

# Bipolar Network News

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## Updates from the 2014 Meeting of the American Psychiatric Association

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### Lithium Superior to Valproate at Preventing Manias, Depressions, and Hospitalizations

In a special symposium on bipolar disorder at the 2014 meeting of the American Psychiatric Association, researcher Mike Bauer reviewed a new meta-analysis that showed **lithium not only has significant effects in preventing manias, but also depressions**. Researcher Geddes et al. had, in a previous study called BALANCE, found that lithium was superior to valproate (Depakote). Together these findings led Bauer to the conclusion that lithium is under-used in the treatment of bipolar disorder, especially in the US, where lithium is prescribed less often than valproate.

An article by researcher Kessing in the *British Journal of Psychiatry* in 2012 relied on naturalistic follow up data and also showed that

lithium was superior to valproate in preventing hospitalizations.

A study by researcher Willem Nolen indicated that in mono-therapy, levels of lithium in the blood needed to be 0.6 meq/L or higher in order for lithium to work better than placebo. Lithium augmentation that produced lower blood levels of 0.3 meq/L was not significant on its main outcome measure of preventing new episodes. However, compared to treatment as usual, those randomized to lithium used lower doses of atypical antipsychotics, and other data indicated that these patients had fewer suicide attempts and increased hippocampal volume.

Bauer noted that lithium-related goiter and low thyroid are easily treated, and that kidney damage

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while taking lithium can be prevented by avoiding episodes of lithium intoxication. It is easy to conclude that lithium should be used more often, especially given its positive effects against suicide and brain gray matter and hippocampal volume loss.

### Lithium and Quetiapine Have Similar Efficacy in Bipolar Disorder

In a recent study comparing the efficacy of lithium and the second-generation antipsychotic quetiapine, the drugs had remarkably similar results. Researcher Andrew Nierenberg et al. presented the results at the 2014 meeting of the American Society of Clinical Psychopharmacology.

In the 6-month study called CHOICE (Clinical Health Outcome Initiative Comparative Effectiveness), 482 patients received either lithium or quetiapine in addition to other medications in a manner consistent with clinical practice. For the purposes of the study, those receiving lithium could not receive quetiapine or another antipsychotic, and those receiving quetiapine could not receive lithium or another antipsychotic,

but both groups could receive other types of adjunctive medications.

**By the end of the 6-month study period, most patients had improved substantially, but only about a quarter of each group became truly well.**

The researchers suggest that patients may need a longer period of treatment or other interventions such as psychotherapy or combination treatment. Clinicians were told to use the maximum dose of lithium or quetiapine that each patient could tolerate. Mean maximum doses were 1007.5mg of lithium and 344.9mg of quetiapine.

One surprise for the researchers was that 24% of lithium patients and 27% of quetiapine

patients required no other medications and improved on monotherapy.

While results were very similar for the two drugs, lithium produced slightly greater side effects and produced slightly better results in patients with anxiety. This may have been due to those patients also receiving benzodiazepines, and the researchers are analyzing data to see whether the patients with anxiety did indeed receive this kind of adjunctive treatment. Quetiapine was slightly better in patients who had more manic symptoms.

In another surprise finding, patients with bipolar II disorder fared better overall than patients with bipolar I disorder. Patients with higher suicide risk did worse than those with lower suicide risk.

## New Antidepressant Vortioxetine May Improve Cognition and Depression

Vortioxetine (Brintellix) is a new antidepressant that has a range of effects on serotonin receptors, making it different from selective serotonin reuptake inhibitors (SSRIs), the most common type of antidepressants, which work only on the serotonin transporter. Researcher Johan Areberg et al. reported at the 2014 meeting of the American Psychiatric Association that the drug is an antagonist at receptors 5-HT<sub>3</sub>, 5-HT<sub>7</sub>, and 5-HT<sub>1D</sub>; a partial agonist at 5-HT<sub>1B</sub>; a full agonist at 5-HT<sub>1A</sub>; and an inhibitor of the 5-HT

transporter. The researchers suggested that at doses of 5mg/day, vortioxetine occupies the 5-HT<sub>3</sub> receptors and 50% of the serotonin transporter. As dosage increases to 20mg/day, vortioxetine is believed to occupy all of the serotonin targets at clinically relevant levels. Doses of 20mg/day were found to be effective in nine studies. Researcher Gennady Smagin et al. also reported that vortioxetine activates central histamine receptors.

**Vortioxetine appears to be useful in patients who have previously failed to respond to antidepressants.** Researcher George I. Papakostas et al. reported that in a cohort of about 500 patients who responded inadequately to previous prescriptions of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), the 252 taking vortioxetine improved more than the 241 taking the antidepressant agomelatine.

*Editor's Note: Vortioxetine's superior effects are impressive, as agomelatine, which is approved for use in at least 41 countries including the UK, Canada, and Australia, but is not available in the US, has previously been shown to be more effective than a number of SSRIs in head-to-head comparisons. Agomelatine improves sleep and circadian rhythms via its dual effects as an agonist at melatonin M1 and M2 receptors and an inhibitor of 5HT<sub>2C</sub> receptors, which results in the release of norepinephrine and dopamine in the frontal cortex.*

**Vortioxetine may be unique among antidepressants in that it appears to improve cognition.** Researcher John E. Harrison et al. reported that patients saw increases in executive function, attention, speed of processing, and memory while taking vortioxetine. This is consistent with studies in aged mice, whose cognition improves more on vortioxetine than on the SSRI fluoxetine, according to researcher Yan Li and colleagues.

### Bipolar Network News

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The *BNN* is published four times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

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## Antidepressant Vilazodone Superior to Placebo, Plus No Sexual Side Effects Reported

Vilazodone (Viibryd) was approved by the Federal Drug Administration (FDA) as an antidepressant in 2011. The drug is a serotonin 5-HT reuptake inhibitor and a partial agonist of the serotonin 5-HT<sub>1A</sub> receptor like the anti-anxiety drug buspirone (Buspar). Neither buspirone nor vilazodone is associated with significant sexual dysfunction, unlike most of the antidepressants that only inhibit the serotonin transporter (selective serotonin reuptake inhibitors or SSRIs).

Researcher Leslie Citrome et al. reported at the 2014 meeting of the American Psychiatric Association that **at 40mg/day, the rate of remission was 32% on vilazodone versus 20% on placebo.**

At the same meeting, researcher Carl Gommoll et al. reported on vilazodone's side effects. The drug was generally well-tolerated. Side effects that occurred in 5% or more of the patients taking vilazodone and half as many taking placebo included diarrhea, nausea, vomiting, and insomnia.

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## Special Treatment Approaches Needed for Bipolar Depression

Bipolar illness affects 4.5% of the US population. According to researcher Kathleen Merikangas, 1.0% have bipolar I disorder, 1.1% have bipolar II disorder, and the remainder have subthreshold symptoms. Mark Frye, Chairman of the Department of Psychiatry at the Mayo Clinic, gave a lecture on antidepressants in bipolar illness at the 2014 meeting of the American Psychiatric Association.

The newest data from meta-analyses indicate that **traditional antidepressants that are effective in unipolar depression are not effective in bipolar depression**. Some patient groups, especially those with very early onset depression and mixed depression, are at increased risk of switching into mania and making a suicide attempt while taking antidepressants.

Unipolar depressed patients with a genetic variation that produces a short form of the serotonin transporter (5HT-LPRs/s) are at increased risk for depression in adulthood following a history of childhood adversity, and tend to respond less well to antidepressants. Frye found that 5HT-LPRs/s is weakly associated with switching into mania when antidepressants are given to patients with bipolar depression.

At the same symposium, researcher Mike Gitlin reviewed data on combination therapy, which is rapidly becoming the norm, indicating that in most circumstances, it is superior to monotherapy.

Researcher David Miklowitz reviewed the impressive data on the **superiority of most forms of targeted psychotherapy or psychoeducation compared to treatment as usual for bipolar depression**. He noted his own finding that Family Focused Therapy (FFT) not only is effective in adolescents and adults with bipolar disorder, but also in reducing illness and dysfunction in those with prodromal disorders (such as depression,

cyclothymia, and bipolar not otherwise specified) in situations where there is a family history of bipolar disorder.

### Eight components of FFT are:

Recognition of prodromal symptoms and development of treatment strategies for them.

Recognition and management of stress and triggers using cognitive restructuring.

Development of a relapse prevention plan and rehearsal of what to do.

Regularization of sleep.

Encouragement of treatment adherence with an eye to a good future.

Enhancement of emotional self-regulation skills, including cognitive restructuring.

Improvement of family relationships and communication.

Education about substance abuse avoidance and treatment for that and other comorbidities.

Many components of FFT are also key components of group psychoeducation, cognitive-behavioral therapy, and interpersonal and social rhythms therapy, and all of these are effective in treating and preventing bipolar depression compared to treatment as usual. It is noteworthy that in the research of Francesc Colom, 90% of patients randomized to treatment as usual relapsed within 24 months, while psychoeducation was highly effective in preventing relapses over the next five years.

This editor (Robert Post), the discussant for the symposium, emphasized that the main take-away messages of the speakers were: use more lithium, use more caution and fewer antidepressants in treating bipolar depression, use more combination therapy for acute illness and for maintenance, and definitely use more psychotherapy.

*Editor's Note: I also emphasized the more severe illness characteristic of patients with bipolar disorder from the United States than from many countries in Europe, and that this demands revisions in our typical treatment practices. Early onset of illness and delay in time to first treatment are both independent predictors of a poor outcome in adulthood, indicating the need to intervene earlier and more effectively in the two-thirds of patients with bipolar disorder from the US who have onsets in childhood and adolescence (before age 19).*

*There is a kindling-like process in the illness, where recurrent episodes yield more rapid relapses and episodes that begin to occur without precipitating stressors. There is sensitization, or increased reactivity to repeated stressors, episodes, and bouts of substance use, which all induce illness progression. Greater numbers of prior depressions are associated with cognitive dysfunction, treatment resistance, medical comorbidities, and neurobiological abnormalities, including shorter telomeres and even dementia in old age. Thus, preventing the onset of new episodes becomes the primary goal of treating bipolar disorder.*

*Preventive intervention must be introduced earlier and more consistently in order to try to reduce the pernicious course of bipolar disorder, particularly in the US. I would definitely recommend family focused therapy for early symptoms in children at high risk for bipolar disorder by virtue of a positive family history. My new mantra is:*

*"Prevent episodes and protect the body, the mind, and the brain." (Lithium, in combination with other agents and psychotherapy, is one of the best ways to do this in patients with bipolar disorder.)*

## Psychotherapy More Effective Than Standard Collaborative Care in Bipolar Depression with Anxiety Disorder

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a long-term study of treatments for bipolar disorder, recently found that psychotherapy was more effective than their normal collaborative care model (consisting of regular illness evaluation and treatment) for patients with bipolar disorder and a current or lifetime presence of an anxiety disorder.

**An anxiety disorder comorbidity is consistently associated with a poor outcome in patients with bipolar disorder.** In a 2014 article by Deckersbach et al. in the *American Journal of Psychiatry*, the STEP-BD research group reported that the effect of psychotherapy was particularly strong in those with comorbid post-traumatic stress disorder (PTSD) or generalized anxiety disorder.

While antidepressants are typically used to treat anxiety disorders in unipolar depression, this has not been proven effective in bipolar disorder. Not only do patients with bipolar disorder tend to respond poorly to antidepressants, but in research collected by this editor Robert Post and colleagues in the Bipolar Collaborative Network, patients with bipolar disorder who had an anxiety disorder fared even more poorly on antidepressants as adjuncts to mood stabilizers than those with bipolar disorder without an accompanying anxiety disorder.

**The poor response to antidepressants in bipolar depression in general, and particularly in those with a comorbid anxiety disorder, together with the finding that psychotherapy is highly effective, suggest that adjunctive psychotherapy is a more appropriate choice for patients with bipolar depression and a comorbid anxiety disorder.**

The choice of the best pharmacological treatment of this comorbid anxiety disorder deserves specific comparative study. Candidates would include the mood stabilizing anticonvulsants valproate, lamotrigine, and carbamazepine; the atypical antipsychotics with efficacy in bipolar depression (quetiapine, lurasidone, and olanzapine combined with fluoxetine); and those used as an adjunct in unipolar depression (quetiapine again and aripiprazole).

## Cariprazine Has Anti-Manic Effects

Cariprazine is an antipsychotic drug being developed by Hungarian company Gedeon Richter. It functions as a dopamine D3 and D2 partial agonist and has shown significant antimanic effects in three placebo-controlled studies. At the 2014 meeting of the American Psychiatric Association, researcher Robert E. Litman presented findings that **32% of patients with moderate to severe mania improved to a point of minimal or no illness while taking cariprazine, versus 22% who improved similarly while taking placebo.** Doses in the studies Litman presented ranged from 3mg/day to 12mg/day.

At the same meeting, researcher Lakshmi N. Yatham discussed cariprazine tolerability. At a mean dose of 7.44mg/day, side effects of cariprazine compared to placebo included akathisia (restless legs) in 20% of patients compared to 5%, extrapyramidal side effects (irregularities in movement) in 13% of patients compared to 5%, vomiting in 9% of patients compared to 4%, and restlessness in

6% of patients compared to 2%. Twelve percent of patients discontinued treatment due to side effects while taking cariprazine, compared to 7% taking placebo. Weight increased by an average of 0.54kg among patients taking cariprazine compared to an average of 0.17kg among those taking placebo. Yatham and colleagues concluded that cariprazine treatment is generally safe and well-tolerated.

It is expected that data on the positive effects of cariprazine in bipolar depression in two placebo-controlled studies will soon be published.

Also at the meeting, researcher Nika Adham et al. reported that in animal studies, cariprazine had greater affinity for the dopamine D3 receptor than aripiprazole (Abilify), another partial agonist at D2 and D3 receptors. D3 receptors are important for the regulation of cognition and mood. It is expected that cariprazine might eventually be useful in the treatment of schizophrenia.

## Acetyl-L-Carnitine May Be Effective in Treatment-Resistant Depression

Not all patients with unipolar depression respond to the currently available antidepressants. Acetyl-L-carnitine is a compound that enhances mitochondrial function and neuroplasticity and is effective in the treatment of peripheral neuropathy (damage to the peripheral nerves, which sometimes occurs in chemotherapy or diabetes). It is now being investigated as an antidepressant for patients who have not responded to typical antidepressants.

According to a review of the treatment by S.M. Wang et al. published in the *Journal of Psychiatric Research* in 2014, **acetyl-L-carnitine treated**

**depression better than placebo did in four randomized clinical studies.** It was better than placebo and equally as effective as the antidepressant fluoxetine and the atypical antipsychotic amisulpride in various studies of dysthymic disorder. It also improved depressive symptoms in people with fibromyalgia and minimal hepatic encephalopathy (liver damage). The usual dose of acetyl-L-carnitine is 1 to 2 grams/day.

*Editor's Note: The role acetyl-L-carnitine will play in treating people with treatment-resistant unipolar or bipolar depression remains to be better clarified.*

## Transcranial Magnetic Stimulation Continues To Show Effectiveness In Depression

At the 2014 meeting of the Society of Biological Psychiatry, David G. Brock et al. reported that 41 of 67 depressed patients achieved remission (61.2%) after acute treatment with Transcranial Magnetic Stimulation without other medication. After three months of continuation treatment in which patients either received one maintenance TMS session per month or were simply observed, 10 of the 16 receiving active TMS continuation (62.5%) did not relapse, while 7 of the 16 who were only observed (43.8%) did not relapse. While this was not a statistically significant difference, it suggests that continuation TMS should be studied further.

Andrew Leuchter et al. reported that **synchronized transcranial magnetic stimulation (sTMS) at a patient's**

**individual alpha frequency (IAF) was more effective than sham treatment in those with prior treatment resistance (34.2% vs 8.3%) but not different from sham treatment in depressed patients who had never received treatment.**

*Editor's Note: This would be important if replicated, as patients with high levels of treatment resistance do not tend to respond well to regular rTMS given at 10Hz and not matched to a patient's alpha frequency.*

### RTMS Reduced Smoking

Dinur-Klein Limor reported that 10 Hz (but not 1 Hz) repetitive transcranial magnetic stimulation (rTMS) over the left pre-frontal cortex decreased cigarette consumption when given in combination with a smoking cue.

## TDCS Promising for a Range of Illnesses

Transcranial direct current stimulation (tDCS) shows promise for a range of problems. In new research presented at the 2014 meeting of the Society of Biological Psychiatry, it was reported to be effective for improving cognition in bipolar disorder, alleviating depression, and reducing hallucinations.

### How TDCS Works

At the meeting, researcher Marom Bikson discussed tDCS technology. The treatment can be delivered with a 12-volt battery. The anode directs current inward and is excitatory, while the cathode directs current outward and is inhibitory. The dendrites at the top of neurons under the anode are hyperpolarized by the tDCS, leading to relative depolarization of the cell soma, thus increasing excitation. TDCS, unlike repetitive transcranial magnetic stimulation (rTMS), which causes cells to fire, is only neuromodulatory, inducing minor changes in membrane polarization.

### TDCS Improved Cognition in Bipolar Disorder

At the 2014 meeting of the American Psychiatric Association, Roberto Delle

Chiaie et al. reported that two mA tDCS for 20 minutes for 15 days (anode over the left prefrontal cortex and cathode over the right cerebellum) improved immediate and delayed recall, trail making with a pointer, and motor coordination in 17 euthymic bipolar patients. This very promising result deserves further study and replication.

### Antidepressant Effects of TDCS

At the 2014 meeting of the Society of Biological Psychiatry, Collen Loo reported that tDCS had positive effects in depressed patients compared to sham treatment. This complements a 2013 article by Brunoni et al. in JAMA Psychiatry that tDCS plus the selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline (Zoloft) was more effective than either treatment alone.

### TDCS for Treatment-Resistant Hallucinations

Jerome Brunelin et al. reported at the meeting that tDCS had positive effects in patients with schizophrenia who had hallucinations that resisted treatment. The positive electrode (anode) was placed over the left

## Theta-burst RTMS Improved Depression

Theta-burst stimulation is a type of repeated transcranial magnetic stimulation (rTMS) currently being investigated for the treatment of severe depression. In rTMS a magnetic pulse applied to the scalp causes neurons to fire. A recent study of 60 patients by Cheng-Ta Li et al. published in the journal *Brain* compared continuous, intermittent, and combined theta-burst treatment with a sham treatment. While all four groups of patients with treatment-resistant depression improved, indicating some placebo effect, **patients in the group who received intermittent stimulation over the left prefrontal cortex and those who received a combination of intermittent left prefrontal cortex stimulation and continuous right prefrontal stimulation showed the greatest improvement in their depression.** Those patients with greater prior treatment resistance responded less well across all of the treatments.

*Editor's Note: Studies continue to explore the optimum parameters for rTMS, but large studies and meta-analyses continue to show that the treatment has positive effects in depression.*

prefrontal cortex and the negative electrode (cathode) over the left temporoparietal area, where hallucinations are thought to originate. Stimulation was at two mA for 20 minutes, five days per week for two weeks. Effects lasted as long as 30 days and were associated with reduced functional connectivity of these brain regions.

Low frequency (1Hz) rTMS, which decreases neural activity, also improves refractory hallucinations when applied over the temporoparietal area, which is important for language. Placing the cathode over this area in tDCS is also inhibitory, so comparisons of rTMS with tDCS for suppressing hallucinations would be of great interest and importance.

## Resilience Important for Several Facets of Mental Health

A symposium at the 2014 meeting of the American Psychiatric Association suggested that resilience may hold the key to healthy aging, and overcoming trauma and stress.

### Resilience in Aging

Former APA president Dilip Jeste began the symposium with a discussion of successful aging. He noted the importance of optimism, social engagement, and wisdom (or healthy social attitudes) in aging. **In a group of 83-year-olds, those with an optimistic attitude had fewer cardiovascular illnesses, less cancer, fewer pain syndromes, and lived longer.** Those with high degrees of social engagement had a 50% increase in survival rate. Wisdom comprises skills such as seeing aging in a positive light, and having a memory that is biased toward the positive (the opposite of what happens in depression, where negatives are selectively recalled and remembered). Jeste encouraged psychiatrists to focus not just on the treatment of mental illness, but on behavioral change and the enhancement of wellbeing. He suggested asking patients not just, "How do you feel?" but instead, "How do you want to feel?"

### Resilience in the Military

Researcher Dennis Charney gave a talk on resilience based on his work with people in the military, some of whom experienced post-traumatic stress disorder (PTSD). He cited a series of important principles that could enhance resilience. The first principle was to reframe adversity — assimilating, accepting and recovering from it. The second principle was that failure is essential to growth. The third principle was that altruism helps, as does a mission for the survivor of trauma. Charney suggested that a

personal moral compass is also critical, whether this is based on religion or general moral principles. Other factors that are important for resilience include having a role model, facing one's fears, developing coping skills, having a support network, increasing physical well-being, and training regularly and rigorously in multiple areas.

Charney and colleagues studied Navy SEALs who went through SERE (Survival, Evasion, Resistance, Escape) training. Those SEALs who had the highest resilience during this severe training exercise had the highest levels of the neurotransmitter norepinephrine and NPY (an antianxiety neuropeptide). NPY levels are low in people with PTSD. Charney and colleagues reasoned that giving a peptide that acted on the NPY-1 receptors intranasally (so that it could cross the blood brain barrier) might be therapeutic. In a rodent model of PTSD, the peptide prevented and reversed PTSD-like behaviors. Further clinical development of the peptide is now planned.

### The Effects of Stress

Researcher Owen Wolkowitz described how stress accelerates the mental and physical aspects of aging. Telomeres are strands of DNA at the end of each chromosome that protect the DNA during each cell replication. Telomere length decreases with stress and aging.

Telomeres also shorten with inflammation, oxidative stress, and increases in stress hormones (all of which occur during depression). The number of depressions a person experiences is correlated with shorter telomeres, and eight studies have indicated that those with depression have a shortening of their telomeres equivalent to 11.7 years of lost life expectancy. In a study of depressed patients, elevated levels of the inflammatory marker IL-6 were associated with telomeres that

were 1.3 times shorter, and elevated levels of another inflammatory marker, TNF alpha, were associated with telomeres that were 1.5 times shorter.

Childhood adversity shortens telomeres and decreases telomerase activity, while positive parenting and a supportive environment increase telomerase activity. High levels of measured resilience are associated with greater telomerase activity. Other factors associated with telomere length or high telomerase activity include: exercise, good diet, vitamins, folate, omega-3-fatty acids, meditation or yoga, good sleep habits, and the drug lithium, which directly stimulates telomerase activity. Having a positive purpose in life also increases telomere length. In contrast, obesity, high homocysteine (a risk factor for cardiac problems that is also associated with cognitive dysfunction), and chronic anger are associated with decreased telomere length.

### Positive Psychology in Psychiatry

At the symposium, researcher Samantha Boardman described the usage of ideas from positive psychology in psychiatry. Instead of focusing on what is wrong, she encourages psychiatrists to "build on what is strong." Boardman discussed the importance of kindness, a positive attitude, and gratitude in countering some of the self-preoccupation that occurs in depression. She suggested that patients write down three good things in life and three good things about themselves, identify their strengths, and identify something they can be grateful for. Boardman suggests encouraging a new act of conscious kindness each week, such as volunteering. She writes a blog and newsletter called "Positive Prescription."

*Continued on Page 7*

## Cultivating Resilience Through Family Focused Therapy

*Continued from Page 6*

Murali Doraiswamy, the discussant of the symposium on resilience, noted that the Connor-Davidson Resilience Scale takes only about one minute to fill out. He emphasized that a positive early childhood is the key to wellbeing and resilience, and that resilience can also be cultivated as a good habit.

*Editor's Note: Of the many lessons of the symposium, I took away the idea of a positive family environment as one of the most critical factors for physical and mental well-being. Given the importance of the family environment for mental health, Family Focused Therapy (FFT), a treatment paradigm developed by researchers David Miklowitz and Kiki Chang, would be an important intervention for a family*

*struggling with childhood-onset psychiatric illnesses such as bipolar disorder or the first symptoms of anxiety and depressive disorders. A positive family environment has been associated with increases in telomere length and children's hippocampal volume. Verbal abuse, which is associated with a worse course of bipolar disorder and many medical comorbidities in adulthood, could be reduced with the FFT focus on good family communication skills.*

*A positive family environment could also reduce chaos and stress and its effect on increased methylation of the glucocorticoid receptor, resulting in decreased expression of the glucocorticoid receptor and increased cortisol. It would also increase chances for good habits such as diet, exercise, and sleep, as well as stress immunization and enhanced self control.*

*Studies have consistently shown that families with a child with bipolar illness are more chaotic and have poorer communication than comparable control families. For this and all of the above reasons, I would recommend FFT or its equivalent for families with a parent who has bipolar disorder and a child who is beginning to show anxiety, depression, or bipolar dyscontrol symptoms. This kind of early intervention has been shown to be highly effective in circumstances where a child has a diagnosis of depression, cyclothymia (slow oscillation between mild depression and hypomania) or bipolar disorder not otherwise specified in an article by David Miklowitz published in the Journal of the American Academy of Child and Adolescent Psychiatry in 2013. Fostering a caring family environment could have lifelong positive consequences.*

## Cynicism Linked to Dementia

A decades-long study called Cardiovascular Risk Factors, Aging and Dementia (CAIDE) observed older participants for signs of dementia, and collected data on participants' levels of cynical distrust, for example, the belief that others will lie or cheat for personal gain and that it's safer not to trust anyone.

A 2014 study by Elisa Neuvonen et al. in the journal *Neurology* reported that after adjusting for demographic and other factors, **those participants with the highest levels of cynical distrust of others were at higher risk for dementia as they aged.** This relationship was not explained by depressive symptoms. The authors suggest that a positive attitude may protect the brain.

The researchers acknowledge that it is possible the distrust may be a result of brain changes leading to dementia, rather than the cause of it.

Those with the highest levels of cynical distrust were also at higher risk for death, but this association disappeared when the researchers controlled for socioeconomic factors and health behaviors such as smoking.

The researchers hope to investigate whether having a cynical attitude early in life is more robustly linked to mortality. It would be exciting to determine whether a shift to a more positive attitude earlier in life could prevent dementia.

*Editor's Note: A high level of chronic anger is associated with shorter telomeres. Telomeres sit at the end of DNA strands and shorten with each cell replication. Shorter telomeres are linked to multiple medical and psychiatric disorders. It may be that cynical distrust shortens telomeres, and is thus associated with dementia.*

## N-acetylcysteine Decreases Smoking

It appears that the nutritional supplement n-acetylcysteine (NAC) may be useful for people who want to quit smoking. Researcher Eduardo S. T. Prado et al. reported at the 2014 meeting of the American Psychiatric Association that compared to placebo, **NAC decreased the number of cigarettes a patient smoked per day and the amount of carbon monoxide they exhaled.** Participants in the study took 1,500mg of NAC twice a day.

*Editor's Note: It looks as though NAC is effective in most addictions, including gambling, cocaine, heroin, marijuana, alcohol, and now smoking. Since it also helps depressed mood and anxiety in patients with bipolar illness (a finding first reported by researcher Michael Berk et al. in 2008), and can improve trichotillomania and obsessive compulsive disorder (OCD), it could be an important adjunctive treatment for many patients with bipolar illness who also suffer from many of these comorbidities. The usual dose in most of these studies was 500mg twice a day for one week, then 1,000mg twice a day thereafter, as opposed to the doses of 1,500mg twice a day that were used in the smoking study.*

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