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Bipolar Network News

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Departments

Fifth European Stanley Conference on Bipolar Disorder Barcelona, Spain, Oct. 5–7, 2006

The Fifth European Stanley Foundation Conference on Bipolar Disorder was held October 5–7, 2006, in Barcelona, Spain. The conference was organized by Professors Eduard Vieta and Francisco Colom. Highlights of the meeting are presented below. Editorial comments are in italics.

Neurobiology

Dr. F. Dickerson (Sheppard Pratt Health System, Baltimore) presented data showing an increase in antibodies to toxoplasmosis in patients with bipolar disorder; however, this increase was not correlated with the patients' degree of inflammatory response as measured by C-reactive protein (which was also elevated).

These data suggest inflammatory responsiveness may be altered in bipolar disorder, as suggested by a variety of other studies as well.

Dr. J. Houenou (University Paris) presented functional magnetic resonance imaging (fMRI) data involving the use of facial emotion recognition tasks to demonstrate the presence of dorsal frontal cortex and striatal hyperactivity in bipolar disorder compared with normal controls. These data support a wide variety of other evidence indicating that mediotemporal structures of the brain (such as the amygdala and hippocampus) may be hyperreactive in bipolar patients. Particularly in the depressed phase, in which there are deficits in prefrontal cortex function, the frontal cortex may fail to adequately inhibit these limbic structures. This study also revealed specifically increased activity in the bilateral orbitofrontal cortical areas, the anterior cingulate, and left insula, in addition to the mediotemporal lobe structures.

Advances in Treatment

Dr. T. Suppes (UT Southwestern Medical Center, Dallas) presented data from two combined multicenter studies of the atypical antipsychotic **quetiapine (Seroquel®)**, indicating that patients with bipolar II disorder had a highly significant antidepressant response to this drug. These antidepressant, antianxiety, and positive sleep effects of quetiapine in bipolar II patients were mirrored by similar findings in bipolar I individuals. In October 2006, quetiapine was FDA-approved as the first monotherapy drug for bipolar depression. Quetiapine has already been approved for the treatment of bipolar mania, suggesting that at least this atypical antipsychotic may have a bimodal spectrum of efficacy in the treatment of acute episodes of both mania and depression.

Dr. Suppes also presented a poster describing data from the previously named Stanley Foundation Bipolar Network (SFBN), now called the Bipolar Collaborative Network (BCN), indicating that longer-term treatment with quetiapine in the range of 100–200 mg/day appeared to have sustained antidepressant effects as well.

Controlled studies of quetiapine in the long-term prevention of depression are needed to supplement these observations in open studies, but at least they suggest the promise of a sustained effect of quetiapine.

Dr. T. Stamm (Charité University, Berlin) presented data on supraphysiological doses of L-thyroxine in bipolar depression. Most investigators agree that low-dose triiodothyronine (T_3) may be a useful adjunct in unipolar depression and perhaps in bipolar depression. However, a number of studies have indicated that higher doses of T_4 (levothyroxine) may be useful in both treatment-refractory and rapid cycling bipolar patients.

"These antidepressant, antianxiety, and positive sleep effects of quetiapine in bipolar II patients were mirrored by similar findings in bipolar I individuals."

This large study compared the addition of 300 mcg/day of L-thyroxine with placebo, and the study has not yet been unblinded because recruitment is several patients short of completion. However, many patients in the acute phase improved significantly, and then in open continuation for 6 months most patients showed further improvement, suggesting the possibility that this drug will be effective in bipolar depression.

Although ambiguity remains about this conclusion until the comparison with placebo is complete, what was important was that these doses of levothyroxine were very well tolerated and few patients dropped out early due to side effects.

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European Conference

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Dr. H. Grunze (Ludwig-Maximilians University, Munich) presented data on the use of **modafinil (Provigil®)** in the treatment of bipolar depression. Dr. Grunze reported on data from both the acute, 8-week, randomized, placebo-controlled data submitted for publication by Dr. M. Frye, as well as on a 6-month open continuation phase. Modafinil is approved for narcolepsy and related shift-work and sleep disorders, as well as for sleep apnea. Open studies had suggested that modafinil might potentiate incomplete effects of antidepressants in unipolar depression, and this study indicated that modafinil had significant benefit over placebo for the treatment of depressed mood, fatigue, and poor concentration in partially treated bipolar depression. What was important about the open continuation phase of this study was the persistence of the effect of modafinil despite the relative absence of problematic switches into mania. Interestingly, modafinil augmentation appeared to work equally well whether or not an antidepressant was already present in the treatment regimen along with at least one mood stabilizer. The doses of modafinil were 100–200 mg/day in the initial blind phase, and 100–400 mg/day in the open continuation phase.

"Together, these data suggest the utility of lamotrigine augmentation of mood stabilizers, particularly lithium."

Randomized comparisons with other adjunctive agents would appear warranted to appropriately sequence the place of modafinil in the therapeutic armamentarium of bipolar depression. However, because many patients complain of atypical or reverse vegetative symptoms in bipolar depression (such as hypersomnia, increased appetite, and psychomotor slowness, as opposed to the more typical symptoms of unipolar depression including insomnia, appetite suppression, and psychomotor agitation), modafinil would appear to have some merit in helping augment other antidepressant approaches that were not completely effective.

Dr. M. van der Loos of the Netherlands presented data from an 8-week randomized trial of **lamotrigine (Lamictal®)** versus placebo augmentation of lithium, which showed a significant advantage for lamotrigine (51.6% response rate versus a 31.7% response rate to placebo). The decrease in magnitude of the reduction in the Montgomery Asberg Depression Rating Scale (MADRAS) score was also statistically significant ($p = 0.024$). Lamotrigine was well tolerated, and interestingly the one severe rash occurred in a patient taking placebo, not lamotrigine.

This trial is of considerable importance because the original highly significant study of lamotrigine using doses of 50 or 200 mg/day compared with placebo by Calabrese and colleagues in 1999 was followed by 4 other studies that showed nonsignificant effects of lamotrigine compared with placebo. However, the original NIMH trial by Frye et al. also showed that lamotrigine was more effective than either gabapentin or placebo, and Sachs et al. reported a positive trial using lamotrigine as well. Thus, this new placebo-controlled augmentation trial adds to the widespread belief that not only is lamotrigine effective in preventing depressive occurrences, for which it is FDA-approved, but it may also have acute effects either in monotherapy or augmentation therapy. Given the slow titration necessary to avoid the higher incidence of severe rash that was originally seen with more rapid titration, this study showing acute antidepressive effects in augmentation of lithium is even more impressive.

Together, these data suggest the utility of lamotrigine augmentation of mood stabilizers, particularly lithium. In this regard, lithium has the advantage of being a better antimanic agent and lamotrigine a better antidepressant agent, such that the combination may be particularly useful for the large group of lithium partially-responsive patients who require augmentation therapy. Lamotrigine also appears to be a highly useful alternative to antidepressants, because the original FDA approval also indicated that lamotrigine was able to prevent manic and mixed episodes, whereas most investigators feel that traditional unimodal antidepressants have some risk of increasing the switch into mania.

Treatment of Mania

Dr. M. Tohen (Lilly Corporation) presented data showing that the effects of **carbamazepine (Tegretol®)** were not significantly augmented by the addition of **olanzapine (Zyprexa®)** compared with placebo. In fact, the antimanic effects of carbamazepine were so robust (a 15-point improvement on the Young Mania rating scale [YMRS]), it would have been difficult to show additional improvement. At the same time, there was evidence that carbamazepine lowered olanzapine levels to some extent. In addition, the combination of carbamazepine and olanzapine produced significantly more weight gain and increases in triglycerides than in the patients treated with carbamazepine alone, which was also true for increases in cholesterol.

Dr. Tohen presented results from a second study indicating significant acute antimanic effects of olanzapine in adolescents, with an effect similar to its effects in adults. In this study, 44.8% of patients improved with olanzapine, compared with 18.5% on placebo. However, compared with the adult studies, there appeared to be a greater degree of intolerance in these adolescent patients (ages 13–17), with increased appetite, weight gain, glucose, cholesterol, and triglycerides. The weight gain and the prolactin increases appeared to be larger and more sustained than those seen in the adult patients.

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Bipolar Network News

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Managing Editor: Chris S. Gavin

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

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in summary or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

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

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European Conference

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These data are consistent with data from a variety of other atypical antipsychotics, showing more problematic side effects) including weight gain and extrapyramidal side effects) in children and adolescents with acute mania compared with those seen in adults with acute mania.

One of the organizers of the conference, Prof. E. Vieta (University of Barcelona), reported substantial antimanic effects of lithium and valproate, which did not differ in their acute or long-term response efficacy or remission rates. In a second study, Dr. Vieta used valproate as the baseline drug and then compared the addition of the atypical antipsychotic **amisulpride (Solian®)** at 600 mg/day with the addition of the typical antipsychotic **haloperidol (Haldol®)** at 10 mg/day. Response rates were not significantly different (72.6% on amisulpride and 65.5% on haloperidol), although haloperidol patients experienced more adverse events, including increased amounts of extrapyramidal side effects.

These data bear some similarity to data from a of study of the effects of ***aripiprazole (Abilify®)*** *versus haloperidol in monotherapy of acute mania, where after 12 weeks of treatment, aripiprazole showed both greater degrees of efficacy and tolerability compared with haloperidol. Thus, while there is considerable debate in the literature on schizophrenia suggesting that the typical antipsychotics are just as good as the newer, more costly, atypical antipsychotics, this does not appear the case for bipolar illness.*

This view is based not only on the data noted above, but also on several other important studies that suggest that the atypical antipsychotics, particularly olanzapine and quetiapine, have significant antidepressant effects in bipolar depression in their own right (as opposed to the often-reported exacerbation of depression severity or prolongation of episode duration with the typical antipsychotics). There is also a highly different rate of tardive dyskinesia (higher rate with the older versus a lower rate with the newer agents). The literature is highly supportive that bipolar patients are at equal or increased risk of tardive dyskinesia when exposed even intermittently to the older typical antipsychotics, whereas this risk appears to be very substantially reduced in the use of the newer atypical antipsychotics.

Dr. A. Yildiz-Yesiloglu (Dokuz Eylul Medical School, Turkey) presented data from a placebo-controlled trial indicating that an agent that inhibits protein kinase C (PKC) shows acute antimanic effects compared with placebo. Previously, Dr. H. Manji and colleagues had noted that both lithium and valproate were PKC inhibitors, and presented open data that **tamoxifen (Novaldex®)** showed remarkable acute antimanic effects. These data confirming those initial suppositions provide evidence that one potential mechanism of antimanic effects is through PKC inhibition, based on the fact that tamoxifen inhibits PKC at concentrations even lower than its better known effects on estrogen receptors (for which it is used in breast cancer prophylaxis).

Using a more selective PKC inhibitor, such replication of the current findings with tamoxifen would provide clear mechanistic support for PKC inhibition in the treatment of acute mania. These data are also partially convergent with those of Dr. R. Belmaker and colleagues who demonstrated that an antibiotic that inhibits adenylate cyclase is also an acute antimanic agent, suggesting that antimanic effects may occur at several different second messenger pathways. The effects on adenylate cyclase inhibition are shared by lithium and carbamazepine.

Psychological Interventions

Prof. J. Scott (Institute of Psychiatry, London) discussed a most interesting study of cognitive behavioral therapy (CBT) for bipolar disorder involving 20 CBT sessions and two booster sessions in patients who were then followed for 18 months. Surprisingly, there was no overall difference between those receiving CBT and treatment-as-usual. However, patients who had more complex presentations, such as more episodes, substance abuse, comorbidities, problems with the law, and suicide attempts, had a differential response: those with only one or two (or none) of these complications benefited dramatically from CBT compared with treatment-as-usual, whereas those with three or more of these factors actually did less well.

These data are of interest from the perspective that it now appears that almost all psychopharmacological and other interventions are less effective in those with a greater number of prior episodes or rapid cycling presentations. This treatment imbalance includes the mood stabilizers, atypical antipsychotics, and now even intensive psychotherapeutic intervention. A critical recommendation appears to emerge from these data; that is, the need to intervene early, before the accumulation of multiple episodes and illness complications that make all forms of treatment more difficult, including CBT and naturalistic treatment in the community or in academic settings.

As part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Dr. E. Frank (University of Pittsburgh School of Medicine) performed a comparison between three intensive psychotherapeutic manipulations in bipolar disorder and treatment-as-usual. Each type of intervention (family focus therapy, CBT, or interpersonal therapy with a focus on enhancing social rhythms), was superior to treatment-as-usual.

"... those [patients] with only one or two (or none) of these complications benefited dramatically from CBT compared with treatment-as-usual, whereas those with three or more of these factors actually did less well."

These data would tend to support more efficient psychoeducational approaches aimed at early detection of minor emerging symptoms to intervene early, and the importance of long-term maintenance treatment. The more cumbersome regularization of circadian rhythms may not be a critical factor in mood stabilization. However, it is interesting to note that the patients in this study were on a median of 5 medications in addition to their various psychotherapeutic interventions. These data are consistent with data from multiple other studies that adequate treatment of bipolar disorder often requires exceedingly complex multimodal regimens with, at times, the need for 5 to as many as 8 or 9 medications, depending on the complexity of the patients' illness and their comorbidities. The addition of supportive educational and focused psychotherapeutic approaches now also appears critical to the best outcome.

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Effectiveness of adjunctive antidepressant treatment for bipolar depression

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME

New Engl J Med 2007; 356 (17): 1711–1722

Methods: In this double-blind, placebo-controlled study, we randomly assigned subjects with bipolar depression to receive up to 26 weeks of treatment with a mood stabilizer plus adjunctive antidepressant therapy or a mood stabilizer plus a matching placebo, under conditions generalizable to routine clinical care. The primary outcome was the percentage of subjects in each treatment group meeting the criterion for a durable recovery (8 consecutive weeks of euthymia). Secondary effectiveness outcomes and rates of treatment-emergent affective switch (a switch to mania or hypomania early in the course of treatment) were also examined.
Results: Forty-two of the 179 subjects (23.5%) receiving a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 of the 187 subjects (27.3%) receiving a mood stabilizer plus a matching placebo ($p = 0.40$). Modest nonsignificant trends favoring the group receiving a mood stabilizer plus placebo were observed across the secondary outcomes. Rates of treatment-emergent affective switch were similar in the two groups.
Conclusions: The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch.

Special Report

Bipolar Disorder and the Use of Antidepressants

New Findings

A recent paper by Dr. G. S. Sachs and colleagues from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was recently published in the *New England Journal of Medicine* (2007; 356 [17]: 1711–1722). The focus of this paper was the effectiveness of adjunctive antidepressant treatment for bipolar depression (see sidebar, left), and it reported important new data regarding the use of the unimodal antidepressants in patients with bipolar depression. The clinical practice of adding an antidepressant to a mood stabilizer has long been a central approach to treating a depressive episode that breaks through ongoing treatment with a mood stabilizer in bipolar disorder. However, the new data of Sachs et al. indicate that this adjunctive antidepressant treatment is no more effective than a placebo, i.e., the maintenance of the mood stabilizer alone with no added active antidepressant. This study has very important implications for routine clinical therapeutics of bipolar depression and suggests that one of the most commonly used approaches to bipolar depression in the past should not only be reevaluated, but also that other approaches should be employed instead.

The STEP-BD study had a substantial patient sample of more than 170 patients in each group, who were randomized to antidepressant treatment with either **bupropion (Wellbutrin®)** to a maximum of 375 mg/day or **paroxetine (Paxil®)** to a maximum of 40 mg/day, compared with a group who received inactive placebo. On every measure, there was not a trend that the addition of an antidepressant was superior to placebo, and on several measures, the placebo group was slightly more effective by a few percentage points. The endpoints that were evaluated in the study included: a remission of depression for at least 8 weeks, transient remission, 50% improvement, and the side effect of switching into mania (which occurred in approximately 10% of patients in either randomized arm).

Thus, two of the most commonly used antidepressants—the serotonin-selective reuptake inhibitor paroxetine and the dopamine-active compound bupropion—were not as effective treatments as placebo when added to a mood stabilizer for bipolar depression. What were not included in this study were the strongly noradrenergic-active antidepressants such as the mixed serotonin and norepinephrine reuptake inhibitor **venlafaxine (Effexor®)**, or the norepinephrine-selective reuptake inhibitor **desipramine (Norpramin®)**. These two medications, however, have been shown previously to be more likely to switch bipolar patients into mania than bupropion, and to be no more effective acutely as antidepressants. Thus, the traditional unimodal antidepressants for unipolar depression as a group do not appear to be effective adjuncts to mood stabilizers in bipolar depression.

Alternatives to Antidepressants

A significant and as yet unanswered question is: What would be better approaches to bipolar depression than using adjunctive antidepressants? A recent paper by Dr. D. Miklowitz and associates from the STEP-BD indicates that psychotherapeutic intervention is helpful (2007; *Arch Gen Psychiatry* 64 [4]: 419–426). These data of Dr. Miklowitz, together with a very considerable number of other studies, indicate that cognitive-behavioral therapeutic (CBT) techniques and psychoeducational approaches are better than treatment as usual for a variety of indices of affective illness recurrence and functioning. Therefore, it would appear highly appropriate to use these modalities for depression breaking through treatment with a mood stabilizer.

In addition, one can also consider a number of other pharmacological alternatives to the initial use of antidepressants as augmentation.

One clear alternative is lithium augmentation, if lithium is not one of the mood stabilizers already in the treatment regimen. There is considerable evidence that lithium augments the antidepressant effects of a variety of agents in unipolar depression, and there is some evidence for lithium's acute efficacy in bipolar depression as well.

Early institution of **lamotrigine (Lamictal®)** has much data to substantiate its use. Although the initial acute antidepressant effects of lamotrigine reported by Dr. J. Calabrese et al. in 2003 were not replicated in a series of pharmaceutical industry-sponsored studies, a meta-analysis of these studies by Dr. J. Geddes and colleagues indicates that there is overall statistical significance of the effects of lamotrigine in bipolar depression (see p. 10). Moreover, the study by Frye et al. (2000) and a new study by Nolen and colleagues (2007; *Acta Psychiatr Scand* 115 [5]: 360–365) indicate acute antidepressant effects of lamotrigine as well. These data, together with lamotrigine's FDA-approved indication for the prevention of episode recurrence (particularly depression), suggest that it would be a highly useful alternative to antidepressants.

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Antidepressants

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Carbamazepine (Tegretol®), another mood stabilizer, is also worthy of consideration because recent data from Dr. Z. Zhang and colleagues (2007; *J Psychiatr Res* 41 [3–4]: 360–369) as well our own earlier on-off-on studies at the NIMH suggest that it may have antidepressant properties, and be effective not only in acute mania, but also in acute depression. Dr. L. Davis et al. (2005) have reported data suggesting the efficacy of **valproate** in acute bipolar depression, and especially good antianxiety effects.

Use of an atypical antipsychotic in bipolar depression should also be given significant consideration. **Quetiapine (Seroquel®)** has now been approved as a monotherapy in the treatment of depression, with particular effects not only on improving depressed mood, but also for markedly reducing anxiety, and for beneficial sleep effects when it is given in one dose at bedtime. **Olanzapine (Zyprexa®)** also has shown statistically significant effects versus placebo, but was particularly effective in conjunction with the antidepressant **fluoxetine (Prozac®)**, and this combination is FDA-approved **(Symbyax®)**.

Studies of the acute antidepressant efficacy of the other atypical antipsychotics have not yet been completed or made public, but several of them appear promising as well. Open-study data on **aripiprazole (Abilify®)** suggest useful antidepressant effects in some patients (*BNN* Vol. 10, Iss. 2), as well as a recent double-blind study by Nickel et al. (2007; *Am J Psychiatry* 163 [5]: 833–838) indicating very robust antidepressant and antianxiety effects of aripiprazole, not in bipolar depression, but in patients with borderline personality disorder.

In those patients who remain depressed and not adequately responsive to these interventions, augmentation strategies such as those involving **liothyronine sodium** (**Cytomel®**, 25–37.5 mcg) and the use of folate (1 mg in women, 2 mg in men) have a modicum of supportive data. There are also studies supporting the use of D_2/D_3 dopamine agonists such as **pramipexole** (**Mirapex®**) by Zarate et al. (2004) and Goldberg and associates (2004).

Future Strategies

If these and other revisions of the mood stabilizer and atypical antipsychotic regimen are unsatisfactory, one might then consider the addition of a unimodal antidepressant later in the treatment sequence as a third or fourth agent, even in the absence of strong data support for such a maneuver at this time. Clearly, what is needed are randomized comparative studies of different interventions for breakthrough bipolar depression, to assess both the effectiveness of these interventions and their relative safety and side effects, including the risk of switching patients into hypomania or mania. Such studies may need to be supported by the NIMH as well as by private funding agencies, because these comparative studies are not always the highest priority of the pharmaceutical industry.

The pharmaceutical industry is interested in placebo-controlled clinical trials that demonstrate efficacy for a compound in monotherapy so that it can be discussed in this regard and marketed as such, and then only secondarily is the industry interested in studies indicating that their particular compound is superior or inferior to another putative antidepressant in adjunctive treatment. Also greatly needed is consideration of clinical and biological markers of which patients may be most responsive to different treatment approaches from the outset, so that optimal choices for individual patients can be made not only on a statistical basis for the population as a whole, but also for specific patients with individual illness characteristics or a given profile of common gene variants, called single nucleotide polymorphisms (SNPs).

The study of Sachs et al. noted here converges with recent data from our group in the Bipolar Collaborative Network (Post et al., 2006; *Br J Psychiatry* 189 [2]: 124–131) indicating that use of adjunctive antidepressants such as bupropion, sertraline, and venlafaxine in general are not as likely to induce long-term improvement or remission, as we had previously surmised. In our data set in patients who entered continuation treatment after a 10-week acute trial, only 23% of the original group, or 17% of all the trials of any of the three antidepressants, resulted in long-term mood improvement without a depressive relapse or a switch into hypomania or mania during the continuation phase.

These data, together with low acute and continuation response rates in the study of Sachs et al. noted here, provide some insight into the reason why depression, compared with mania, continues to be the major problem in episodes breaking through naturalistic treatment. In the studies of Judd et al. (2003) and our own studies, well characterized and treated patients spent three times longer in episodes of depression than in mania, despite the use of multiple medications in naturalistic treatment; antidepressant augmentation had composed a substantial portion of the therapeutic approaches to these patients' bipolar depression. One may hope that as we move the use of unimodal antidepressant treatment much further down the priority list and lower in the treatment algorithm for bipolar depression, that depression will become much less problematic than it continues to be at the present time. ■

Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, Nierenberg AA, Calabrese JR, Marangell LB, Gyulai L, Araga M, Gonzalez JM, Shirley ER, Thase ME, Sachs GS

Arch Gen Psychiatry 2007; 64(4): 419–426

Objective: To examine the benefits of 4 disorder-specific psychotherapies in conjunction with pharmacotherapy on time to recovery and the likelihood of remaining well after an episode of bipolar depression.
Design: Randomized controlled trial.
Patients: A total of 293 referred outpatients with bipolar I or II disorder and depression treated with protocol pharmacotherapy were randomly assigned to intensive psychotherapy (n = 163) or collaborative care (n = 130), a brief psychoeducational intervention.
Interventions: Intensive psychotherapy was given weekly and biweekly for up to 30 sessions in 9 months according to protocols for family-focused therapy, interpersonal and social rhythm therapy, and cognitive behavior therapy. Collaborative care consisted of 3 sessions in 6 weeks. Primary outcomes included time to recovery and the proportion of patients classified as well during each of 12 study months.
Results: Patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64.4% vs. 51.5%) and shorter times to recovery than patients in collaborative care. Patients in intensive psychotherapy were 1.58 times more likely to be clinically well during any study month than those in collaborative care. No statistically significant differences were observed in the outcomes of the 3 intensive psychotherapies.
Conclusions: Intensive psychosocial treatment as an adjunct to pharmacotherapy was more beneficial than brief treatment in enhancing stabilization from bipolar depression.

Meeting Highlights: Society of Biological Psychiatry Meeting

May 17th–20th, 2007, San Diego, California

The 62nd Annual Convention and Program of the Society of Biological Psychiatry was held in San Diego on May 17–20, 2007. Dr. Robert Post, M.D., Editor-in-Chief of the BNN, *attended the meeting, and presents highlights in this article. Editorial comments are in italics.*

SNPs and BDNF

As noted in a previous article in the *BNN* (Vol. 10, Iss. 2), a considerable scientific literature now documents that a common single nucleotide polymorphism (SNP) of the brain-derived neurotrophic factor (BDNF) gene appears to be a vulnerability factor for bipolar illness. Surprisingly, having the better functioning val66val allele of the proBDNF gene appears to convey vulnerability to the onset of bipolar illness with either an early onset or a rapid cycling course, whereas the less well-functioning val66met or met66met alleles of BDNF appear to be associated with smaller frontal cortical and hippocampal volume and subtle neuropsychiatric defects in a variety of normal and patient populations.

Dr. A. Stern (NIMH) et al. reported that the met allele is associated with decreased hippocampal neuronal integrity as measured by decreases in N-acetylaspartate (NAA) on magnetic resonance spectroscopy (MRS). Similarly, research by Dr. K. Matsuo (University of Tokyo) and colleagues indicates that bipolar patients with a val66met allele have smaller left and right anterior cingulate gyrii and small dorsolateral prefrontal cortices. Dr. B. Frey (University of Texas Health Science Center at San Antonio) and coworkers found that the val66met allele of BDNF was associated with low phosphocreatine and creatine in the left dorsal prefrontal cortex of bipolar patients as well.

All of these data suggest that the less efficient functioning met allele of BDNF appears to convey some neuroanatomical vulnerability to minor structural deficits associated with the cognitive alterations.

In this regard, it is interesting that Dr. C. Zai (University of Toronto) indicated that there is an association with one of the forms of BDNF and the development of tardive dyskinesia in patients with schizophrenia. It is also clear that the findings of low serum BDNF during depression and mania are not specific to those conditions as previously reported by multiple authors, because Dr. A. Pillai (Medical College of Georgia, Augusta) et al. revealed that in medication-naive, first-episode schizophrenic patients, both plasma and cerebrospinal fluid (CSF) BDNF were reduced.

Dr. M. Catena (University of Pisa, Italy) reported that both plasma and serum BDNF levels were lower in depressed patients than in healthy controls, and plasma increases towards normal concurrent with amelioration of depression and the serum BDNF remains low, suggesting more of a trait finding of low BDNF. At the same time, it appears that the evidence for low BDNF levels in patients with bipolar illness has been extended by Dr. L. Young (University of British Columbia) and associates, who found that BDNF protein levels continue to be low in transformed lymphoblasts in patients with bipolar disorder. In addition, there is evidence that other growth factors, such as insulin-related growth factor-1 (IGF-1), are low in both bipolar children and adults.

These data suggest that a number of growth factors important for neuronal development and plasticity may play a role in relationship to either bipolar illness onset or its cognitive dysfunction. Also, we have previously noted that many preclinical studies had indicated that BDNF decreases with stress, and there are now clinical data to support these same findings.

Common Gene Variations and Antidepressant Response

A number of prior studies have indicated that individuals with the short form of the serotonin transporter ($5\text{-}HT_{SS}$) gene were more vulnerable to depression onset and had decreased responsiveness to treatment with antidepressants. Another such replication of this finding has been reported by Dr. J. Rauch (The Medical College of Georgia, Augusta) et al., indicating that a convergence of having the $5\text{-}HT_{SS}$ variant and environmental adversity was associated with both more depression and decreased antidepressant responsivity.

Thus, these data now provide strong support for the importance of genetic and environmental interactions in depression, such that environmental stressors appear more likely to be associated with depression in the context of some genetic variants compared with others.

Another interesting example of a genetic/environmental interaction is how the presence of a neurotensin SNP confers increased resistance to cocaine-related psychosis, as observed in the study of Dr. E. Binder (Emory University). These data are similar to that of a common SNP polymorphism of the catechol-O-methyltransferase (COMT) gene that confers vulnerability or risk for psychosis in adolescents who are heavy smokers of marijuana. Another related finding is the study of Dr. K. Ressler (Emory University) and colleagues, indicating that a variant of the corticotropin-releasing hormone receptor (CRHR-1) was associated with an increased incidence of depression in the context of environmental adversity.

Dr. G. Valentine (Yale University) and colleagues indicated that an infusion of 0.5 mg/kg of the NMDA receptor antagonist ketamine over 40 minutes produced a rapid onset of antidepressant effects in 10 patients with major depression in proportion to the changes in brain gamma-aminobutyric acid (GABA).

These data further support findings of glutamatergic influences on depression and its treatment.

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Biological Psychiatry

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Folate and Homocysteine

Considerable evidence now supports the potential role of elevated homocysteine in not only representing a cardiovascular risk factor, but also a role in cognitive dysfunction in both schizophrenia and bipolar illness.

The folate/homocysteine story involves the finding that the substance S-adenosyl methionine (SAMe, which is an antidepressant) is metabolized by COMT into S-adenosyl-L-homocysteine, which is then converted to homocysteine itself. Homocysteine is increased in both Alzheimer's disease and in schizophrenia and is noted in relationship to a variety of cognitive dysfunctions in patients with bipolar disorder as well.

Dr. G. Sachs (Massachusetts General Hospital) et al. reported that levels of homocysteine were inversely related to scores on the Young Mania Rating Scale (YMRS) and that folate changes correlated both with YMRS scores and Montgomery-Asberg Depression Rating Scale (MADRS) scores in patients with bipolar disorder. Not only was homocysteine reported to be elevated in first-episode psychosis (especially schizophrenia) in the work of Dr. S. Joshi (Interactive Research School for Health Affairs, India) and colleagues, but high levels of homocysteine are also associated with increased measures of oxidative stress, diabetes, cardiovascular disease, and vascular dementia. Previously, it had been reported that high levels of homocysteine in umbilical cord blood at birth was a risk factor for the subsequent development of schizophrenia.

Together with previous data by Coppen et al. that folic acid was associated with increased responsivity to antidepressants in unipolar depression and to lithium in bipolar illness, this set of new findings continue to support the potential use of folate in its own right and as a substance that can decrease levels of homocysteine, which are apparently not healthy for the brain.

rTMS, VNS, and ECT

Dr. J. O'Reardon (University of Pennsylvania) reported that repetitive transcranial magnetic stimulation (rTMS) at 10 Hz and 120% of motor threshold was associated with a response in 113 of 301 patients with major depression, and that two-thirds of these patients sustained their response without relapse over 6 months. However, 41 of the 72 patients needing additional rTMS treatments yielded a response rate of 63.4%, indicating both a high level of initial responsivity and re-response should continuation treatment need to be reinstituted.

Dr. D. Avery (University of Washington, Seattle) and colleagues conducted a study of rTMS in patients who did not receive benefit from their randomized assignment in a previously reported 6-week randomized controlled trial of TMS. These investigators reported significantly greater improvement in the initially sham rTMS group that was converted to active rTMS (42.4% responding and 20% remitting) compared with those patients who had done less well on rTMS and continued it (only 24.7% responding and 11% remitting).

Dr. I. Cavus (Yale University) and associates reported that 1-Hz rTMS decreased glutamate efflux whereas 200-Hz rTMS increased it.

These data replicate previous observations by Speer et al. at the NIMH of the differential impact on brain metabolism of 1-Hz versus 20-Hz (in our study) rTMS.

Dr. J. Camprodone (Harvard Medical School) et al. reported that one session of right dorsolateral prefrontal cortical rTMS at 10 Hz decreased cocaine craving for 4 hours, which was not observed with left dorsolateral prefrontal cortical rTMS.

These data are consistent with a number of preclinical findings suggesting that stimulation of discrete areas of the brain may be associated with decreases in substance craving.

Several studies reported on results from vagus nerve stimulation (VNS) studies in major depression, including Dr. C. Conway (St. Louis University School of Medicine) who reported that VNS after 3 to 6 months involved temporal deactivation, whereas VNS after 12 to 24 months decreased prefrontal cortex activity.

A study of electroconvulsive therapy (ECT) by Dr. R. Berman (New York State Psychiatric Institute) found that ECT, as used in clinical practice, could be associated with memory decrements as well as a high rate of relapse into depression, as previously reported.

In 2007, Dr. H. Sackeim et al. (Neuropsychopharmacol 32 [1]: 244–254) reported that the degree of retrograde memory loss measured by deficits in autobiographical memory at 6 months after ECT correlated with the number of bilateral ECT sessions administered. Patients should be warned about this potential that has now been well documented for the first time.

Childhood-Onset Bipolar Disorder

Dr. S. Jain (University of Texas Health Science Center at San Antonio) reported that bipolar children with a positive family history for bipolar illness had decreased volume of the left subgenual prefrontal cortex, findings that are identical to those in several previous studies.

Dr. K. Mezzano (University of Texas Health Science Center at San Antonio) et al. indicated that white matter abnormalities were already present in pediatric patients with bipolar illness in the medial prefrontal cortex, as had previously been widely noted in adults. These data raise the possibility that these abnormalities could be a vulnerability marker that even predates illness onset. In a similar study, Dr. C. Bearden (UCLA) reported that the earlier the onset of childhood-onset bipolar illness, the smaller the hippocampal volume in those measured as adolescents.

These data are convergent with a number of studies suggesting that childhood-onset bipolar illness may also be associated with decreased amygdala volumes, in contrast to a number of studies reporting increased size of the amygdala in adults with bipolar illness.

The STAR*D Trial

Findings from the STAR*D trial were reviewed by Dr. John Rush (University of Texas Southwestern Medical Center) and colleagues. The STAR*D clinical outcome trial entered depressed patients in clinical practice settings into a sequence of clinical trials beginning with **citalopram (Celexa®)** in Step 1, providing either switching or augmentation strategies in Steps 2 or 3, and then a randomization to a monoamine oxidase

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Child and Adolescent Bipolar Illness: Implications of New Landmark Data

Important new data about the incidence of childhood- and adolescent-onset bipolar illness have been revealed recently from several different sources. The primary findings from these sources are that childhood-onset bipolar illness is common, is associated with extraordinarily long delays before first treatment for mania or depression, and is associated with an adverse course of illness and worse prognosis in adulthood compared with adult-onset illness. These clear new findings and realities reemphasize the importance of earlier recognition and treatment of childhood-onset bipolar illness in an attempt to prevent its adverse course.

New Data: Early Onset

Data from two adult outpatient Networks consisting of patients with bipolar disorder (with an average age of 42) found that between 15% and 28% of patients with bipolar illness had a childhood onset (before age 13) and another 35–46% had illness onsets in adolescence (between ages 13 and 18). The National Institutes of Mental Health (NIMH)-sponsored Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and our Bipolar Collaborative Network (BCN) thus found that between 50% and 74% of bipolar illness begins before age 19. In the BCN dataset we found that those patients with childhood onsets had the longest delay to first treatment for mania or depression, which on average was more than 15 years. Even adolescent-onset illness was not treated for more than 10 years on average. In contrast, early adulthood (19 to 29 years) and late adulthood (after 30 years) onsets of illness were treated after much shorter delays of 4.6 and 2.6 years, respectively.

Both outpatient Networks found that those patients with the earliest onset had more episodes, more rapid cycling, more suicidality, and more dysphoric mania, as well as more anxiety and substance abuse comorbidities than the patients in the other groups. These data regarding substance abuse suggest that if a child or adolescent patient is experiencing extreme mood dysregulation, they may be more prone to attempt to self-medicate.

Those patients with the earliest onsets also had a more serious and treatment-refractory course of illness when observed prospectively, as rated by clinicians on the daily Life Chart Methodology (LCM)™. These patients had more severe depression and mania and less time euthymic (without mood episodes) than those with illness onset in adulthood, despite treatment with a wide range of agents by experts in the field.

The recent epidemiological data of Kessler et al. (2005), based on a national comorbidity survey, also revealed that childhood-onset affective disorders were common, and that the time delay until first treatment was also inversely proportional to the age of onset, i.e., those patients with the earliest onsets had the longest delay until first treatment.

Together, these data indicate the critical importance of earlier and more effective treatment in hopes of diminishing the long-term toll of the illness on these youngsters with the earliest onset of affective dysregulation.

Diagnostic Controversy

Confounding this goal are some of the ongoing diagnostic controversies about the incidence rate of bipolar illness and its diagnostic boundaries in childhood. However, much of the controversy is now moot because of the recent data of Birmaher and colleagues at the University of Pittsburgh (2006; *Arch Gen Psychiatry* 63 [2]: 175–183). Most of the controversy originates from children given the diagnosis of bipolar-not otherwise specified (BP-NOS), because their episodes are not long enough to meet Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria for bipolar I disorder (associated with mania lasting 1 week or more) or bipolar II (associated with hypomania lasting 4 days or more). These patients with BP-NOS thus have brief episodes and often have extreme mood dysregulation without distinct periods of euthymia or well intervals. Therefore, some investigators have argued that this form of the illness is not necessarily similar to, or convergent with, the adult variety.

On the contrary, the data of Birmaher et al. indicate that children with BP-NOS are significantly ill and have considerable dysfunction similar to those with bipolar I and II diagnoses. Moreover, in their study it took much longer for patients with BP-NOS to stabilize acutely, compared with children with bipolar I or II, in whom the average time to achieve remission required about 9 months. In contrast, their patients with BP-NOS required an average of 2.6 years to achieve this same endpoint.

In addition, these investigators found that during the several years of follow-up, approximately 30% of children with BP-NOS converted to the bipolar I or II forms with longer durations or more severe manic components. Thus, it appears that BP-NOS is, in part, a precursor to these more diagnostically accepted bipolar I and II syndromes, suggesting illness course continuity with the more classic adult forms of the illness.

BP-NOS comprised about 35% of the population in the study by Birmaher et al., with an average patient age of approximately 12, and it is likely that BP-NOS is even more common in children of even younger ages. Extreme periods of mood lability appear to be the symptoms most characteristic of this group. The earliest signs of what may later emerge as clear bipolar illness are brief and extended periods of euphoria and decreased need for sleep.

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Early Onset

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ADHD vs. Bipolar Illness

Irritability and poor frustration tolerance are common in those with attention deficit hyperactivity disorder (ADHD), but these symptoms tend to be more common, extreme, and severe in those with bipolar illness. Because the majority of childhood-onset bipolar children have comorbid ADHD, the typical ADHD symptoms of hyperactivity, decreased attention span, and impulsivity are not helpful in making a differential diagnosis between the two illnesses.

Also making the diagnosis more complicated is the fact that many of the affective signs and symptoms that yield a clear diagnosis do not begin to emerge until the child is 7 or 8 years old, when depression, suicidality, and hypersexuality may become considerably more manifest; these symptoms do not typically occur with ADHD. A clear differential symptom is also the presence of hallucinations or delusions and either suicidality or homicidality, both of which are also completely inconsistent with an uncomplicated ADHD diagnosis. In BP-NOS, moods may fluctuate dramatically multiple times within a day, from periods of unexpected and out-of-context mood elevation to periods of depression and withdrawal. High levels of irritability and aggressiveness are often additionally present.

The distinction between bipolar illness and uncomplicated ADHD is of considerable importance from the treatment perspective. Stimulants and the noradrenergically active antidepressant **atomoxetine (Strattera®)** are the treatments of choice for uncomplicated ADHD. In contrast, initial mood stabilization with either anticonvulsants or lithium, or the atypical antipsychotics, is the first recommended treatment for those with bipolar disorder (Kowatch et al., 2005; *J Am Acad Child Adolesc Psychiatry* 44 [3]: 213–235). Only after the child's mood is stabilized and there is evidence of residual ADHD are small doses of the stimulants (amphetamine or methylphenidate) to be added to the treatment regimen.

Despite these consensus recommendations by experts in the field, what is all too common is that the comorbid ADHD components of bipolar illness are diagnosed and the bipolarity is missed, and children are treated with stimulants and antidepressants alone in the absence of a mood stabilizer or an atypical antipsychotic. This treatment usually results in little to no improvement, and in some cases exacerbation of the bipolar disorder, and occasionally the induction of full-blown manic psychosis.

Treatment Implications

Thus, children presenting with extreme mood dysregulation and dysfunction, particularly if there is a positive family history of bipolar illness, should be carefully assessed for the presence of bipolar disorder and not simply treated as if they had conventional ADHD. The positive family history of bipolar illness in first degree relatives (as well as a history of other affective disorders) is a definite clue to more intensively observe the child for bipolar disorder, because multiple studies indicate that childhood-onset bipolar disorder is associated with an increased risk of bipolar disorder in relatives compared with the incidence in relatives of those with adult-onset bipolar disorder. Birmaher and colleagues also observed that the rate of conversion of those with BP-NOS to more full-blown bipolar I and II syndromes differed as a function of family history, i.e., those children with a positive family history of bipolar illness converted at a rate of 50%, even within the first several years of observation, compared with very low rates in those without such a positive family history.

Thus, an adult parent with bipolar disorder, particularly if there is affective disorder in the other spouse, should be alert to the possibility of affective disorder in their children and seek appropriate evaluation and treatment, as indicated by the development of abnormal behaviors associated with dysfunction in the child's usual family, social, or educational role. This greater care, observation, and follow-up are much like processes already in place in many other medical syndromes. Positive family histories of myocardial infarction lead to early attempts at prevention with attention to the risk factors of hypercholesterolemia and high blood pressure. Those with a family history of young-adult-onset breast cancer are recommended candidates for early preventive treatment with tamoxifen and related agents.

Conclusions

In the past, many have argued that we would merely stigmatize children with such an early diagnosis of bipolar disorder. On the contrary, it would appear that this attitude is allowing stigma to confuse our diagnostic and medical clarity about the importance of early intervention and treatment, particularly given the considerable short- and long-term disabilities associated with bipolar disorder if left inadequately treated. Moreover, in our experience, the children and often their parents are typically relieved to receive this diagnosis, with its positive implications for treatment response and illness amelioration. It is also important in conceptualizing the nature of the child's extreme emotional and behavioral dysregulation as part of an illness that requires concerted treatment, rather than just willful misconduct that engenders harsher and harsher punishment. ■

European Conference

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Dr. F. Colom (Barcelona Stanley Foundation Center), a co-organizer of the symposium, presented remarkable data that group psychoeducation (compared with treatment-as-usual) led to reduced relapse, not only in the first several years after the initial intensive approach to illness education, but also for at least five years.

Again, these data make the very strong case for intensive, initial orientation to bipolar illness and its management after the patient is first stabilized, to help produce a more favorable long-term outcome.

Long-Term Treatment Data

Prof. Vieta also presented data from a placebo-controlled prophylactic trial of **oxcarbazepine (Trileptal®)** in bipolar disorder. The study was not adequately funded enough to recruit a sufficient number of patients to have sufficient power for a positive outcome, and most of the effects of the drug were of marginal statistical significance. However, the effects of oxcarbazepine on impulsivity, aggression, and dyscontrol significantly exceeded those of placebo when oxcarbazepine was added to a baseline regimen of lithium carbonate.

These data, in combination with the recent data from Dr. K. Wagner showing that oxcarbazepine did not exceed placebo in the treatment of child and adolescent mania, continues to leave the issue of oxcarbazepine efficacy in acute and long-term treatment ambiguous. In the trial of Prof. Vieta, the drug at 1200 mg was well tolerated and without any instances of problematic hyponatremia, which is more likely to occur with this compound than with carbamazepine. Thus, for those patients unwilling or unable to tolerate carbamazepine, oxcarbazepine remains a potential option, given the initial positive blinded studies of the drug by Dr. Emrich and associates in comparison with haloperidol and lithium in acute mania.

Dr. J. Geddes (University of Oxford) performed a meta-analysis on all the existing multicenter lamotrigine trials in bipolar depression funded by GlaxoSmithKline, and found that although the last 4 studies were nonsignificant, all of the combined data showed that lamotrigine exceeded placebo by a 27% increased chance of responding. A second BALANCE trial had been the intended (and much needed) comparison of lamotrigine versus an SSRI. However, with the imminent approval of quetiapine for treatment of bipolar depression, this British group is now planning a study comparing the combination of lamotrigine and quetiapine to quetiapine alone. The combination would have the hypothetical advantage of both the acute onset effect of quetiapine for improvement in sleep, mood, and anxiety, and the more gradual onset of lamotrigine's antidepressant effects with its good long-term tolerability in the prevention of relapse and recurrence.

Dr. B Amann (LMU University, Munich) presented a clinical trial of the addition of the heavy metal chromium for inadequate responders to other treatment modalities. The rationale for the use of chromium is based on its capability to increase amino acid transport in the brain and increase serotonin and norepinephrine, as well as tryptophan and melatonin levels. It also decreases the sensitivity of 5-HT_{2A} receptors and increases insulin utilization. Several previous open studies with chromium had suggested clinical improvement, and this study examined chromium (600–800 mcg/day) as an open-label adjunctive treatment. Six of 7 patients improved in their first year of open treatment, but only 4 patients remained on the drug in the proposed 2-year study. Chromium had shown positive effects in a prior study of atypical depressed patients, 70% of whom responded to chromium and none of whom responded to placebo. However, in another study by Dr. J. Docherty and colleagues in 113 patients with atypical depression, 600 mcg of chromium was not significantly better than placebo, although it did appear to decrease carbohydrate craving.

For those with increased carbohydrate craving, an individual clinical trial of chromium picolinate may be worth considering. However, one should not exceed the recommended doses, because Dr. Rick Weisler reported seeing seizures in several patients who used two to three times the recommended dose of chromium picolinate in concert with bupropion.

Dr. W. Nolen (University of Groningen, Sweden) presented a randomized, open comparison of the addition of the monoamine oxidase inhibitor (MAOI) **tranylcypromine (Parnate®)** versus lamotrigine in those patients in whom depression emerged despite taking at least one mood stabilizer. Patients were offered this clinical trial if they failed to respond to a more typical traditional antidepressant in a first randomized trial of bupropion, sertraline, or venlafaxine. Surprisingly, more patients responded to tranylcypromine (75%) versus lamotrigine (30%), but the difference was not statistically significant in this small study. However, the completion rates were significantly higher for tranylcypromine than lamotrigine.

It would appear that a clinical trial of an MAOI may still be useful to consider. Often MAOI treatment it is complicated by sleep disturbance, which had previously been treated using the addition of trazodone. However, with the newly demonstrated dramatic effects of quetiapine on sleep and anxiety, as well as on mood, quetiapine might be preferable to use to either augment the effects with MAOIs or counter their effects on insomnia.

Childhood Onset

New data from the BCN presented by Dr. R. Post indicate that the incidence of childhood bipolar illness is vastly higher in the U.S. compared with Europe, where only 2% of the population had illness onsets before age 13 compared with 22% in the U.S. If one examines both childhood and adolescent illness onsets, the percentage of these patients in the U.S. is double that of those in Europe. In accordance with some of the known vulnerability factors for early onset, those patients in the U.S. had a higher incidence in first degree relatives of a positive family history of bipolar illness, as well as unipolar illness, and a family history of a serious suicide attempt or a completed suicide in the family. Thus, somehow there is an increased genetic vulnerability to bipolar illness in the U.S. compared with our European cohorts, at least as studied in Utrecht, The Netherlands, and Freiberg and Munich, Germany. ■

Biological Psychiatry

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inhibitor or the combination of **venlafaxine (Effexor®)** and **mirtazapine (Remeron®)** in Step 4 for those who had not previously responded. Disappointingly, remission rates declined with each successive treatment step, beginning at 36.8% in Step 1, dropping to 30.6% in Step 2, 13.7% in Step 3, and 13.0% in Step 4 (tranylcypromine versus the venlafaxine/mirtazapine combination). Although these remission rates were low to begin with and became successively lower in later treatment steps, the opposite happened in relationship to the rate of relapse, which was 40.1% in those who responded in Step 1 but then grew to 55.3% in Step 2, 64.6% in Step 3, and 71.5% in Step 4.

These data indicate the relatively low achievement and persistence of remission in routinely treated outpatients and suggest the need for systematic exploration of alternatives.

Thus, these data are mirrored by those of the STEP-BD indicating that antidepressant augmentation of ongoing treatment with a mood stabilizer is much less satisfactory than had previously been surmised. Response rates are low and those who remain well during moderate term of follow-up without the recurrence of a depression or the onset of mania are very few indeed.

As noted in many previous editions of the BNN, perhaps earlier and more consistent institution of long-term prophylaxis in the recurrent affective disorders (both unipolar and bipolar) may begin to change this otherwise apparently poor prognosis for a good response seen in large numbers of patients in the STAR*D and STEP-BD networks.

Maternal Depression

We have previously noted the importance of treating depression in mothers until remission for the sake of the young children in the family. These results have been further highlighted by Dr. M. Weissman (Columbia University) and colleagues in her presentation indicating that if depression in mothers in the STAR*D trial were remitted compared with those without remission, many findings about the child's behavior were significantly improved. For example, in mothers whose depressions remitted, there was 11% decrease in the diagnoses of their children at three month's time, as opposed to an 8% increase in those children whose mothers were not remitted. Similarly, a high number of children whose mothers remitted achieved a remission of their own diagnosis (33%, as opposed to 12% of the children of mothers who were not remitted). In mothers who were remitted, no new diagnoses were given to their children, as opposed to this occurring in 17% in those whose mothers were not remitted.

These data then begin to expand the multiple parameters and domains of disability and dysfunction in those whose depression is inadequately treated. Not only is this a risk factor for the occurrence of more major full-blown episodes in the future and some degree of cognitive decline, but it is also associated with increased risk of behavioral problems in the offspring. ■

Research Words

Readers have asked us to provide definitions for some technical or medical terms we often use in the context of describing bipolar disorder research. Here are a few terms used in this and other issues of the *BNN* and their meanings in the context of bipolar disorder research:

interpersonal therapy (IPT) one of the short term therapies that have been proven to be effective for the treatment of depression; although depression may not be caused by interpersonal events, it usually has an interpersonal component (it affects relationships and roles in those relationships), and IPT was developed to address these interpersonal issues; the precise focus of the therapy targets interpersonal events (such as interpersonal disputes / conflicts, interpersonal role transitions) that seem to be most important in the onset and / or maintenance of the depression

protein kinase C (PKC) a family of protein kinases consisting of approximately 10 isozymes; PKC transduces the cellular signals that promote lipid hydrolysis

single nucleotide polymorphisms (SNPs) a common DNA variation in a single nucleotide (A, T, C, or G) in the genome (or other shared sequence) that differs between individuals, leading to the insertion of a different amino acid into a protein that may change the function of that protein from not at all to a great deal

supraphysiological pertaining to an abnormal or artificially created state in which a naturally occurring substance is at a concentration greater than that occurring naturally

toxoplasmosis an infection with the protozoan intracellular parasite Toxoplasma gondii; found in humans worldwide, and in many species of animals and birds; cats are the definitive host of the parasite.

Sources: Modified from Stedman's Medical Dictionary (www.stedmans.com); and Wikipedia (en.wikipedia.org).

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