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20-Year Study Finds Clozapine and Long-Acting Injectable Antipsychotics Most Effective at Preventing Re-Hospitalizations for Schizophrenia

Few studies have evaluated the comparative long-term effectiveness of antipsychotics in preventing relapse, but a 2017 study from Finland published in the journal *Schizophrenia Bulletin* by Heidi Taipale and colleagues did just that, and found that clozapine and long-acting injectable antipsychotic drugs were most effective at preventing psychiatric re-hospitalizations.

The Finnish health care registry was used to prospectively collect data on the treatment of every person who received inpatient care for schizophrenia between 1972 and 2014. The patients totaled 62,250 including 8,719 in their first episode of schizophrenia. Follow-up to evaluate antipsychotic use began at 1996 for those with ongoing treatment, and upon first discharge from the hospital for those patients in their first episode. The follow-up time ranged from 6.9 to 20 years with an average of 14.1 years. During the follow-up period, 59% of patients were readmitted to psychiatric inpatient care.

Among the drugs with the lowest rates of relapse, olanzapine long-acting injection, clozapine, and paliperidone long-acting injection were associated with the least risk of psychiatric re-hospitalization. Among patients in a first episode, taking flupentixol long-acting injection, olanzapine long-acting injection, or perphenazine long-acting injection had the lowest risk of psychiatric re-hospitalization. Clozapine and the long-acting injections also had the least risk of hospitalization for any cause.

Sodium Benzoate Helps Treat Schizophrenia In Patients Already Taking Clozapine

In a 2017 article in the journal *Biological Psychiatry*, Chieh-Hsin Lin and colleagues reported that sodium benzoate, a common food preservative, may augment the effects of clozapine in patients with schizophrenia.

Clozapine is the most effective antipsychotic available, but as many as 40–70% of patients with treatment-resistant schizophrenia do not respond to it. For those with a poor response to clozapine, sodium benzoate may offer some hope.

In a randomized, double-blind trial, sixty inpatients taking clozapine for schizophrenia were divided into three groups. One group received an additional 1 g/day of sodium benzoate, another received 2 g/day, and the third received placebo in addition to clozapine. **Both groups taking sodium benzoate and clozapine showed improvements in negative symptoms of schizophrenia (which can include apathy and inability to experience pleasure) compared to the group taking only clozapine. The larger 2g dose also improved positive symptoms of schizophrenia (such as hallucinations or delusions) and quality of life.** Changes in levels of the antioxidant catalase were linked to the total improvement in symptoms and the improvement in positive symptoms. Sodium benzoate did not seem to cause any side effects.

Editor's Note: Sodium benzoate is a D-amino acid oxidase inhibitor that activates NMDA receptors and increases levels of the amino acid D-serine in the brain by preventing it from breaking down. D-serine can reverse the effects of the illicit drug PCP, and very high doses of D-serine have improved the effectiveness of atypical antipsychotics in people with schizophrenia. By increasing levels of D-serine, sodium benzoate may offer new benefits to people with schizophrenia, especially those who have not responded to other treatments.

In This Issue:

Cannabidiol Drug Approved For Rare and Severe Types of Epilepsy

In June, the US Food and Drug Administration (FDA) for the first time approved a drug derived completely from the cannabis plant. The drug, Epidiolex, a syrup, contains cannabidiol, the cannabis component that has been found to treat certain ailments. In a news release, the FDA stated that cannabidiol does not cause intoxication or a 'high'. Tetrahydrocannabinol, or THC, is the cannabis component that makes people high, impairs cognition, and can induce paranoia.

The approval led, in September, to the Drug Enforcement Agency re-classifying FDA-approved drugs containing cannabidiol derived from cannabis and less than 0.1% THC as schedule V controlled substances. So far only Epidiolex meets these criteria. Cannabis had previously been classified as a schedule I controlled substance, in the same legal category as heroin, LSD, or ecstasy.

Epidiolex is now approved to treat two rare, severe types of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients aged two years and older. It is the first FDA-approved treatment for Dravet syndrome, a genetic condition that appears in the first year of life when babies

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Cannabidiol May Help Treat Positive Symptoms of Schizophrenia

A 2017 article by researcher Philip McGuire and colleagues in the *American Journal of Psychiatry* reports that **when added to antipsychotic medication, cannabidiol, a component of marijuana, improved positive symptoms of schizophrenia, such as hallucinations and delusions, more than did the addition of a placebo.**

In the double-blind, parallel-group study, 43 participants received 1000 mg/day of cannabidiol in addition to their regular antipsychotic medication, while 45 participants received a placebo alongside their regular medication.

Side effects were minimal, and after six weeks those who received cannabidiol had decreased positive symptoms and were more likely to be considered improved and not severely unwell.

Editor's Note: It is important to emphasize that cannabidiol is only a minor component of marijuana, which contains much more tetrahydrocannabinol (THC), which is psycho-mimetic, i.e. it can worsen psychosis. Pure cannabidiol is not readily available to the public.

Herb Withania Somnifera May Normalize Sensory Processing Measure in Schizophrenia

One of the best biomarkers of schizophrenia is low auditory mismatch negativity. Auditory mismatch negativity describes the pattern of electrical activity that occurs in the brain when a repeated sound is interrupted by a mismatched sound, such as a change in pitch or volume.

At the International Congress on Schizophrenia Research, Paulina S. Marell and colleagues described their pilot study of the antioxidant and anti-inflammatory herb Ashwagandha or Withania Somnifera (also known as Indian ginseng, poison gooseberry, or winter cherry). In 11 patients with schizophrenia, the herb normalized mismatch negativity compared to placebo.

Marell and colleagues wrote that **the herb "recover[ed] some of the impaired early sensory/cognitive potentials in schizophrenia." Since normal cognition relies on sensory processing, normalizing these functions in people with schizophrenia could improve their symptoms.**

A 2018 study by researcher K.N. Roy Chengappa and colleagues in the *Journal of Clinical Psychiatry* reports that adding Withania Somnifera to patients' regular antipsychotic medication improved negative symptoms of schizophrenia and total symptoms compared to adding placebo.

Editor's Note: These studies, taken together, suggest the utility of adding this supplement to the treatment regimen for schizophrenia.

Early Intervention Works in Schizophrenia: Needed in Bipolar Disorder

For twenty years, evidence has shown that early intervention can ameliorate many of the adverse consequences of schizophrenia. In a 2018 article in the journal *Annual Review of Clinical Psychiatry* titled "Transforming the treatment of schizophrenia in the United States: The RAISE Initiative," Lisa B. Dixon and colleagues described the importance of early intervention in schizophrenia. RAISE stands for Recovery After an Initial Schizophrenia Episode.

Dixon and colleagues emphasize that shortening the time that a patient's psychosis goes untreated, which averages 74 months, is critical to achieving good outcomes.

In parallel to these consistent findings, researchers of bipolar disorder (including this editor Robert M. Post and colleagues) have found that an increased length of the interval before treatment is initiated in childhood-onset bipolar disorder is associated with a poor outcome in adulthood.

The RAISE program consists of four interventions: personalized psychopharmacology using a computerized decision support system, individual resilience therapy, family psychoeducation and therapy, and supportive employment and education.

Compared with patients receiving standard treatments, patients who participated in the RAISE program showed greater improvements on almost all measures, including the Heinrichs-Carpenter Quality of Life Scale (main outcome), the Calgary Depression Scale for Schizophrenia, the Positive and Negative Syndrome Scale, treatment duration, and engagement in work and school. Moreover, the improvements were more substantial among patients with a shorter duration of untreated psychosis.

Editor's Note: These findings are of great importance in their own right, but they also have great implications for treatment and research efforts in bipolar disorder. A 2013 randomized study by Lars Kessing and colleagues published in the British Journal of Psychiatry *found that in bipolar patients hospitalized for a first or second episode of mania, two years of comprehensive treatment with psychotherapy, pharmacotherapy, and illness education that included mood monitoring and early symptom recognition was vastly superior to typical treatment, and this held true even six years later. In a 2014 article in the* Journal of Clinical Psychiatry *and a 2016 article in the journal* Bipolar Disorders*, researcher Jan Marie Kozicky and colleagues reported that in patients hospitalized with a first episode of mania, cognitive functioning and brain imaging abnormalities, respectively, returned to normal over the next year only if the patients experienced no further mood episodes. The message is clear: we must treat the first episode of mania comprehensively to avoid long-term deterioration, which occurs as a function of the number of episodes of mania or depression a patient experiences. However, this early multimodal approach is rarely taken in the US.*

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In schizophrenia, Dixon and colleagues noted that: "After the RAISE study reports were made available, Congress allocated additional funding to the community mental health … program, leading to growth in the number of…programs across the United States; they were expected to reach 48 states in 2018."

The contrast between these efforts in schizophrenia and their virtual absence in bipolar disorder is incomprehensible and tragic. Studies in early schizophrenia have been funded for 25 years, while almost none have been funded in bipolar disorder, even in recent years. Community mental health programs for early schizophrenia will soon exist in 48 states; for patients with bipolar disorder there are no programs available in any state that I am aware of.

The incidence of bipolar is about three times that of schizophrenia, and the long-term outcomes are often as devastating in bipolar disorder as in schizophrenia. There is a high incidence of drug abuse; social, educational and occupational deficits; and suicide in bipolar disorder. Early intervention with the many safe supplements, nutraceuticals, and well-tolerated drugs that are currently available to adult patients should be studied in young people with bipolar disorder, but such studies neither being funded nor conducted.

The reality is that childhood-onset bipolar disorder is poorly recognized and treated in the US, largely because of a paucity of treatment-related studies and knowledge about the best options for these young patients. If a reader of the BNN *knows how to influence advocacy groups, leaders in the Substance Abuse Mental Health Services Administration (SAMHSA) and the National Institutes of Mental Health (NIMH), or influential politicians, it would be useful to take the initiative in bringing some of these deficits and disparities to their attention. Something must be done; ideas about how to do it are welcome.*

My own efforts to get funding for a childhood-onset bipolar research network in collaboration with such luminaries in the field as David Miklowitz (UCLA), Kiki D. Chang (Stanford University), Boris Birmaher (University of Pittsburg), Benjamin Goldstein (Stonybrook Research Institute), Eric Youngstrom (UNC, Chapel Hill), Soledad Romero (Hospital Clinic of Barcelona), and Josefina Castro Fornieles (University of Barcelona) have not been successful. We will keep trying, but the field needs to reach beyond the many investigators who are advocating for more treatment research to other people with more influence.

Repeated Ketamine Reduces PTSD and Depression in the Short Term

In a 2018 open study by C. Sophia Albott and colleagues in the *Journal of Clinical Psychiatry*, **veterans with post-traumatic stress disorder (PTSD) and a simultaneous diagnosis of major depression were treated with 6 infusions of intravenous ketamine over a 12-day period (Mondays, Wednesdays, and Fridays for two weeks).**

Ketamine produced large improvements in both conditions. The remission rate was 80.0% for PTSD and 93.3% for depression. The median time to first relapse after the treatment was 41 days for PTSD and 20 days for depression.

One side effect of ketamine was that dissociative symptoms increased temporarily with repeated infusions. PTSD symptoms did not worsen among those participants taking ketamine.

The study was intended to evaluate the efficacy, safety, and durability of repeated ketamine infusions. Ketamine has been used in emergency rooms to rapidly treat depression and suicidality, but the effects of a single infusion fade within days. Albott and colleagues reported that this treatment scenario with multiple ketamine infusions produced rapid results that lasted longer than single ketamine infusions.

Editor's Note: While this study found that repeated ketamine infusions were safe, it is possible that long-term use may lead to addiction. Researcher Nolan R. Williams and colleagues reported in a 2018 article in the American Journal of Psychiatry that ketamine works via activation of the opiate receptor. The drug naloxone, which rapidly reverses opiate overdose, completely blocked ketamine's antidepressant effects.

Meta-Analysis Finds Single Dose of IV Ketamine Reduces Suicidal Ideation

A systematic review and meta-analysis by Samuel T. Wilkinson and colleagues in the *American Journal of Psychiatry* analyzed individual patient data from 10 studies in which a single intravenous dose of ketamine was given to patients with suicidal ideation. The review included data from a total of 167 participants.

Wilkinson and colleagues found that **ketamine reduced suicidal ideation within 24 hours, and these effects lasted for up to seven days.** Mood also improved, but the reduction in suicidal ideation was independent of the degree of improvement in depression.

Among the participants, 54.9% were free of suicidal ideation at 24 hours after the infusion, 60.0% were free of suicidal ideation one week after the infusion, and 61.1% were free of suicidal ideation at two weeks.

Editor's Note: The authors report that there is much to clarify about ketamine treatment before it can be used clinically to treat patients at risk for suicide. However, ketamine's powerful and rapid effects offer an interesting alternative to other slow-acting treatment options, and could be an ideal acute treatment for patients arriving in an emergency room because of high suicide risk. Ketamine injections could be especially useful for those who are not admitted to the hospital, as they could produce anti-suicidal effects that could help carry a patient over until their next psychiatric appointment.

Mixed Findings for the Tolerability of Intranasal Ketamine in Severe Depression

The drug ketamine can rapidly and temporarily improve depression when delivered intravenously. Researchers have been working on extending ketamine's effects and finding easier ways of delivering the medication. One new delivery method under investigation is nasal spray, which could be used repeatedly to extend ketamine's effects.

Unfortunately, researcher Colleen Loo reported in the *Journal of Psychopharmacology* in 2018 that **a pilot study of self-administered intranasal ketamine for severe depression was suspended when 5 of the 10 participants had side effects that included high blood pressure, psychotic symptoms, and motor incoordination that made them unable to keep using the spray.** Early in the four-week study, dosage was adjusted to leave more time between sprays, but this was not enough to prevent the problems with side effects.

Loo said that the nasal spray version of ketamine has complications including variations in absorption among different people and on different days, depending on factors like mucus in the nose and exact application techniques. Its rapid absorption into the bloodstream could lead to high peak levels in certain people.

Loo and colleagues had previously found that elderly patients receiving injections of ketamine under the skin required highly individualized dosing to avoid side effects. This may also be the case with nasal spray.

While Loo's study found intranasal ketamine infeasible for the moment, Janssen Research and Development, a pharmaceutical company owned by Johnson & Johnson, reported positive results in phase 3 clinical trials of intranasal esketamine, a component of ketamine, at the annual meeting of the American Psychiatric Association in May. Researchers for Janssen reported that **intranasal esketamine was highly effective for depression and well-tolerated both in acute treatment and over a year-long period.** Janssen is now pursing approval for the drug from the US Food and Drug Administration.

Pilot Study Finds Intravenous Ketamine Improves Tough-to-Treat Adolescent Depression

A 2018 open study by Kathryn R. Cullen and colleagues in the *Journal of Child and Adolescent Psychopharmacology* suggests that intravenous ketamine may improve depression in adolescents who have not responded to at least two antidepressants.

Thirteen patients ranging in age from 12 to 18 with treatment-resistant depression were given six ketamine infusions over a period of two weeks, at doses of 0.5 mg/kg of body weight. A 50% drop in scores on the Children's Depression Rating Scale-Revised (CDRS-R) was considered a good response, and the average drop in participants' scores was 42.5%. **Five of the thirteen participants (38%) met the criteria for a good response. Three of these participants were still in remission at six weeks, while the other two relapsed within two weeks.**

Ketamine was fairly well-tolerated by the young participants. Some had temporary dissociative symptoms or blood pressure changes. Higher absolute doses of ketamine were linked to better response.

The response rates in this group were not as good as in some studies of adults. More research using larger sample sizes and placebo controls is needed to optimize dosing and clarify the safety and efficacy of intravenous ketamine in adolescents with tough-to-treat depression, but this is a promising finding in a small number of adolescents.

Cannabidiol Drug Approved for Rare Types of Epilepsy (cont.)

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develop fever-related seizures. Other types of seizures, even including a continuous seizure state, can occur later.

Lennox-Gastaut syndrome also develops in young children, usually between the ages of three and five. They have multiple types of seizures with debilitating consequences.

In three randomized, double-blind, placebo-controlled clinical trials that included a total of 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome, the drug reduced the frequency of patients' seizures compared to placebo.

Side effects of Epidiolex include sleepiness, sedation and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise and weakness; insomnia, sleep disorder and poor quality sleep; and infections. The FDA also warned in its approval that "[a]s is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression and panic attacks." The drug is produced by GW Pharmaceuticals, which has already gained approval outside the US for a cannabis-based drug to treat multiple sclerosis.

Editor's Note: It is important for readers to know that most marijuana available in the US contains mostly THC with minimal cannabidiol.

Micronutrient Curcumin Improves Memory and Depression

Recent studies suggest that curcumin, the micronutrient in turmeric that gives Indian curry its bright color, may reduce depression and improve memory.

A 2018 study published in the *American Journal of Geriatric Psychiatry* by Gary Small, director of geriatric psychiatry at UCLA's Longevity Center, and colleagues found that a curcumin supplement improved mild, age-related memory loss in people without dementia.

Forty adults between the ages of 50 and 90 received either placebo or 90 mg of Theracumin, a bioavailable form of curcumin, twice daily for 18 months. The participants took cognitive tests at the beginning of the study and every 6 months during the study. Thirty of the participants also received positron emission tomography (PET) scans upon beginning and ending the study to evaluate the appearance of plaques and tangles in their brains.

Participants who received curcumin saw improvements in verbal and visual memory and attention over the course of the study compared to those who received placebo. The curcumin participants also saw mild improvements in mood, and less accumulation of amyloid plaques and tau tangles in the amygdala and hypothalamus, brain areas that play a role in memory and emotion. A few participants had mild gastrointestinal effects after taking Theracumin.

In India, where diets are high in curcumin, there is a lower incidence of Alzheimer's than in the west, and older people also have better cognitive performance than in the west.

Curcumin has anti-inflammatory, antioxidant, and neuroprotective properties. Researchers speculate that curcumin may reduce brain inflammation, which has been implicated in both depression and Alzheimer's disease.

A 2017 meta-analysis by Qin Xiang Ng and colleagues of 6 studies of curcumin including a total of 377 patients found that the substance has significant antidepressant effects compared to placebo. Half of the studies also reported improvements in anxiety. No adverse events were reported. Ng's meta-analysis was published in the *Journal of the American Medical Directors Association*.

Marijuana Use in Early Adolescence Triples Risk of Psychosis At Age 18

Hannah J. Jones and colleagues reported in the journal *JAMA Psychiatry* in 2018 that **early- and late-onset marijuana use increased the risk of psychosis at age 18** (odds ratio 3.7 to 2.97). Interestingly, early-onset cigarette use also increased risk of psychosis, but much of the link between cigarette use and psychosis disappeared after correcting for confounding variables.

The data on 5,300 participants born from 1991 to 1992 came from the Avon Longitudinal Study of Parents and Children. Researchers followed up with the participants about their use of marijuana and cigarettes at least three times between the ages of 14 and 19.

Editor's Note: These data add to a host of epidemiological data that smoking marijuana doubles the risk of psychosis. Risk is further increased among people with a common genetic variant (val/val) of the gene for COMT (catechol-O-methyltransferase), which metabolizes prefrontal dopamine. The variant, which includes two valine amino acids, functions better than other variants that include methionine amino acids. People with val/met or met/met COMT genes metabolize dopamine more slowly, making them relatively protected.

The data are also pretty strong that early heavy use of marijuana is a risk factor for new onset of both bipolar disorder and schizophrenia (and not just an earlier onset in those who might have been vulnerable otherwise).

While marijuana use has become more mainstream with its legalization in many states, its recreational use still carries risks of mental illness. In addition to increasing psychosis risk, marijuana use can also make bipolar disorder more difficult to treat.

A minor component of marijuana, cannabidiol, can have some positive effects, but what you get most of when consuming marijuana is tetrahydrocannabinol (THC), which produces symptoms that resemble psychosis.

Data in rats indicate that a father rat's use of THC as an adult increases the risk that his offspring (with which he has no contact) will be prone to opiate addiction. The effect is an epigenetic one, conveyed by chemical changes in the father's DNA that get passed on to the next generation via changes that persist in his sperm. We don't know if this also happens with humans. So even if you are not worried about your own health, avoiding marijuana use might be good for your children.

Recent Cannabis Use Linked to Greater Symptoms of Anxiety and Mood Disorders and Less Response to Treatment

In a 2018 systematic literature review published in the *Journal of Clinical Psychiatry*, researcher George Mamman and colleagues reported that across 12 studies of people with anxiety and mood disorders, **participants who had used cannabis in the previous six months had more symptoms than those who had used less cannabis or no cannabis during that period.**

The 12 studies reviewed included a total of 11,959 participants. Four studies looked at post-traumatic stress disorder (PTSD), one at panic disorder, five at bipolar disorder, and 2 at depressive disorder. In addition to finding that recent cannabis use was associated with greater symptoms, the authors of the review also found that in 10 of the 12 studies, recent cannabis use was associated with less symptom improvement in response to treatment for bipolar disorder, depression, and PTSD; including both medication and psychotherapy.

In bipolar disorder, cannabis use was associated with greater symptom severity. Cannabis use for more than one year was linked to more recurrences of mania and shortened time to a recurrence. Compared to participants with no prior use of cannabis, those with a cannabis use disorder had more depressive symptoms, including sleep troubles and loss of interest in activities one had previously enjoyed.

In PTSD, any cannabis use at the beginning of the analysis period and sustained use of cannabis over time were both linked to greater symptom severity in the four months following the beginning of the analysis.

Mammen and colleagues cautioned that these results are limited based on the differences in measurements across the 12 studies, the inpatient populations under study, and the uncontrolled nature of the cannabis the participants accessed on their own time. However, the authors suggest that the findings may inform patients' and doctors' conversations about whether or not to use cannabis.

See page right for a study of children at risk for mood disorders.

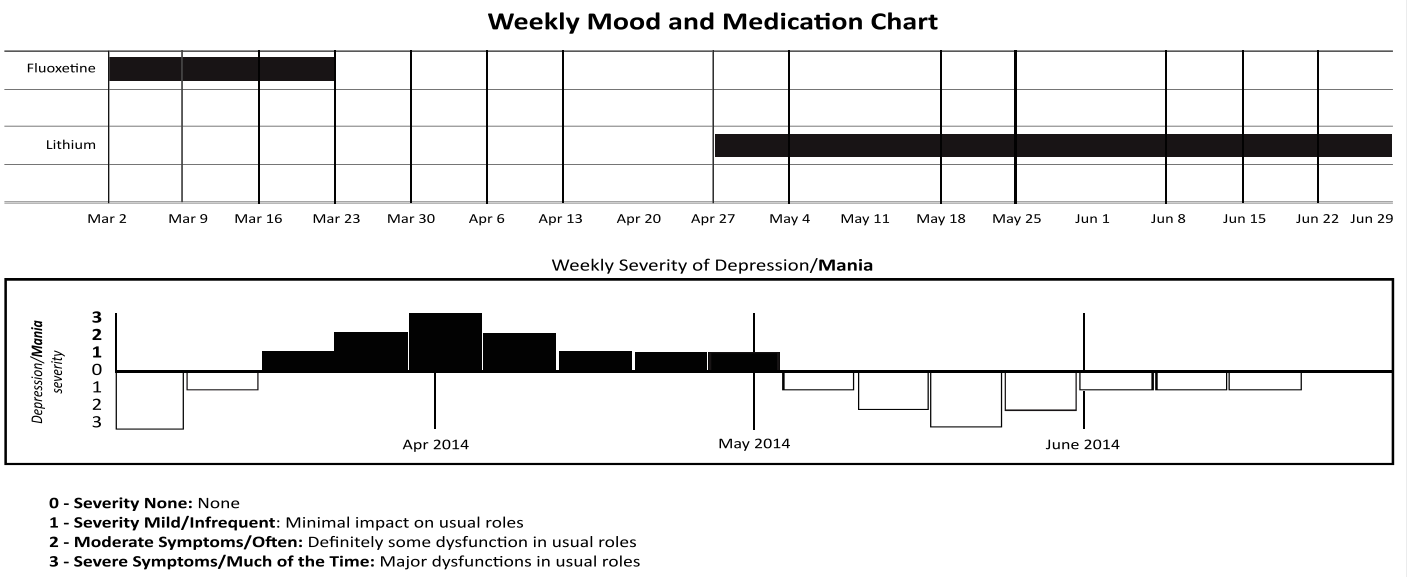
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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).



0 - Severity None: None
1 - Severity Mild/Infrequent: Minimal impact on usual roles
2 - Moderate Symptoms/Often: Definitely some dysfunction in usual roles
3 - Severe Symptoms/Much of the Time: Major dysfunctions in usual roles

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
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