Episode 025: The History and Nuances of Bipolar Illness

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There are no conflicts of interest for this episode.

Below is a detailed review of the podcast episode, with most of the content that Dr. Michael Cummings and I (Dr. Puder) discussed. Special thanks to Arvy Wuysang (MS4) for his work in the initial transcription and organization.

The History & Nuances of Bipolar Illness

Bipolar Illness was first discovered by Emil Kraepelin, who was also the first to describe schizophrenia in the 19th century.

Kraepelin noticed another major mental illness in which people had episodic disturbances of mood. He saw either elevation of mood and increased energy, along with a decreased need for sleep, and often impulsive or psychotically related behaviors.

Then, the same patient would experience the opposite, sleeping through the day, demonstrating lowered energy and depression. These patients were noted to have normal function in-between these episodes.

Nuances of the bipolar illness diagnosis

The Diagnostic Statistical Manual of Mental Disorders (DSM) identifies bipolar illness primarily by the presence of at least one episode of mood elevation to help distinguish it from unipolar or major depressive disorder.

Here are some defining symptoms:

- Patients are fairly normal between episodes.
- When they're manic, their mood elevates their lack of sleep. They will sleep four to five hours at first, later progresses to no sleep at all on a nightly basis.

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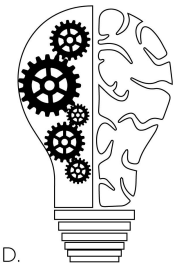

- Every true manic episode will end in three places: hospitalization of some type, jail, or death.
- Initial peak is in the 20s and 30s. Although, people suspect that many individuals who become bipolar don't initially declare themselves.
- They often present with a series of recurrent depressive episodes and then, at some point, they exhibit a period of mood elevation meeting the criteria for either hypomania or mania, which earns them the diagnostic label of bipolar mood disorder.
- There are two types. Type I, in which the person has fully evolved to mania or mood elevation and fully evolved episodes of depression. Type II, in which the person may have a milder form of mood elevation but still has fully evolved periods of depression.
- Grandiosity is a major part of mania. Although historically some people with bipolar illness have often been incredibly productive during episodes of mood elevation, before they become disorganized or psychotic.
- There is often impaired judgment during manic episodes. For example, someone who is manic will propose to 5 different girls, max out multiple credit cards, buy extra houses/cars/boats, etc.

Bipolar and the Limbic System

Underlying pathophysiology is centered around the limbic system. Involves the temporal lobes and and structures which swings upward into the mamillary bodies into the anterior cingulate gyrus, which then projects forward into the frontal lobe. That circuit goes through periods of hypo-activity or depression in people who are bipolar. They have depressed metabolic rates of the system upto 30 to 40 % below normal. During periods of mood elevation, there is an increase in metabolic activity and instability in that limbic circuit. The mood is an element of that, but the person's overall activity, sleep-wake cycle, circadian rhythms, along with all the things related to the functioning of the limbic system are disturbed in bipolar illness.

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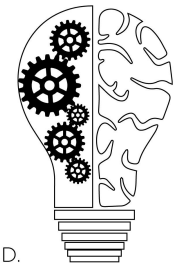

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Bipolar Illness and Sleep Patterns

There are some models of the illness that suggest that perhaps the core of the pathophysiology of bipolar illness is an abnormally regulated biological clock.

In most of us, the nerve cells, the neurons that make up the biological clock, are very tightly linked to each other in terms of their operation. They literally form two pacemakers or oscillators in a very small structure that sits right on top of the optic chiasm called the supraoptic nucleus.

Normally all of our circadian rhythms are regulated by this master clock. In healthy people, it's very difficult to get the two oscillators to separate from each other. In bipolar people, those oscillators drift apart relatively easily. Something as simple as loss of sleep during the latter half of the night will cause them to diverge from each other.

When that begins to happen, the overall functioning of the limbic system begins to oscillate in an unstable manner.

People have looked at things like disturbed sleep as being a very common precipitous of a mood episode. If somebody has a difficult day or disturbing event, and they're genetically vulnerable to being bipolar, they may not sleep well at night, and the next night they may not need to sleep as much. The night after that, they really don't sleep, and then their mood begins to elevate and another episode is initiated.

Genetic Markers of Bipolar Illness

Bipolar is typically passed on genetically, and can be linked with other similar markers of illness. Around 100 genetic markers have been linked to bipolar illness.

They overlap with schizophrenia in part, but not entirely. People with bipolar illness have a much more normal brain in terms of development then do people with schizophrenia. But, there appears to be an inherent defect in the operation of the limbic system

elements with these periodic repeating of overactivity and underactivity, plausibly related to the core biological clock.

Mood stabilizers have an effect in terms of decreasing and stabilizing the activity of the limbic system. They tend to push that clock back toward being phase-linked or operating together as a single oscillator, rather than as divergent oscillators.

Mood Stabilizers

History of Lithium

The very first mood stabilizer discovered was lithium. It was very popular in the 19th century for the treatment of gout because it decreases uric acid crystals.

In the 1940s, a psychiatrist named John Cade (1912-1980) served in World War II and was a prisoner of war for three years. After the war, he worked in a repatriation hospital in Australia and became fascinated with bipolar illness. At the time, he looked at the earlier history and thought that uric acid somehow caused bipolar illness. That turned out to be a wrong hypothesis. But, it led him to use lithium urate, a soluble form of uric acid, in hamsters, to see what would happen. The hamsters got lethargic and sleepy upon administration.

He decided to give his lithium compound to ten patients—six of them were bipolar, four of them were schizophrenic. They all became less agitated, though the schizophrenics didn't change all that much. However, all of the bipolar patients' moods stabilized.

It's amazing how he didn't kill any of these patients in spite of giving them gigantic doses of lithium. His initial dose was 1300 mg, three times a day. Most of the patients got ill with that. If you give somebody too much lithium, they develop nausea, tremor, and diarrhea. You can make them very seriously ill with lithium because it has a very narrow therapeutic index. The distance between therapeutic and toxic is not very far. Optimal dose for most patients 0.6 - 1.0 mmol/L. Toxicity usually begins at about 1.5 mmol/L, serious toxicity begins at about 2.0 mmol/L.

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At Loma Linda and at patton State Hospital, most patients start at 900 mg at night, obtain a plasma concentration five to seven days later, and then adjust the dose.

Dosing lithium

Lithium should never be given in divided doses.

The kidneys is spared by having a long trough period between lithium doses, so it is best to give it at bedtime.

Lithium tends to decrease urine concentrating capacity. Almost everyone who takes lithium, their urine output will increase by about 20%, and their water intake will correspondingly increase by about 20% to compensate. There are a few people who get much more severe diabetes insipidus, an insensitivity to anti-diuretic hormone in the kidney.

Over the course of many years, about 5% of people who take lithium will develop mild to moderate degrees of renal failure or insufficiency. That risk is minimized by keeping the lithium level < 1.0 meq/L and also by giving Lithium only once a day.

Lithium and suicidality

It's clear that lithium reduces suicidality, which may be a product of its ability to inhibit impulsivity. Suicide rates are substantially lower when people take lithium.

In the healthy population, when they've done studies in areas with very low concentrations of lithium in the groundwater, rates of suicide and rates of homicide are lower in areas with lithium in the groundwater compared to areas that don't have lithium in the groundwater.

The amount of lithium that people are getting from the groundwater would be roughly the equivalent of taking 3 milligrams of lithium a day. This means that in the healthy non-bipolar non-mood disordered brain, it doesn't take very much lithium to make people somewhat less violent.

When would you take someone off Lithium?

- The best measure for lithium is to measure the eGFR (estimated glomerular filtration rate). If the eGFR declines to 50 or less, the person should not take lithium.
    1. The other common adverse effect that lithium has is to make the person hypothyroid.
        - Lithium tends to decrease the synthesis and secretion of thyroid hormone. The good news is that if it makes somebody hypothyroid, we can easily replace the thyroid hormone with Levothyroxine, a synthetic analogue of the hormone. Frankly, your body doesn't care whether you get your thyroid hormone from your thyroid gland or from a tablet.
    2. Dermatologic side effects
        - Psoriasis is a contraindication to lithium use. It will greatly worsen psoriasis.
        - If the person is prone to cystic acne, lithium will typically cause a worsening of cystic acne.
        - One of the effects of lithium is to increase oil secretion in the skin. That can lead to both increased psoriatic plaques and cystic acne.

History of Other Mood Stabilizers

The reason we have other treatments for bipolar illness, is largely the result of the work of Robert Post.

Post was a psychiatrist who worked at NIMH and was doing an unrelated experiment. He was looking at kindling, or increased sensitivity of the limbic system, by putting electrodes into mouse temporal lobes and giving them a one second electrical stimulus once a day.

Initially, when you do that, nothing happens.

But about day two or three, the mouse will have a complex partial seizure, a temporal lobe seizure. If you keep doing it pretty soon the mouse will start having spontaneous

seizures. Robert Post looked at that and thought that the nerve cells of the limbic system can become more and more sensitive, more and more hyperactive, less and less well-controlled. He thought that he could block that effect, in terms of seizures, with anticonvulsants. He then, made a leap in logic, thought that perhaps mood episodes are acting like electrical stimulus causing kindling in the limbic system for people with recurrent mood episodes, like in bipolar patients.

He decided to treat some bipolar patients with an anti-epileptic.

The first medicine he used was Carbamazepine (Tegretol). Tegretol is a very difficult drug to use because it induces its own metabolism, so the level keeps falling. It also is fairly toxic with respect to the bone marrow. So, you have to watch out for loss of white cells, red cells, platelets.

He fairly soon turned to another anti-epileptic, valproic acid, which is a branched-chain fatty acid. He found that it was also effective in treating bipolar illness. **Turned out that compared to lithium, valproic acid was more effective if the person was a rapid-cycling bipolar patient having more than four episodes a year.** (Although lithium remain superior if the person is a classic type I bipolar patient.)

In young women in general, valproic acid it can be problematic because it can cause Polycystic Ovary Disease.

- In pregnancy, it causes not only a risk of neural tube defects such as spina bifida, it also decreases the intellectual capacity of the offspring by about 10 IQ points, and roughly doubles the risk of autism in the offspring. It also causes hirsutism and weight gain.

Psychiatry has pretty much examined every anti-epileptic introduced since to see if it had mood stabilizing properties.

Lamotrigine (Lamictal) for example, does treat bipolar depression and does stabilize mood cycling, but has almost no benefit with respect to mood elevation. In fact,

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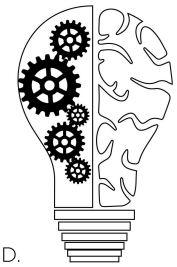


Lamotrigine as a monotherapy may actually cause switches into mania in some patients.

People have looked at **Topiramate** and found that it may have some prophylactic capability but doesn't seem very effective at all if the person is already manic or depressed. If their mood is already stable, and you're just trying to decrease the cycling, it may have some benefit.

Lamictal, used as a mood stabilizer, may have gotten more use than it should because although it does have antidepressant properties in bipolar illness, it is certainly not a benign drug.

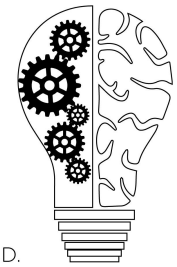
People were initially attracted to it because there's not a lot of laboratory monitoring involved. The plasma concentrations of lamotrigine don't correlate very well with its efficacy because it is very rapidly cleared from the blood compartment and taken into tissue. It's easy to administer and when you're not using it for seizures, usually can be dosed all at bedtime.

It does carry a risk of Stevens-Johnson Syndrome, which is severe malignant rash, and which the person winds up looking like a burn victim because their skin literally dies and falls off.

It also can cause lymphohistiocytosis, which is a similar autoimmune process, but involving the blood vessels and internal organs. Luckily, that is rare, but it's also typically a life threatening response to the drug

The risk of the side effects above are increased by titrating the drug to rapidly. They discovered the side effects when they were using the drug initially for seizures. They were often increasing the dose by a hundred milligrams a day starting at 100 mg, and by day four, the person was on 400 milligrams. They found a 9% increased rate of malignant rash. If you slow down and don't go faster than around 25 to 50 milligrams a week in the titration, the risk is reduced, but it's still not zero. It's probably less than one half of 1%, but it is a caution.

The other caution with the drug of course in bipolar patients is it sometimes is not a very good monotherapy because it doesn't provide any protection against mood elevation. It



seems to be effective in treating the depressed phase of the illness, but not the manic or hypomanic phase.

Oxcarbazepine has flunked multiple trials as a mood stabilizer. Oxcarbazepine differs from Carbamazepine in only one bond. In carbamazepine the bond between carbons 10 and 11 is an epoxide bond, while in oxcarbazepine that same bond is an ester bond.

It appears, however, that the mood stabilizing properties of carbamazepine result from the epoxide metabolite, and of course oxcarbamazepine does not produce that metabolite.

Oxcarbazepine can, in some individuals, reduce impulsivity, which seems to be a truism across the anti-epileptic drugs, but it's not an effective bipolar treatment.

There was only one study looking at it in forensic settings for impulsive or violent patients. It was a self-funded single investigator study and it's been the only study that was ever produced, never replicated. It was suspicious in that the patients were all outpatients, self-recruited via newspaper ad. It's database even for impulsivity and so forth is pretty limited. It does have some application in that regard, but it is not as good as people hoped.

People became enamored with it simply because it was easier to use than carbamazepine, which isn't to say that it's benign. It induces hepatic enzymes, it causes dangerous hyponatremia in about 2.5% of the people who take it.

There haven't been any really good studies identifying it as an anxiolytic. Like most anti-epileptics, it can be sedating and somewhat calming, but you could get the same effect from literally any of the anti-epileptic drugs, probably safer would be gabapentin.

Antipsychotic use as mood stabilizer

Some of the second generation antipsychotics have also shown mood stabilizing properties, albeit as an addon to a primary or classic mood stabilizer. This include drugs

like Aripiprazole, Brexpiprazole, Cariprazine, Olanzapine, and Quetiapine. Quetiapine in particular is effective in treating bipolar depression, as is Lurasidone.

Antidepressants as Mood Stabilizers

Do not give an antidepressant to a bipolar depressed patient!

There are now a host of studies suggesting that antidepressants offer little or no benefit with respect to depression in bipolar illness. It serves only to increase the rate of mood cycling and to risk a switch into mania.

Cognitive Side Effects of Mood Stabilizers

Lithium typically causes cognitive impairment only if the plasma concentration is too high, in which case it can cause decreased brain function all the way up to coma if the concentration is high enough. However, lithium used at therapeutic concentrations actually is neurotrophic.

It's been used now in some demented patients with modest results. MRI scans will show a thickening of the cortex if you put somebody on lithium.

In contrast to lithium, antiepileptic drugs almost universally tend to dull cognitive performance. For example, one of the tip-offs that you're giving the person too much topiramate is they start to lose the ability to find nouns, they become anomic.

Barbiturate and Benzodiazepine use in Bipolar Illness

Barbiturates were introduced in 1903. At that time, they were essentially the only psychiatric medication available. They treated literally everything that involved mood elevation or agitation with a barbiturate.

In the middle ages, individuals that seemed to have manic episodes as we understand it today, were considered witches. They were given doses of sedation that would bring a

normal person down. These manic individuals, however, would not be sedated with those doses.

This is described in the book The Witches' Hammer. Most of these tests were designed so that if you were the accused, you most likely won't pass them. For example, one of the tests was being tied up and thrown into a mill pond. If you drowned, you were concluded not to be a witch, but of course you were dead. If you manage to float and you survived, you were concluded to have done so via witchcraft, in which case they retrieved you from the water and subsequently burned you.

Frankly, psychiatry has come a long way!

Importance of Sleep Hygiene in Bipolar Illness

One of the most important things to teach bipolar patients is to emphasize the importance of sleep hygiene. They should go to bed at the same time every night. It's dangerous for them to casually stay up to watch tv or a movie etc. That may be a setup for them to have the next episode of mood disturbance.

If they're having difficulty sleeping, this is a group in which long term use of one of the Z drugs may be appropriate.

Dr. Cummings' personal favorite in that group is Eszopiclone (Lunesta), because it has a longer half-life. It's half-life is around 4-6 hours, so it's long enough that the person will actually stay asleep. It also has a broad dose range, 1 mg - 8 mg at night.

It's been used to treat primary insomnia in some individuals for up to decades without development of complete tolerance, or resulting in any withdrawal syndrome if the medication is stopped.

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Education for Bipolar Patients

Patients and families need to realize that the more episodes of illness they have, the more resistant to treatment the illness will become, and the less responsive the illness will become to medications. This idea goes back to Robert Post's study on kindling.

Additionally, when people have more episodes, the cycle tends to become progressively shorter. If they were initially having an episode every two or three years, it may suddenly occur every year, to having multiple episodes for a year.

One of the major costs for both families and individuals who are bipolar is that severe depression or severe mania is incredibly disruptive to the individual's life. It can destroy their marriage, their job, and cause large setbacks.

I (Dr. Puder) will bring patient's families in, get them on board with a plan to identify early symptoms such as decreased sleep, increased energy, and change in physical activity. I want the family to keep in close contact with me if these things are developing, and I will always get them in within the week.

Role of Psychotherapy in Bipolar Illness

- For many bipolar patients, the common pathway into a mood episode is an environmental stressor that causes sleep disturbance, which then sets off the instability that they have innately in their internal clock, and then they're off into a mood episode. Teaching the person good sleep hygiene, teaching them to be better able to cope with stressors is crucial.
    1. Psychotherapy can also train them to become more self aware, so that they may be able to spot earlier changes in their mood and recognize an impending episode sooner. This allows them to seek for intervention before things get out of hand.
    2. Focus on developing healthy habits like exercise and healthy diet.