after major depression is nearly back to original baseline, particularly in recurrent depression, or in people who alternate between major depression and a more minor form of depression called dysthymia, their brain may undergo gradually increasing anatomical damage (cortex and dendritic spines). The accumulating pathology appears to set them up for the next episode, to be more vulnerable to stress diathesis and the occurrence of the next episode of depression.
    - One of the key chief characteristics of major depression is a rise in the release of Corticotropin Releasing Hormones (CRH), which in turn produces an increase in the release of Adrenocorticotropic hormone from the pituitary that stimulates the adrenal glands to produce more cortisol.
        - Cortisol functions as a stress hormone. The intent is to help counterbalance stress and return us to a baseline state. However, in major depression that positive benefit fails, and essentially the person's brain winds up being exposed to chronically elevated levels of cortisol, which has an involutional effect on DNA transcription in cells in the brain, particularly in the limbic system. This have been suggested as the source of treatment resistance as people develop more episodes of depression.
- How does melancholic depression differ from other types of depression?
    - Melancholic depression is at the severe end of the depressive spectrum. These people have a severe loss of enjoyment, they're anhedonic, they



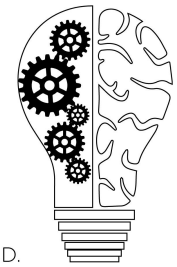
lack energy. They often develop mood congruent psychotic symptoms, such as delusions that they are guilty for everything in the world. They have very pronounced negative rumination. They lose interest in food. In fact, if they're not treated, they just sort of curl up and die.

- Tends to be the most resistant form of depression. These people often wind up requiring electroconvulsive therapy to them out of that depressive state.
- Depression comes in a range of severity. Dysthymic disorder, is the chronic milder form of depression. Major depression, starts just above dysthymia, and progresses to Melancholic depression.

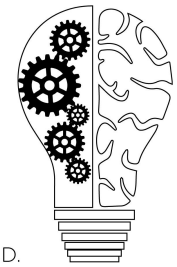
- How severe of a depression warrants a treatment with antidepressants?
  - If the initial episode of depression is not severe to the point that it's inducing suicidal ideation or impairing their ability to engage in activities of daily living, then psychotherapy should be the first treatment. Psychotherapies such as cognitive behavioral therapy, interpersonal therapy, and brief analytic psychotherapy have been demonstrated to be effective in treating depression. Exercise also can be a benefit in mild to moderate depressions.
  - If, however, the person doesn't respond to those treatments, or the depression is becoming severe, or in particular, if this is somebody whose family is somewhat genetically loaded for depression, then treatment with antidepressants becomes a larger consideration. Overall, it's thought that about 40% of the probability of becoming depressed is genetically determined, the other 60% arising from the environment. There are also important gender differences, women during their reproductive years have about twice the rate of major depression compared to men. Premenarche and postmenopausal women have the same rate of depression as men, suggesting that hormonal cycling during the reproductive years may add an additional burden in terms of vulnerability to depression in women.
  - If somebody has recurrent episodes of depression, the thinking is very much along the lines of they should be on an antidepressant and it should be continued indefinitely. It used to be that if somebody recovered from

depression, then after a year, everyone would be tapered off and discontinued. That changed when people began to recognize the progressive nature of major depression. Each episode makes the next one more likely, and the more episodes people have, the more resistant it is to treatment. We should be working to avoid the circumstance in which we now have an elderly depressed person who has lost the capacity to respond to most of the tools we have to work with. That's a very difficult position to be. These are cases where we find ECT to be the only treatment that works.

- The advent of SSRIs
    - The first antidepressants, the TCAs, were never a comfortable medication class in usage. This is largely because these drugs are cardiotoxic at relatively low concentrations. Six to eight times the therapeutic concentration is a potentially lethal concentration. So, taking a week's worth at one time stood a pretty good chance of killing somebody. In a population prone to suicidal thoughts, that's not a very comfortable position to be in. In the case of MAOIs, if the person is exposed to tyramine from food, or to sympathomimetic agents, cold medications in many cases, can produce hypertensive crisis with blood pressures that can cause vascular damage or death.
    - The SSRIs were almost instantly popular after the introduction of Fluoxetine, in large part not because they were more effective than the older antidepressants, but because they were much safer. These drugs selectively inhibit the reuptake transporter for serotonin, thereby increasing the amount of serotonin available in the brain. But by and large, they don't do a great deal else that is toxic or likely to produce problems. So that if somebody overdoses on an SSRI antidepressant alone, it's almost impossible to kill the person. If you mix it with an agent that has other means for increasing serotonin, it can produce serotonin syndrome, which can cause death, but that's a relatively rare negative outcome.
    - The SSRI became very widely used very quickly for treatment of both major depression and dysthymia. For a host of anxiety disorders they have been found useful because increased serotonin input to the limbic



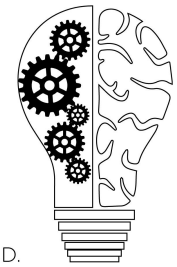
system, particularly the anterior temporal lobe and the amygdala, decreases the amount of anxiety and vigilance that the person has. SSRI was also found to be effective for PTSD, OCD, GAD, social phobias, and even in impulse based disorders like binge eating.
    - The SSRI antidepressants account for about 70% of the antidepressant prescriptions in the United States each year. They are as effective as the mix serotonin norepinephrine antidepressants, in mild to moderate levels of depression. They tend to become less effective than mixed mechanism agents in severe and melancholic depressions.
    - The current model for depression have moved away from the basic idea of norepinephrine or serotonin deficiency. We now view depression as the inability of the limbic system to be modulated by the neurotransmitters. Antidepressants target this dysfunction by increasing the modulatory range of these molecules. It may be that in more severe depression, using a single lever to try to push the limbic system back into operating normally just isn't as effective as using more than one lever.
- What are our treatment options for patients with melancholic depression that are resistant to antidepressants?
    - ECT would be the best option in severe melancholic depression. There are other adjuncts available that have been looked at that show promise. Transcranial magnetic stimulation has shown positive benefit in terms of augmenting antidepressants, as has vagus nerve stimulation in some chronic recurrent depressions. Combining the antidepressant with an effective psychotherapy has been shown to have additive benefits. In many cases of depression, it calls for a multimodal intervention.
    - One of the caveats with the antidepressants is that their efficacy is more limited than we would like it to be. If you look at most antidepressant studies, they report effectiveness in around 60 to 65 percent of samples based on the definition of response as a 50 percent reduction in depressive symptoms. If you're severely depressed, it's great to have a 50% reduction, but that doesn't mean that you're well. If you look at how many people go into remission in those studies, you're now talking about numbers down in the range of about a third. That's not a very satisfactory



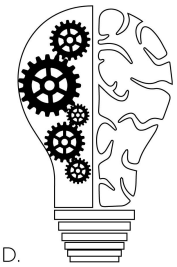
outcome if you're the depressed patient. So, our antidepressant treatments indeed do have limits.

- We've looked at ways of augmenting antidepressants. Combining antidepressants with different mechanisms. Augmentation with mood stabilizers like lithium. In women in particular, supplementation with thyroid hormone is effective in some patients. One of the caveats in this as well, is that many people who are depressed and receive treatment don't really receive adequate treatment. A number of years ago, the American Psychiatric Association (APA) did a survey in both primary care and psychiatric offices looking at dose and duration of treatment for major depression. They found that depressed people in primary care offices got what they judged to be adequate treatment about 41% of the time, and in psychiatric offices about 61% of the time. As psychiatrists, one of the things we can do is to be sure that our patients receive an adequate dose of antidepressants for an adequate duration. Duration in this case means at least six to eight weeks to see if the person will respond, while pushing the dose to the upper therapeutic range.

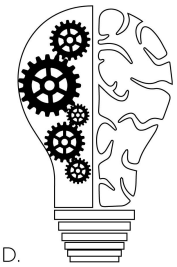
- The black box warning of SSRIs in increasing suicidality for younger patients.
  - When you start treating somebody with an antidepressant, their energy level and their neurovegetative signs often respond before their mood does. This means that you have a more energetic depressed person. Studies going back decades suggests that that exposes the person to a period of vulnerability to suicidal ideation and impulse. The warning that the FDA issued was correct, that in giving somebody an SSRI will increase their risk of suicidal ideation early in the course of treatment. Their intent in issuing the warning was to try to clinicians to follow the patients closely during the first few weeks of starting the SSRI. Unfortunately, what happened because of the warning was that many prescribers stopped prescribing SSRIs for children, adolescents, and young adults. As a result, the actual rates of suicide went up, because young people were suffering from depression and were not receiving appropriate treatment. It was a great example of unintended consequences.



- Studies that looked at this concluded that the group receiving SSRIs had more suicidal thoughts, but their rate of completed suicide did not differ from the placebo group. And overtime, as their depression improved, their risk of suicide declined.
- Increased anxiety in the early stages of SSRI usage.
    - Serotonin decreases dopamine release and that may cause akathisia in some patients, particularly elderly patients who may not have a lot of dopamine reserve to begin with. Increased anxiety initially is possible. When these drugs are used to treat anxiety disorders, it's very important to educate the patient that initially their intensity of anxiety is likely to increase before it decreases because these drugs increase the amount of serotonin available within a few hours. In contrast, the improvement of symptoms is dependent on more downstream processes, such as downregulation of postsynaptic receptors and changes in second messenger populations inside the neurons, those processes take weeks. In many cases, you may need to use an anxiolytic to transiently dampen the effect of the antidepressant.
- Panic Disorders
    - Initial panic attacks can be severe. Individuals with these conditions literally feel as if they are dying. This is a result of a false triggering of our fight or flight response. Essentially, having a panic attack would be a normal response to a life-threatening event of some kind. That system is largely located in the non-dominant temporal lobe, and involves the amygdala, the anterior temporal lobe, and the parahippocampal complex. That part of the brain is there to chronically monitor the environment for threats and allow you to either fight or run away before something bad happens to you. In some people, though, it appears that that system is triggered way too easily, it goes off when there is no threat. This becomes a horrible experience. People develop all sorts of anticipatory anxieties depending on what their environment is at the time the panic happens.



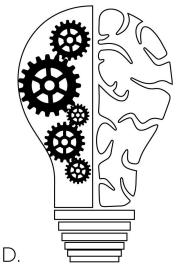
        - These people often need help with behavioral exposure therapies to make them less sensitive to those environments. In fact, that's thought to be how people with panic disorder, if it goes untreated, eventually become agoraphobic. They can't go out of their own house, or in some cases their own room, because they've become phobic to the entire world.
    - Use of Chlomipramine in OCD
        - A number of studies have demonstrated that Chlomipramine are more effective for OCD than SSRI. SSRI can be highly effective for OCD if dosing is increased beyond what is required for depression, in the range of 300 mg a day or more. And instead of taking four to six weeks to get a response, it may take eight to twelve weeks. Chlomipramine, on the other hand is more effective because the effect is felt sooner. It is a very robust increaser of serotonin and may have some affinity for norepinephrine as well. It's antihistaminic, tends to be anxiolytic. The combination of these effects may be why it is overall more effective. It's a somewhat difficult drug to tolerate because it's also a good alpha-adrenergic blocker, so it lowers blood pressure. People can get dizzy or can faint if they are taking too much. It's very anticholinergic, which gives people blurry vision, dry mouth, constipation, and urinary retention.
    - Decreased libido and difficulty of ejaculation as a side effect of SSRI use.
        - Increasing serotonin tends to dramatically impair sexual function. In males it can result in erectile dysfunction, delayed orgasm, or anorgasmia. In females, it can result in vaginal dryness or anorgasmia as well.
        - Arousal is based on activity by the parasympathetic nervous system using acetylcholine. Orgasm is based on the triggering by the sympathetic system using norepinephrine, increasing serotonin. The spinal cord can interfere with both of those processes.
        - In most of the original package inserts for SSRI, they quoted dysfunction figures of 5-7%. Those were falsely low because they



only reported those cases where people stated this spontaneously. When you actually ask people, how many were having difficulties, it's more like 50-70% have some degree of sexual dysfunction. The dysfunction can be mild or it can be severe, with loss of functioning all together.

- Moving to a mixed mechanism agent will help fix that. Use of Buproprion, which is mostly noradrenergic, can sometimes reverse that effect of the SSRI. More recently, there is now a SSRI (vilazodone) that also is a partial agonists for the 5HT-1a receptors. Their rate of sexual side effects is much lower. But because they are proprietary drugs, they are much more expensive than generic SSRI antidepressants.

- Buproprion and Mirtazapine use for males with previous sexual dysfunction due to SSRI
  - Buproprion is almost purely noradrenergic, consequently does not interfere with sexual functioning. In fact, it may actually improve the libido much more than the SSRIs.
  - Mirtazapine is a unique drug that in that at higher doses it increases norepinephrine release by inhibiting auto-receptors for norepinephrine, alpha-2 receptors in the locus ceruleus. So you get more norepinephrine output. It also blocks 5-HT2a receptors, so it acts as a serotonin antagonist which may also provide some benefit with respect to sexual functioning.
- Benefits of optimizing testosterone levels in relation to depression.
  - Unlike women, men don't go through a tightly defined menopause with a sharp drop off in testosterone production. The peak of testosterone production in most men, however, is around 18 or 19 years of age. And then there's a gradual steady decline thereafter. So that by the time somebody is in their fifth or sixth decade, erectile dysfunction becomes fairly common. It's estimated that about 40% of males over 50 have some degree of erectile dysfunction. Checking their testosterone is worthwhile, because



you may find out that they're in a subpopulation that have had a more rapid decline than other people.

- Sildenafil, the PDE5 inhibitor can be highly effective in treating erectile dysfunction as a side effect of antidepressants. Cialis daily can be more effective if taken daily due to the long half life and build up.
- Trazodone is less often effective than the PDE5 inhibitors. Because it's an alpha antagonist it can work. The adverse effect, commonly known, is to cause priapism, a prolonged and painful erection. The other caveat is that it is a very potent antihistaminic drug. So you can wind up with the unfortunate situation of somebody who now is sexually functional but is too sleepy to be interested.
- We further talked about psychosocial details in the podcast.

- Concluding thoughts
  - If we learn how to better modulate cortisol, that may help us a lot with treating refractory depression. There also are continuing developments going on in terms of learning more about direct electrical stimulation of the brain, which may be helpful in treating depressive and anxiety disorders. Once we evolve to the point where we have medications that can directly help increase some of the neurotrophic factors in the brain, that also may go a long way toward altering the long term course of depressive illness. With the medications we have now, we currently have to work with ⅔ response rate and ⅓ remission rate, which is just not adequate by anyone's standards.