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News from the Pediatric Bipolar Conference, Mass. General Hospital and Ryan Licht Sang Bipolar Foundation, March 2010 in Cambridge, Massachusetts

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Carbamazepine Extended Release Has Mixed Effects in Children with Bipolar Illness

In a poster presentation at the Pediatric Bipolar Conference in Cambridge, Massachusetts in March, Gagin Joshi from Massachusetts General Hospital (MGH) presented positive data from a study on the use of carbamazepine extended release (Equetro) in 27 children ages 6 to 12 with childhood-onset bipolar illness. These data were published this year in the *Journal of Child and Adolescent Psychopharmacology*.

Joshi found substantial overall improvement using an average dose of 788 mg/day, achieving blood levels averaging 6.6 mcg/l. Surprisingly, antidepressant effects were as robust as antimanic effects.

Major side effects included headache in 23% of participants, gastrointestinal upset in 18%, sedation in 15%, and dizziness in 8%. However, eleven children dropped out of the study prematurely (two for rash, three for mania, three for lack of efficacy, and three who did not participate in follow up). Joshi felt that carbamazepine extended release was a useful backup strategy, but he was not overly impressed with its overall profile in children, in part because of the high dropout rate.

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Treatments Studies for Childhood Onset Bipolar Illness Are Inadequately Funded

A Pediatric Bipolar Conference was hosted by Massachusetts General Hospital (MGH) and the Ryan Licht Sang Bipolar Foundation this past March in Cambridge, Massachusetts. 92 experts in the area of childhood-onset bipolar disorder attended, and Joseph Biederman of MGH and Joyce and Dusty Sang from the foundation opened the proceedings. The conference continued with a series of four plenary talks, an update from the NIMH, a memoriam to Elizabeth Weller (a recently deceased pioneer in the study of childhood-onset bipolar disorder), a series of poster presentations, and a discussion about changes in the diagnosis for the next Diagnostic and Statistic Manual of Mental Disorders (DSM-V), which are described on page 3.

It was remarkable that none of the plenary talks, although they were excellent and given by leaders in the field of child psychiatry, dealt directly with the topic of the conference–childhood-onset bipolar disorder. There were also no systematic placebo-controlled clinical trials evaluating treatment approaches in any of the subsequent presentations or posters. A number of open and uncontrolled studies examined new treatment possibilities.

It is notable that the National Institute of Mental Health (NIMH) no longer sponsors this conference, as it did for many years. Moreover, STEP-BD, an NIMH-sponsored research program on the course and treatment of adult-onset bipolar disorder, is now defunct, and the head of STEP-BD and one of the most productive researchers in bipolar illness, Andrew Nierenberg from the MGH, has been forced to search for other funding opportunities.

These developments highlight the ongoing deficient funding and study of both childhood-onset and adult-onset bipolar disorder despite the enormous public health impact, extraordinary morbidity, and early mortality from suicide and medical illnesses like cardiovascular disease that are associated with these disorders.

Over the past several years, Dr. Nierenberg has submitted multiple grants to the NIMH without receiving funding support. These included multiple studies of treatment, others designed to reveal the role of mitochondrial dysfunction in the illness (for which there is a growing amount of evidence), and studies of the offspring of the adults in the STEP-BD program, which would have provided an insight into the onset and development of pediatric bipolar disorder.

Thus, despite acknowledgements at NIMH conferences in the 1980s

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Treatments Studies for Childhood Bipolar Inadequately Funded

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and 1990s that the field had failed to adequately study and fund research in adult-onset bipolar disorder for more than 30 years, and repeated calls for greater focus on treatment-related research, there has been no visible movement by NIMH in this direction in the ensuing decades. There may even be a trend in the opposite direction, i.e. away from support for treatment-related research. This trend could also be exacerbated by a new set of NIMH initiatives that focus on the study of common symptoms (such as irritability) across multiple psychiatric illnesses with the hope that this will provide new insights into pathophysiology and genetics that will eventually lead to new treatments.

This editor and many other individuals in the field have published extensively on the need for an increase in treatment-related research for both adults and children with bipolar disorder. These publications include my article "The Perfect Storm of Childhood-Onset Bipolar Illness" published in *Psychiatric Annals* last year,

> ***A search of PubMed since 1980 reveals 8 times more research on "schizoprenia" than on "bipolar disorder."***

which highlights knowledge gaps in the study and treatment of this illness, discusses some of the reasons for the sustained neglect of this topic, and proposes a variety of corrective actions. In the *Psychiatric Annals* article, I again called for a new national initiative to focus on the treatment of bipolar illness, particularly in children, where recognition of this disorder or its close imitators has increased explosively in the past decade and a half. The formation of a treatment outcome network for these children would help by providing much-needed treatment-related information to the field.

Not only are a million children in the US alone severely affected by bipolar illness, but there is also a paucity of studies suggesting appropriate treatments for them. Several drug companies have made progress in establishing most of the atypical antipsychotics as efficacious treatments for childhood-onset bipolar I illness in children ages 10 to 17, but data on appropriate sequencing of treatment and the development of treatment algorithms for combination treatment, which is frequently needed, are virtually nonexistent. For children under 10 years of age, many of whom have the BP NOS (not otherwise specified) subtype, almost no systematic treatment studies are available.

A New Initiative is Needed

One hopes that someone with appropriate political and scientific connections will take on the task of fostering initiatives and programs that will redress some of the deficits in the research and treatment portfolio on bipolar illness. Scores of recent articles by investigators in the field have called for such an increase in research in childhood onset bipolar illness, but to no avail. Thus, it appears that some outsider, some advocacy group, or someone with political clout must take the lead in order to begin to ameliorate this shortcoming.

Bipolar Network News

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Consistent Deficits In Facial Emotion Recognition Found in Non-Ill Children of Parents with Bipolar Disorder

A poster presented at the Pediatric Bipolar Conference in Cambridge, Massachusetts in March by Aditya Sharma of Newcastle University indicated that children without bipolar disorder but at risk because a parent has the illness showed deficits in facial emotion recognition. Similar results were reported by Brotman et al. in the *American Journal of Psychiatry* in 2008. Thus, this deficit in labeling facial emotion may be a marker of early disease or a risk factor for its onset.

Editor's Note: These types of deficits in facial emotion recognition have been consistently observed in adults and children diagnosed with bipolar disorder, so assessing whether children can successfully identify others' facial emotions could become part of the assessment of risk for bipolar disorder. This deficit could also be targeted for psychosocial intervention and rehabilitative training to enhance emotion recognition skills. Such an approach could improve interpersonal communication and lessen hypersensitive responses to perceived emotional threats and negative emotional experiences.

Revisions of the DSM-V Related to Bipolar Disorder in Children

The Pediatric Bipolar conference in March ended with a discussion led by Ellen Leibenluft and Danny Pine of the NIMH about possible changes in the diagnostic criteria for childhood onset bipolar disorder being considered for the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which will be finalized in the next few years. There has been an increase in the diagnosis of bipolar disorder in children in the past decade, and many have attributed this to over-diagnosis. Controversy about the precise symptoms and thresholds for diagnosis has been prominent in the literature and in the popular press.

The major change proposed was that the syndrome of severe mood dysregulation (SMD) described by Leibenluft et al. in 2003, may be called Temper Dysregulation Disorder (TDD), and would not be considered part of the bipolar spectrum. This is in part because SMD is not associated with an increased incidence of a positive family history of bipolar illness. Part of the motivation for separating TDD from bipolar illness is to cut down on what some consider the over-diagnosis of bipolar disorder in children.

Many in the audience voiced concerns about the suggested name of the disorder (TDD), which may have pejorative and stigmatizing connotations to it. Others felt that a new diagnosis was not necessary as the syndrome is adequately described by ADHD with a severe comorbid oppositional defiant disorder (ODD) and that there are no specific treatments yet delineated for TDD. This editor has concerns that a new diagnosis will increase rather than decrease diagnostic controversy about childhood onset bipolar disorder, and that the differentiation of BP NOS (not otherwise specified) and TDD from each other may be particularly problematic.

Leibenluft and Pine indicated that they are continuing to solicit input on the proposed DSM-V revisions, so there is still time for a consensus to be reached that helps stimulate better recognition and treatment of these ill children and fosters more treatment-related research in this understudied area.

Incidence of Childhood Onset Bipolar Disorder Varies Geographically: More in US than Europe

A poster by Aditya Sharma of Newcastle University and colleagues at the Pediatric Bipolar Conference assessed the incidence of childhood-onset bipolar illness based on monthly letters sent to approximately 750 consultants in child and adolescent psychiatry in the British Isles. Only five confirmed cases were reported, with the youngest child being 11 years old.

EDITOR'S NOTE: These data are of particular interest in relationship to earlier data indicating that childhood-onset bipolar disorder may be relatively rare in some European countries, including the British Isles, France, the Netherlands, and Germany, as well as in Australia, South Korea, and New Zealand. In contrast, childhood-onset bipolar illness with an onset prior to age 13 appears to be prevalent in the US, with one-fifth to one-quarter of adult outpatients reporting onsets of either depression with dysfunction or mania prior to age 13. Another substantial group of patients report onsets in adolescence, indicating that some 50-66% of bipolar illness in the US begins in either childhood or adolescence.

Similar amounts of childhood-onset bipolar illness are reported in Italy, Turkey, and Norway as well as in the US, indicating some heterogeneity of vulnerability factors and course of illness outcomes among different European countries.

In the treatment network in which this editor is an investigator, we have found that this younger age of onset in the US is associated with more genetic/familial vulnerability and more experiential vulnerability in the form of more psychosocial adversity compared to that seen in the Netherlands and Germany. We published these results in the British Journal of Psychiatry *in 2008 and will publish more detailed data in a paper submitted to the* International Journal of Clinical Psychopharmacology. *These genetic, psychosocial, and early onset vulnerability factors are associated with a more adverse course of illness in the US compared with Germany and the Netherlands, in terms of increased comorbid anxiety disorder, substance abuse, experiencing more than 20 episodes prior to network entry, and experiencing rapid cycling in the year prior to network entry.*

In addition, these individuals from the U.S. compared with the Netherlands and Germany did less well in naturalistic followup treatment, as rated by clinicians in the network. While early onset illness is a risk factor for poor outcome, we also found that the time delay to first treatment of mania and depression from the onset of illness was itself an independent risk factor for a poorer outcome in adults averaging age 42. This duration of lag to first treatment (which averaged 15 years in those with childhood onsets) was associated with prospective ratings of increased severity and duration of depression, fewer days euthymic, more episodes, and more days of ultradian cycling. This research will be published soon in the Journal of Clinical Psychiatry.

The origin and mechanisms of these transcontinental differences, with better outcomes in Europe than in the US, deserve further study and clarification, because they may reveal clinical and public health measures of therapeutic importance.

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5 Myths About Unipolar Depression

Recent news stories such as *Newsweek*'s "The Depressing News About Antidepressants" (published January 28, 2010) and "Antidepressant Drug Effects and Depression Severity" in the Journal of the American Medical Association (JAMA) (published January 6, 2010) have offered an inadequate picture of the seriousness of clinical depression, and for those with several depressive recurrences, the importance of preventing further episodes with long-term antidepressant treatment.

Instead, stories suggesting that pharmaceutical manufacturers and the doctors who collaborate with them are motivated by profits get more press. Articles published in prestigious medical journals are quoted widely with the most skeptical interpretation of the data and without a critical view of the limitations of the research.

The consequences of this distorted depiction of depression and its treatment are potentially dire for individuals' health. Some of the popular myths about depression deserve critical review so that patients can make more informed decisions about their own treatment.

1. Depression is all in your mind
2. Depression is over-treated
3. Antidepressant efficacy barely exceeds that of placebo
4. Because of the potential for side effects, antidepressants should be stopped as soon as possible
5. Depression is a minor medical problem

Myth 1: Depression is all in your mind

This might appear valid, as depression is classified as a mental illness. But depression is not abstract, imaginary, or lacking a solid physical foundation. There is now overwhelming evidence that depression coincides with disturbances in multiple brain and body systems.

Numerous brain imaging studies have found that during depressive episodes, neural activity in the prefrontal cortex decreases in proportion to the severity of the depression, while overactivity occurs in several parts of the emotional brain, such as the amygdala. Meta-analyses indicate there is also a significant reduction in hippocampal volume during depression, and consistent abnormalities in physiology, the endocrine system, inflammatory cytokines, and blood levels of neuroprotective factors such as brain-derived neurotrophic factor (BDNF), which helps keep nerve cells healthy and is necessary for normal long-term memory.

Thus, depression is a disorder of the brain and body with potentially lethal consequences (both increased risk of suicide and marked increases in medical mortality).

Myth 2: Depression is over-treated

The large increases in prescriptions for antidepressants in the U.S. and England could suggest overtreatment. However, the facts are otherwise; depression is under-treated. Some 30% to 40% of major depressions are not treated at all, either with psychotherapy or with medications. Evidence indicates that there is a "cohort effect" in the U.S., such that every generation (birth cohort) since World War I has had a higher incidence of depression and an earlier age of onset.

Even when depression is treated, many patients stop their medication pre-maturely and risk early relapse, and those with recurrent depression often fail to maintain long-term preventive treatment.

Myth 3: Antidepressant efficacy barely exceeds that of placebo

The meta-analysis published by JAMA claimed that the overall effect of antidepressant medication was weak, and that antidepressants failed to perform significantly better than placebo in milder forms of depression. However, of the hundreds of placebo-controlled studies of antidepressants in the literature, only 6 studies were analyzed in this meta-analysis, and two of these utilized sub-optimal doses of the antidepressant imipramine. Additionally, the meta-analysis excluded data from studies in which patients who responded to placebo were weeded out in an early stage. This may have artificially removed the difference between antidepressants and placebo in this meta-analysis.

Unfortunately the explosive promulgation of this article as a "new discovery" obscures the real story about the effectiveness of antidepressants in long-term prevention.

Myth 4: Because of the potential for side effects, antidepressants should be stopped as soon as possible

For patient with a history of two or three prior major depressions, antidepressant treatment should be maintained in the long term for

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prevention of future depressions. In 1992, John Davis analyzed studies in which people who were better on antidepressants were randomized on a double-blind basis to either continue the antidepressant or substitute it with a placebo. Maintaining antidepressant treatment cut the risk of a recurrence by about half—a huge effect—and the chances that the findings were due to chance (random variation) was statistically minute ($p<10^{-34}$). Similar studies after 1992 also concluded that antidepressants markedly prevent future depressions (by 70% compared to placebo).

Antidepressants may also help protect the brain. They increase BDNF directly, prevent stress from decreasing BDNF in the hippocampus, and also increase the number of new neurons made daily. Yvette Sheline from St. Louis found that people treated with antidepressants more of the time did not exhibit decreases in hippocampal volume (as measured via MRI) as did people treated with antidepressants less of the time.

Myth 5: Depression is a minor medical problem

Depression is one of the top causes of disability worldwide, even more problematic than cardiovascular disease. It not only can impair patients' performance in the arenas of academics, social life, and employment, but it is also associated with a 10-15% lifetime risk of suicide. In addition, if depression goes untreated, an individual can lose a decade or more life expectancy, primarily through the association between depression and cardiovascular disease.

If you or a family member has experienced recurrent depressions, talk to your doctor about antidepressants. Life long treatment of high blood pressure and cholesterol is a widely accepted public health strategy for those at risk for another heart attack. Depression deserves the same attention in those with recurrent episodes.

A quick screening for depression, anxiety, PTSD, and bipolar disorder is available at:

http://mymoodmonitor.com

This validated scale will provide the likelihood of a diagnosis for these conditions and allow for continuing followup to assess symptom improvement.

Dialectical Behavior Therapy Effective for Adolescents with BP Disorder

In a poster at the Pediatric Bipolar Conference in Cambridge, Massachusetts in March, Tina Goldstein of Western Psychiatric Institute in Pittsburgh presented an open study indicating that dialectical behavior therapy (DBT) was effective for adolescents with bipolar disorder. This is the second study that has produced these results. In DBT, patients are taught coping skills and mindfulness in order to break the cycle of responding to dysregulated emotions with problematic behaviors.

The DBT approach has proven efficacy in those with borderline personality disorder, which shares a number of symptom targets with those of bipolar disorder. These include emotional dysregulation, suicidal behavior, self-injurious behavior, interpersonal deficits, and poor treatment adherence.

In Dr Goldstein's study, suicidal ideation decreased very substantially over one year of DBT, as did emotional dysregulation. There were also substantial improvements in other treatment endpoints, including an increase in the duration of time well. The acute treatment period consisted of one to six months of semimonthly one-hour sessions of DBT for the patient and separate family skills training sessions, after which there were monthly visits with one-hour individual sessions for the patient and for other family members.

For more information about psychotherapeutic approaches to bipolar disorder and related illnesses, see page 6.

EDITOR'S NOTE: This form of therapy appears to be an excellent approach for adolescents with bipolar disorder who are often difficult to treat with just pharmacological agents. Other psychotherapeutic approaches have also resulted in positive data, leading to the conclusion that some form of individual or family psychotherapy or psychoeducation is necessary for the adequate management of this difficult-to-treat illness.

Children with illnesses such as diabetes get information, guidance, counseling, and illness education from a host of sources, including doctors, nurses, social workers, dietitians, and caseworkers. A similar model of treatment and education could be just as useful for those with bipolar illness, but it is not always available, even to the well-insured.

Psychotherapeutic Approaches to Bipolar Disorder and Severe Mood Dysregulation (SMD) Appear to Be Necessary

Dr. Janet Wozniak of Massachusetts General Hospital initiated a survey, both at her institution and in the field, to ascertain practitioners' experience with individual and family psychotherapeutic and educational approaches to childhood-onset bipolar illness. As noted on page 5, these types of approaches appear fundamental to treating children or families in which there is bipolar illness.

It was the view of Wozniak, her survey, and many other investigators in attendance at the Pediatric Bipolar Conference in Cambridge, Massachusetts in March that such psychotherapeutic approaches are needed, and often recommended, but the availability of effective treatment and of therapists skilled in administering any of these psychotherapies in children is often lacking.

At the Pediatric Bipolar Conference in Cambridge, Massachusetts in March, James Waxmonsky, a researcher at the University of Buffalo, presented a pilot trial of a novel group-based therapy for school-age children with attention deficit hyperactivity disorder (ADHD) and severe mood dysregulation (SMD). These children were simultaneously being treated with stimulants, and following the group therapy, improvements were seen in affective symptoms and global functioning. Further controlled clinical trials of this type of therapy are indicated.

SMD is characterized by chronic irritability and profound temper outbursts in children who do not otherwise meet the mood criteria for bipolar I, II, or NOS (not otherwise specified). The SMD phenomenon has been carefully described by Dr. Ellen Leibenluft and colleagues at the National Institute of Mental Health, but psychotherapeutic and pharmacological approaches to it have not been well-delineated. In a small clinical trial of lithium for these children, the drug did not show superiority to placebo.

Waxmonsky's treatment consisted of ten 90-minute therapy sessions for a group of parents, and ten sessions for a group of the children.

The sessions for parents consisted of the following: an introduction; social learning theory; listening and positive attending; emotion recognition; coping skills, house rules planning, and ignoring outbursts; commands and time out; anger triggers and negative family cycles; verbal and non-verbal communication; problem solving; depression; and applying skills in the real world.

The sessions for children included: an introduction; symptoms versus self; goals; emotion recognition promoting the positive; how anger looks and feels; identifying triggers and building a coping tool kit; how to stay in control of anger; perspectives and consequences; verbal and nonverbal communication; problem solving; depression and self esteem; and putting it all together.

EDITOR'S NOTE: As emphasized on page 5, some form of psychotherapeutic intervention for child and adolescent-onset bipolar illness appears necessary. This may also be true for other non-bipolar externalizing disorders, such as SMD. A substantial amount of psychoeducation for patients and family members appears crucial to short- and long-term approaches to these debilitating illnesses.

The literature is now highly supportive of the efficacy of various psychotherapeutic approaches compared with treatment as usual in adults, adolescents, and children with bipolar disorder. Considerable data support the effectiveness of the cognitive behavioral techniques, and now the dialectical behavior therapy described by Tina Goldstein (p. 5) appears to be a useful alternative. Utilizing family-focused treatment appears to have some merit, and Mary Fristad of Ohio State University has also developed a multi-family psychoeducational approach.

These data in children are supported by controlled clinical trials in adults. David Miklowitz and colleagues at UCLA demonstrated that in adults, interpersonal social rhythm therapy, interpersonal therapy, and cognitive behavioral therapy were all superior to treatment as usual for bipolar depression, with greater improvement on these therapies in both measures of time to improvement and time to relapse into the next episode.

Lamotrigine (Lamictal) in Childhood Bipolar Disorder

In contrast to his skeptical opinion of carbamazepine described noted on page 1, Dr. Gagin Joshi of Massachusetts General Hospital (MGH) was more enthusiastic about the results of another study at MGH using lamotrigine (Lamictal) for 12 weeks in 39 children with bipolar disorder. In this case, average dose was 160 mg/day and was titrated very slowly because of the increased risk of rash in children treated with lamotrigine compared with adults.

Thirty-eight percent of the children achieved remission in mania, and 42% in depression. In terms of side effects, 28% of individuals experienced gastrointestinal upset; 26% headache, 18% allergy, and 18% dermatological problems which led seven patients to discontinue the trial. However, none of the rashes were severe. This article is to be published in the journal *CNS Science and Therapeutics* this year.

One Expert's Personal Treatment Algorithm for Bipolar Disorder in Young Children

EDITOR'S NOTE: Dr. Gagin Joshi of Massachusetts General Hospital, who presented the work on carbamazepine and lamotrigine on page 1 and at left, provided this editor with his own general treatment algorithm for approaching youngsters with bipolar disorder.

Joshi typically starts with 0.5 to 2 gms of omega-3 fatty acids because of their benign side-effects profile, the many studies suggesting they are effective in adult mood disorders, and a recent article indicating that they were effective in preventing the conversion of prodromal schizophrenia into full-blown illness in a randomized double-blind controlled study in Australia.

After the omega-3 fatty acids, Joshi's second choice is typically the atypical antipsychotic aripiprazole (Abilify) because of its lesser degree of weight gain compared to atypicals quetiapine (Seroquel) or risperidone (Risperidol). Risperidone can be a third option if aripiprazole is not effective or tolerated.

Depending on the presentation of the individual, particularly if substantial amounts of depression are present, Joshi would next utilize lamotrigine. However, if mania was more problematic, he would use either lithium or valproic acid.

Editor's Note: When dealing with BP-NOS and other presentations involving depression or mild mania, a number of childhood bipolar investigators like Joshi do prescribe lamotrigine. This is despite the fact that lamotrigine lacks acute antimanic efficacy in adults and that children are more prone to severe rashes on lamotrigine. (One in 2,500 children will develop a rash on lamotrigine versus 1 in 5,000 adults.) When used in children, insomnia can also be a side effect.

Other childhood experts with whom this editor has communicated indicate that they like to start with the combination of valproate and quetiapine for children with Bipolar I disorder, while still others report good effects with lithium plus valproate. Other sequences used by several experts in the field for a BP NOS child (age 6) and a BP I child (age 9) are detailed in an article this editor and Janet Wozniak contributed to Psychiatric Annals *in 2009.*

A Mixed Vitamin/Mineral Preparation May Be Helpful for Treatment-Resistant Childhood Bipolar Disorder

Researcher Mary Fristad from Ohio State University completed a small, uncontrolled study of a novel treatment approach, the multi-vitamin and mineral preparation labeled EMPowerplus. Initial case reports from other researchers indicated that the compound led to remarkable and sustained effectiveness in children with bipolar disorder who were unresponsive to most other psychopharmacological approaches.

Fristad's open study included ten children. Participants were slowly titrated to a minimum of 12 capsules/day with a maximum of 15 capsules/day.

Fristad and colleagues saw 37% improvement in depression and 45% improvement in mania in the entire group of patients who began treatment, while in those who completed the study, there was 71% improvement in depression and 58% improvement in mania. Side effects were benign, but the preparation needs to be administered judiciously in conjunction with a physician's supervision.

Dr. Fristad hopes to conduct further double-blind, placebo-controlled trials of this compound, which also showed promising open results in case studies by Kaplan et al. in 2002 and 2004 and was written about by Charles Popper, a researcher at Massachusetts General Hospital, in 2001.

The EMPowerplus preparation is available at the web site http://truehope.com and costs approximately $100-200 per month, but is not recommended for use without careful supervision by a physician.

EDITOR'S NOTE: Controlled clinical trials to demonstrate efficacy have not yet been undertaken, partly due to lack of support from funding organizations and uncertainty about which of the many ingredients is active. Studies of pharmaceutical agents for treatment-resistant children without a cogent theoretical rationale are rarely a high priority despite the great need for effective treatment approaches.

Nonetheless, given initial promising results of the Fristad group and others, systematic clinical trials of this preparation are now clearly indicated.

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