Bipolar Network News

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FDA Approves Lurasidone for Bipolar Depression in Children and Adolescents

In March 2018, the US Food and Drug Administration approved the antipsychotic drug lurasidone (Latuda) for the treatment of bipolar depression in children and adolescents aged 10–17 years. Lurasidone was already approved for adults with bipolar depression, as an add-on treatment to the mood stabilizers lithium and valproate, and for schizophrenia in people aged 13 years and up.

A 6-week clinical trial in 347 youth compared lurasidone (in doses ranging from 20 to 80 mg/day) to placebo and found that those who received lurasidone showed significant improvements in depression compared to those who received placebo. The average dose was below 40 mg/day. The research by Melissa P. DelBello and colleagues was published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2017.

In the study, lurasidone was well-tolerated. Side effects included nausea, sleepiness, minimal weight gain, and insomnia. Lurasidone did not seem to affect glucose, triglycerides, cholesterol, or blood pressure.

Editor's Note: This is the first drug to be approved for bipolar depression in this age range. This editor (Robert M. Post) has written extensively on the high incidence of childhood onset bipolar disorder in the US, and especially in the offspring of parents with bipolar disorder.

It is important to be alert to the possibilities of depression and bipolar disorder in children in the US (along with related illnesses such as anxiety, oppositional defiant disorder, and attention deficit hyperactivity disorder (ADHD)), as early-onset illness tends to have a more severe long-term course than adult-onset depression and bipolar disorder. A longer

delay between the emergence of symptoms and the first treatment for bipolar disorder is also a risk factor for more severe depression, more time depressed, and a poorer outcome in adulthood.

Parents of children aged 2-12 who have mood or behavioral problems are encouraged to consider joining the Child Network at our website, bipolarnews.org (click on the tab for the Child Network). By participating in this research network, parents are able to make a weekly rating of the severity of their children's symptoms of anxiety, depression, ADHD, oppositional behavior, and mania via the secure website. The ratings can then be shared with the child's clinicians for easy visualization of the course of symptoms over time, which may help with treatment decisions.

Pediatric Bipolar Disorder Diagnoses Much More Common in US than England

A 2014 article by Anthony James and colleagues in the *Journal of the American Academy of Child and Adolescent Psychiatry* reported that hospitalizations for pediatric bipolar disorder are 72.1 times higher in the US than in England.

The researchers determined that there were 100.9 diagnoses of pediatric bipolar disorder per 100,000 people in the US, but only 1.4 cases per 100,000 people in England. The discrepancy in diagnoses for adult bipolar disorder and for other childhood psychiatry illnesses were smaller but still notable: While 158.2 adults per 100,000 in the

US were diagnosed with bipolar disorder, only 22.1 adults per 100,000 in England received such a diagnosis, making the diagnosis of bipolar disorder in adults 7.2 times more common in the US. Diagnoses of childhood attention-deficit hyperactivity disorder (ADHD) were 13.0 times more common in the US than in England, while cases of childhood depression were 4.2 times more common in the US.

James and colleagues hypothesized several potential reasons for the dramatic difference in diagnosis rates at

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hospital discharge of bipolar disorder in children in the US versus England. The lower hospitalization rates for pediatric bipolar disorder in England may reflect the better availability of community or outpatient treatment options there.

Diagnostic practices may also differ. James and colleagues suggested that in the US, pediatric diagnoses of bipolar disorder are often used to describe children and adolescents with irritability and frequent mood shifts, whereas English diagnostic practices rely more on episodic bouts of euphoria to diagnose bipolar disorder in children.

Bipolar Network News

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Dr. Post has consulted on behalf of drug companies including Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

The opinions expressed in the BNN are solely those of Dr. Post, and do not represent the views of any scientific entity or foundation.

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However, children in the US may simply be more likely to have a variety of childhood psychiatric disorders than those from England.

Editor's Note: A 2011 meta-analysis of epidemiological studies by researcher Anna R. Van Meter in the Journal of Clinical Psychiatry supports the view that bipolar disorder not otherwise specified (BP-NOS), which is often the earliest manifestation of bipolar disorder, is about twice as common in the US than in other countries.

Even if there are some diagnostic differences that contribute to the immense 72.1 fold higher rates of hospitalization for childhood bipolar in the US compared to Britain, one cannot overlook the findings that these children are requiring hospitalization for something resembling bipolar disorder and are in need of treatment.

In England the researchers found no diagnoses of bipolar disorder in preadolescent children, whereas in the US, diagnoses in children under age 6 exceeded the rates of pediatric bipolar disorder in 19-year-olds in England. In a 2017 review article in the journal Neuroscience & Biobehavioral Reviews, this editor Robert M. Post and colleagues reviewed research on incidence of childhood onset bipolar disorder and found higher rates of the illness in the US than in Canada, Argentina, and several European countries. Genetic and environmental factors contributed to this vulnerability in US patients. Compared to Europeans in the Netherlands and Germany, those with bipolar disorder in the US have more family history of psychiatric illness and face more psychosocial stress in childhood.

Several studies have also found that general medical health in adult males is worse in the US than in other developed countries, as is life expectancy.

A 2006 study by James Banks and colleagues in JAMA, the Journal of the American Medical Association, reported a disparity in the medical health

of adult males aged 55–64 in the US versus England. US men had a higher incidence of virtually every common medical condition, including diabetes, hypertension, heart disease, heart attack, stroke, lung disease, and cancer, and these results held up even when the researchers controlled for socio-economic status and access to health care. Banks and colleagues concluded that American men are in much worse health than British men.

In a 2018 editorial in the journal BMJ, Steven H. Woolf and Laudan Aron further highlight that after losing ground for decades, US life expectancy has now fallen below the average for other developed countries.

It looks like in addition to Americans suffering poorer general health than people in other developed countries, children in America may also be psychiatrically much sicker. The high rates of bipolar disorder in US children are catastrophic, not to mention the toll of conditions that tend to accompany bipolar disorder and other mood, anxiety, and behavioral disorders. Yet there does not appear to be any recognition of the magnitude of the problem or public sector attempts to ameliorate it.

Woolf and Aron end their BMJ editorial on a pessimistic note: "Ironically, leaders are outspoken about ending the opioid epidemic and bemoan spiraling and unsustainable healthcare costs. Solutions to both problems – which involve investment to support struggling families and communi*ties and thereby improve public health – are* often rejected, usually by leaders with competing self-interests or ideological objections. The consequences of these choices are dire: not only more deaths and illness but also escalating healthcare costs, a sicker workforce, and a less competitive economy. Future generations may pay the greatest price." This editor (Robert M. Post) would further emphasize that most adult psychiatric disorders begin in childhood, and our current generation of children are already paying the greatest price.

Children Who Are Bullied Have Poorer Mental Health

A 2017 study of twins between the ages of 11 and 16 found that being bullied around age 11 caused anxiety, depression, hyperactivity and impulsivity, inattention, and conduct problems, some of which lasted for years. Participants recorded their experiences with physical or verbal bullying, social manipulation, and property attacks (trying to break one's belongings, for example).

The effects of bullying decreased over time. The bullied children were still significantly more anxious than their non-bullied twins two years later, but this difference faded by the five-year mark. However, paranoid thoughts and cognitive disorganization did persist for 5 years.

The twin study design helped researchers zone in on the causal effect bullying might have on the children's mental health, rather than other factors the twins shared, such as genetics or family environment. The study included 11,108 twins born in England and Wales.

The research by Timothy Singham and colleagues was published in the journal *JAMA Psychiatry*. Interestingly, the researchers found that prior mental health difficulties increased children's likelihood of being bullied, such that being bullied could be considered a symptom of preexisting vulnerabilities. Singham and colleagues suggest that in addition to interventions to reduce bullying and address familial factors that might make children susceptible to bullying, children should also be taught resilience skills.

Cannabinoid Gel Treats Fragile X Syndrome

Fragile X syndrome is a genetic disorder characterized by developmental problems such as intellectual disabilities, cognitive impairment, and behavioral and learning challenges. Zynerba Pharmaceuticals announced in 2017 that a cannabinoid gel they have produced improved symptoms of fragile x syndrome in children and adolescents when applied daily to the upper arm.

Multiple cannabinoids are derived from cannabis plants, and include cannabidiol, which likely conveys some of the plant's positive effects, and tetrahydrocannabinol (THC), which lends marijuana its psychoactive or psychomimetic effects, such as delusion or delirium. Cannabidiol is the active ingredient in the gel, and no THC was found in participants' blood tests after using the gel.

The open study of 20 patients aged 6 to 17 years found that the participants showed improvement on a scale measuring anxiety, depression, and mood after 12 weeks of using the gel. The gel also appeared to improve aberrant behaviors including social avoidance, temper tantrums, repetitive movements, and hyperactivity. Treatment began at a dose of 50mg per day, and could be increased up to 250 mg per day within the first six weeks of the study. The dose then remained stable for the next six weeks.

Zynerba Pharmaceuticals hope to begin controlled clinical trials in 2018, with the goal of attaining approval for the drug from the US Food and Drug Administration. Other companies are also competing to garner the first FDA approval of a cannabis-based drug. Many of the drugs currently in development are intended to target neurological or behavioral conditions.

Playing Tackle Football Before Age 12 May Be Bad for the Brain

A 2017 study found that men who began playing American tackle football before age 12 were more likely to have depression, apathy, problems with executive functioning, and behavioral issues in adulthood than their peers who began playing football after age 12. Duration of football play did not seem to matter — those men who stopped playing football after high school were just as likely to be affected in adulthood as those who went on to play football in college or professionally.

The study by Michael L. Alosco and colleagues was published in the journal Translational Psychiatry. It included 214 men (average age 51) who had played football in their youth, but not other contact sports. The men reported their own experiences with depression, apathy, cognitive function, and behavioral regulation. Those who began football before age 12 were twice as likely to report impairment in behavioral regulation, apathy, and executive function than those who began playing later. Those who started younger were also three times more likely to have clinical depression in adulthood than those who started older.

According to Alosco and colleagues, between ages 9 and 12, the brain reaches peak maturation of gray and white matter volume, and synapse and neurotransmitter density also increases. The repeated head injuries that can occur during youth football play during this time may disrupt neurodevelopment, with lasting negative effects.

One drawback to the study was that recruitment was not random—men who volunteered for the study might have done so due to a recognition of their own cognitive problems. However, the results suggest more study is needed, and caution is encouraged when making decisions about youth football participation. Some youth football leagues have begun placing greater limits on the type of contact allowed during play.

Treatment Approaches to Childhood-Onset Treatment-Resistant Bipolar Disorder

Dear readers interested in the treatment of young children with bipolar disorder and multiple other symptoms: In 2017, BNN Editor Robert M. Post and colleagues published an open access paper in the journal *The Primary Care Companion for CNS Disorders* titled "A Multi-Symptomatic Child: How to Track and Sequence Treatment." The article describes a single case of childhood-onset bipolar disorder shared with us via our Child Network, a research program in which parents can create weekly ratings of their children's mood and behavioral symptoms, and share the long-term results in graphic form with their children's physicians.

Here we summarize potential treatment approaches for this child, which may be of use to other children with similar symptoms.

We present a 9-year-old girl whose symptoms of depression, anxiety, attention-deficit hyperactivity disorder (ADHD), oppositional behavior, and mania were rated on a weekly basis in the Child Network under a protocol approved by the Johns Hopkins School of Medicine Institutional Review Board. The girl, whose symptoms were rated consistently for almost one year, remained inadequately responsive to lithium, risperidone, and several other medications. We describe a range of other treatment options that could be introduced. The references for the suggestions are available in the full manuscript cited above, and many quotes from the original article are reprinted here directly.

Depression

ADHD

Anxiety

Overall Illness

Oppositionality

Sep '15 Dec '15 Mar '16 Jun '16

As illustrated in the figure, after many weeks of severe mania, depression, and ADHD, the child initially appeared to improve with the introduction of 4,800 micrograms per day of lithium orotate (a more potent alternative to lithium carbonate that is marketed as a dietary supplement), in combination with 1 mg per day of guanfacine, and 1 mg per day of melatonin.

Despite continued treatment with lithium orotate (up to 9,800 micrograms twice per day), the patient's oppositional behavior worsened during the period from November 2015 to March 2016, and moderate depression reemerged in April 2016. Anxiety was also generally less severe from December 2015 to July 2016, and weekly ratings of overall illness remained in the moderate severity range (not illustrated).

In June 2016, the patient began taking risperidone (maximum dose 1.7 mg/day) instead of lithium, and her mania improved from moderate to mild.

There was little change in her moderate but fluctuating depression ratings, but her ADHD symptoms got worse.

The patient had been previously diagnosed with bipolar II disorder and anxiety disorders including school phobia, generalized anxiety disorder, and obsessive compulsive disorder.

Given the six weeks of moderate to severe mania that the patient experienced in October and November 2015, she would meet criteria for a diagnosis of bipolar I disorder.

Targeting Symptoms to Achieve Remission

General treatment goals would include: mood stabilization prior to use of ADHD medications, a drug regimen that maximizes tolerability and safety, targeting of residual symptoms with appropriate medications supplemented with nutraceuticals, recognition that complex combination treatment may be

necessary, and combined use of medications, family education, and therapy.

Mood Stabilizers and Atypical Antipsychotics to Maximize Antimanic Effects

None of the treatment options in this section are approved by the US Food and Drug Administration for use in children under 10 years of age, so all of the suggestions are "off label." Further, they may differ from what other investigators in this area of medicine would suggest, especially since evidence-based medicine's traditional gold standard of randomized placebocontrolled clinical trials is impossible to apply here, given the lack of research in children with bipolar disorder.

As we share in the original article, reintroducing lithium alongside risperidone could be effective, as "combinations were more effective

than monotherapy in a study [by] Geller et al. (2012), especially when they involved an atypical antipsychotic such as risperidone. This might include the switch from lithium orotate to lithium carbonate," the typical treatment for bipolar disorder, on which more research has been done. "Combinations of lithium and valproate were also more effective than either [drug alone]...in the studies of Findling et al. (2006)," and many patients needed stimulants in addition.

"Most children also needed combinations of mood stabilizers (lithium, carbamazepine, valproate) in the study [by] Kowatch et al. (2000)." In a 2017 study by Berk et al. of patients hospitalized for a first mania, randomization to lithium for one year was more effective than quetiapine on almost all outcome measures.

Targeting ADHD

"[The increased] severity of [the child's] ADHD despite improving mania speaks to the...utility of adding a stimulant to the regimen that already includes...guanfacine," which is a common non-stimulant treatment for ADHD. "This would be supported by the data of Scheffer et al. (2005) that stimulant augmentation for residual ADHD symptoms does not [worsen] mania, and that the combination of a stimulant and guanfacine may have more favorable effects than stimulants alone."

However, the consensus in the field is that mood stabilization should be achieved first, before low to moderate (but not high) doses of stimulants are added. "Thus, in the face of an inadequate response to the lithium-risperidone combination in this child, stimulants could be deferred until better mood stabilization was achieved."

Other Approaches to Mood Stabilization and Anxiety Reduction

"The anticonvulsant mood stabilizers (carbamazepine, lamotrigine, and valproate) each have considerable mood stabilizing and anti-anxiety effects, at least in adults with bipolar disorder. With inadequate mood stabilization of this patient on lithium and risperidone, we would consider the further addition of lamotrigine.

Lamotrigine appears particularly effective in adults with bipolar disorder who have a personal history and a family history of anxiety (as opposed to mood disorders), and it has positive open data in adolescents with bipolar depression and in a controlled study of maintenance (in teenagers 13–17, but not in preteens 10–12) (Findling et al. 2015). With better mood stabilization, anxiety symptoms usually diminish..., and we would pursue these strategies [instead of using] antidepressants for depression and anxiety in young children with bipolar disorder."

"Carbamazepine appears to be more effective in adults with bipolar who have [no] family history of mood disorders," unlike lithium, which seems to work better in people who do have a family history of mood disorders.

"While the overall results of oxcarbazepine in childhood mania were negative, they did exceed placebo in the youngest patients (aged 7–12) as opposed to the older adolescents (13–18) (Wagner et al. 2006).

"There are long-acting preparations of both carbamazepine (Equetro) and oxcarbazepine (Oxtellar) that would allow for all nighttime dosing to help with sleep and reduce daytime side effects and sedation. Although data [on] anti-manic and antidepressant effects in adults are stronger for carbamazepine than oxcarbazepine," there are good reasons to consider oxcarbazepine. First, there is the finding mentioned above that oxcarbazepine worked best in the youngest children. Second, there is a lower incidence of severe white count suppression on oxcarbazepine. Third, it has less of an effect on liver enzymes than carbamazepine. However, low blood sodium levels are more frequent on oxcarbazepine than carbamazepine.

Other Atypical Antipsychotics That May Improve Depression

"[In a study by Geller et al., the atypical antipsychotic] risperidone had more side effects than lithium or valproate, including more weight gain and prolactin elevations. These findings, along with the fact that risperidone is not FDA-approved for unipolar or bipolar depression in adults, suggests the possibility of switching this child to another atypical [antipsychotic] with better antidepressant and anti-anxiety effects."

Lurasidone was recently approved for bipolar depression in young people aged 10–17 years old, and does not seem to cause much weight gain or other metabolic side effects.

Ziprasidone has anti-manic effects in adults and children, has the advantage of being relatively weight neutral, and recent data indicate its effectiveness as an adjunctive treatment in adults with mixed depression.

A widely used atypical antipsychotic, **quetiapine**, is approved for mania and bipolar depression in adults, but not in children. Weight gain on quetiapine is about equal to that of risperidone, but a study of quetiapine in young people with bipolar depression was not successful.

Aripiprazole, a dopamine partial agonist, is another atypical antipsychotic option. In children, weight gain on aripiprazole can range from minimal to substantial, and aripiprazole decreases the hormone prolactin. While aripiprazole failed to show efficacy in bipolar depression in adults, it is FDA-approved for use alongside antidepressants for unipolar depression.

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Two new drugs that are also dopamine partial agonists may be of some use. **Brexpiprazole** was recently approved by the FDA for adults with schizophrenia and as an adjunct to antidepressants in unipolar depression. **Cariprazine** is FDA-approved for adults with schizophrenia and mania, was superior to placebo in three studies of bipolar depression, and has been successful as an adjunctive treatment for unipolar depression.

Olanzapine and clozapine are less appealing options because they cause more weight gain than most other atypical antipsychotics, and clozapine also requires weekly monitoring of white blood cell count. However, among atypical antipsychotics clozapine has the highest rate of anti-manic response in adults, and has been used successfully in childhood-onset schizophrenia.

It is clear that comparative studies of the efficacy and tolerability of atypical antipsychotics in children with bipolar disorder are sorely needed.

In a patient like the one we've discussed, if an excellent mood and anxiety response is achieved using mood stabilizers and atypical antipsychotics, but substantial residual symptoms of ADHD and oppositional behavior remain, a stimulant could then be added, as noted above.

Nutraceutical Approaches to Depression, Anxiety, and Oppositional Behavior

For children like the one in our case study, who have shown some improvement but still have residual symptoms, we would add a series of adjunctive treatments to the combination of an atypical antipsychotic, lithium, and another mood stabilizer.

An excellent option for residual anxiety and depression is **N-acetylcysteine** (NAC). In studies in adults, this antioxidant has performed better than placebo at reducing bipolar depression, and it can also improve the effects of selective serotonin reuptake

inhibitor antidepressants (SSRIs) in obsessive compulsive disorder (OCD). It can also improve a variety of habit-based behaviors such as addictions.

In children with autism, three placebo-controlled studies found that NAC reduced irritability. (One study looked at NAC by itself, and the other two used the supplement as an adjunct to risperidone.) NAC is sold without a prescription in health food stores, and doses of 500mg twice per day can slowly be increased (on a weekly basis) to 2,000–2,700mg/day.

There is some support for the use of omega-3 fatty acids to target depression and ADHD, and their safety suggests there is little risk in trying them for patients who have symptoms of both.

Many children with serious psychiatric illness have deficiencies in vitamin D3, and open data in 6–17-year-old patients with bipolar disorder suggests that taking vitamn D3 supplements can improve symptoms.

In children who have undergone genetic testing that identified a methyltetrahydrofolate reductase (MTHFR) deficiency, supplementation with **l-methylfolate** should be used (rather than folate itself) and could also improve depression, as it seems to in adults (when taken alongside SSRIs).

For children with oppositional behavior that persists despite multiple attempts at mood stabilization and stimulant augmentation, there are complex combinations of vitamins and minerals that may have some effect. EMPowerplus is one branded supplement designed to support children's mental health that has been found to be safe and effective in small open trials with children with bipolar disorder and behavioral dyscontrol. It may have some interactions with other drugs, especially lithium, doses of which would need to be reduced.

Psychotherapeutic approaches

There are several psychotherapeutic approaches that can help children manage their illness, particularly those that involve the family as a whole and focus on illness education, improved communication, mood and behavioral charting, cognitive behavioral therapy, problem solving, and alternatives to punitive discipline. Family-focused therapy, an approach developed by researcher David Miklowitz and colleagues, is one good option.

It may be difficult to find a therapist trained in such techniques, but the efforts are likely worthwhile. Research by Lars Kessing has shown that patients hospitalized for the first time with mania who were randomized to two years of treatment at a specialty clinic fared better than those who received treatment as usual. They had fewer relapses and did better even years after the specialty treatment ended, suggesting that a good initial intervention that includes education may improve the long-term course of illness.

Researcher Lakshmi Latham and colleagues have found that that cognition returns to normal after a first manic episode only if there are no recurrences over the following year, suggesting the importance of initiating intensive treatment that incorporates both medication and therapy aimed at prevention after a first manic episode.

Mood Charting

Since systematic treatment data in children are so lacking, the best guidance for treatment is the individual child's actual response. Charting the child's improvement or deterioration after trying a given treatment can facilitate parental and clinical decision-making.

We thus encourage parents to provide this type of input and feedback to physicians in a format such as the one used in our Child Network, which can be accessed at our website, bipolarnews.org (click on the tab for the Child Network).

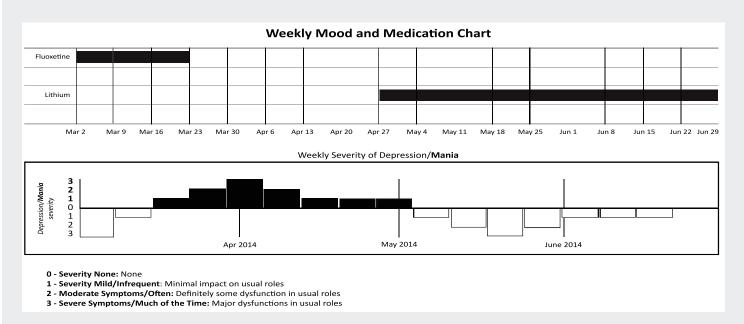
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

74% of children who have a parent with bipolar disorder (Axelson et al. 2015) and 80% of those who have a parent with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness upon long-term follow up. These illnesses, including depression, anxiety, oppositional behavior, substance abuse, often go unrecognized for long periods of time.

Joining the Child Network could help families and doctors identify these illnesses earlier.

The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographic questionnaire and a more detailed symptom checklist to be filled out once a year. The network will collect information about which treatments children are already taking, how effective they are, and for which children.

We believe that this network will be helpful to its participants. Parents will be able to print out the ongoing weekly ratings in a graphic form so that the child's symptoms and responses to any treatments they receive over time can easily be visualized (as illustrated below).



We hope that this brief description of the Child Network study helps to orient you to its purpose. Please urge parents to use this new tool. Visit **bipolarnews.org** and click on the tab for the Child Network or go directly to http://bipolarnews.org/?page_id=2630 to learn more about the Child Network and to access the informed consent documents.

Thank you for your time and interest in the Child Network.

Robert M. Post, MD and Michael Rowe, PhD Bipolar Collaborative Network, and Robert L. Findling, MD, MBA, Principal Investigator This research study is IRB approved by the Johns Hopkins University School of Medicine Research Study, Principal Investigator: Robert L. Findling, MD, MBA, IRB Study #00026940

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