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Bipolar Network News

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Highlights from the Pediatric Bipolar Disorders Conference

The information in this issue of the BNN comes from the 2008 Pediatric Bipolar Disorder Conference held March 28-29 in Cambridge, MA. The meeting was co-sponsored by the National Institute of Mental Health (NIMH), Massachusetts General Hospital (MGH), and the Ryan Licht Sang Bipolar Foundation.

Dr. Joe Biederman of MGH opened the meeting and was followed by Dusty Sang of the Ryan Licht Sang Foundation, who discussed the goals of the foundation and its motto, "Quest for the test." The motto emphasizes the importance of finding biological markers for the illness, which could be used in concert with a child's clinical presentation to make earlier and more reliable diagnoses of bipolar disorder. Like many parents with severely ill children with bipolar illness, the Sangs lost their son Ryan to suicide in his early 20s. They hope the foundation can fund research that enables earlier and more effective intervention in the illness.

Many of the presentations and posters at the meeting demonstrated the considerable progress made recently in many areas of diagnosis and clinical therapeutics of childhood-onset bipolar disorder. Bob Kowatch's review of the current state of controlled clinical trials of treatments for childhood onset bipolar disorder, which is summarized below, particularly illustrated the progress made since 2005, when a collaborative group first published consensus treatment guidelines without a substantial clinical-trials literature to support them. Now in 2008, the guidelines are similar, but they are supported by more robust, and in many cases, FDA-approved data concerning choice of therapeutic agents in the treatment of this increasingly recognized syndrome. Findings show that all of the atypical antipsychotics produce anti-manic effects in children, as is likely but less well-documented for lithium and the mood-stabilizing anticonvulsants valproate and carbamazepine.

In this issue:

Kowatch Literature Review of Clinical Trial Results in Pediatric Bipolar

In a discussion session at the 2008 Pediatric Bipolar Disorder Conference, Bob Kowatch summarized the results of all controlled clinical trials of psychopharmacological treatment for childhood mania. There is now a wealth of evidence-based support for such treatment, including 11 randomized and controlled clinical trials (RCTs) of a substantial size, which convey unequivocal evidence of the efficacy of atypical antipsychotics in BP-I mania in children and adolescents.

Evidence for other classes of drugs is less substantial. Among mood stabilizers, lithium is approved for children aged 12 and up, but a large parallel group, placebo-controlled RCT has not been completed. Valproate (Depakote) had the largest effect size in a randomized open comparison with lithium and carbamazepine (Tegretol), but a recent parallel group, placebo-controlled RCT of long-acting divalproex was negative. However, there were questions as to whether doses were high enough in the study and whether concurrent stimulant treatment, which occurred in most patients, confounded the results.

Among anti-convulsants, carbamazepine has yet to be studied in a parallel group, placebo-controlled RCT. The long-acting preparation of carbamazepine, Equetro, is FDA-approved for adults, based on two large positive RCTs. A close structural relative of carbamazepine called oxcarbazepine (or Trileptal) did not show efficacy over placebo for childhood mania in a RCT, so it remains to be seen whether Equetro would be as effective in childhood mania as it is in adults.

The anticonvulsant topiramate (Topamax) was positive on some secondary outcome measures in adolescent mania, in contrast to its negative results in adult mania in four large RCTs. However, because the adult studies were negative, the adolescent study was terminated before definitive evidence of efficacy was established. Weight loss is sometimes a side effect of topiramate, so if it is found to have anti-manic properties in children, it could be an attractive choice for treatment of mania and simultaneous weight loss assistance.

Anticonvulsant lamotrigine does not have acute antimanic efficacy in adults, and presumably would not in children either. However, it is FDA-approved for the prevention of mood episodes (especially depression, but also mania and mixed episodes) in adults, and its role for treatment of bipolar depression in children is just beginning to be explored in open studies. Children on lamotrigine have twice the risk (1 in 2,500) of a serious rash as adults (one in 5,000), so any use of this drug in youngsters must proceed with extreme caution, i.e., very low starting doses and very slow upward titration.

Although atypical antipsychotics were found to be effective for acute mania in many parallel group, placebo-controlled RCTs with children and adolescents, and risperidone, olanzapine, aripiprazole and quetiapine are FDA-approved for youngsters (with ziprasidone soon to follow), these drugs have a wide and differential range of side effects. Of particular concern are weight gain and extrapyramidal symptoms (tremor, stiffness, dysthymic parkinsonism, and akathisia or restless legs), which can be more problematic in children. Excess daytime sedation can also be problematic with some of the atypicals.

Some of the atypical antipsychotic drugs also predispose patients to diabetes and the metabolic syndrome, which is considered present when three

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Clinical Trials with Children Update Earlier Treatment Guidelines

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or more of the following problems are evident: increased waist circumference, elevated blood sugar (or insulin resistance), elevated cholesterol, elevated triglycerides, and elevated blood pressure.

Since all of the atypical antipsychotics now appear to be effective in childhood-onset manic illness, better tolerability in children becomes a deciding factor among the different drugs. This editor (R.M. Post) has preliminarily ranked the utility of the atypicals (see Table I) based on a subjective assessment that integrates the current state of efficacy, safety data, and tolerability for long-term treatment.

Tolerability in the long term is of paramount importance because evidence suggests that it may take an average of nine months to stabilize a BP-I or BP-II youngster, and more than two years for a child with BP-NOS. Since rates of relapse are also high, it appears appropriate to consider long-term continuation and prophylactic treatment even in initial good responders.

Aripiprazole and ziprasidone appear to be first-line agents among the atypicals because of their good tolerability and relative weight neutrality. Quetiapine (Seroquel), because of its breadth of actions in acute or prophylactic treatment of both mania and depression in adults, as well as recent positive data in adult unipolar depression and generalized anxiety disorder, is also ranked highly. Quetiapine is also widely used in children. Some claim that even in the relatively high doses needed to treat childhood mania (400-800 mg/night), it is relatively well tolerated for sedation and causes acceptable degrees of weight gain.

Dosing of aripiprazole is best started at low amounts (2 mg/day) and increased as tolerated, since higher starting doses (10-15 mg/day) have been associated with nausea and vomiting and/or activation and restless legs.

The complications in dosing of ziprasidone may account for its current less-than-wide clinical usage. Inadequate doses (20-40 mg/day) may activate and cause anxiety in adults, while higher doses (in the range of 80 to 160 mg/day) appear better tolerated. Use of the higher doses had initially been circumscribed by concerns about lengthening the QTc interval on the cardiogram (a widening of the depolarization spike that could predispose patients to arrhythmias). However, recent data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study and a new unpublished study of 18,000 patients randomized to either ziprasidone or olanzapine (which does not increase the QTc interval) showed that the small increases in the QTc interval with ziprasidone were not dose-related, and that ziprasidone resulted in no more cardiac events than olanzapine in the extremely large randomized comparison.

When a mood stabilizer (valproate, lithium, or carbamazepine) is added to a treatment regimen for childhood mania, many would choose valproate first. It does not require the careful blood level monitoring needed for lithium, and it does not come with the concerns about the possibility (however rare) of severe rash or hematological suppression on carbamazepine. However, where blood draws are not a problem, and especially when there is a positive family history of bipolar illness in first-degree relatives, lithium is a reasonable option. In the absence of a response to valproate, carbamazepine (with or without lithium) can be a useful alternative as well.

The original recommendations of Kowatch et al. in their 2005 consensus guidelines still provide generally good guidance, with just a few modifications needed. The earlier guidelines suggest starting with a mood stabilizer or atypical antipsychotic, and then, only after mood improvement, adding small doses of a stimulant for any residual ADHD symptoms. One might now shift to starting with a better tolerated atypical in preference to a mood stabilizer, given the robust data on efficacy of the atypical as a class in child and adolescent mania and the more ambiguous results of mood stabilizers in RCTs in children.

Combinations of drugs such as an atypical plus a mood stabilizer or two mood stabilizers (lithium plus valproate) appear to be commonly needed to achieve adequate response or remission. The exact algorithm and sequence of drug use in childhood remains to be further refined in the literature, but concerted pharmacotherapy appears necessary to the treatment of these highly impaired children.

First treatment with stimulants or antidepressants, which is the recommended treatment for uncomplicated ADHD, should be avoided in the child with bipolar disorder and comorbid ADHD; instead, mood stabilizers and/or atypicals should be utilized first.

If only stimulants are being used and they are not effective, parents should seek a second opinion or consultation with a physician more attuned to the possibility that the child has ADHD complicated by oppositional defiant disorder (ODD), conduct disorder (CD), or bipolar disorder. If stimulants are going to be effective, their efficacy should be relatively immediately apparent. Years of exploring the effectiveness of the many different ADHD preparations, using higher and higher doses in the face of inefficacy, should be avoided in favor of other approaches for ADHD complicated by bipolar disorder or another externalizing disorder such as ODD or CD. The immediate effect of stimulants on ADHD symptoms contrasts with the slower onset of action of mood stabilizers and atypicals. These typical treatments for bipolar disorder should be evaluated over many days or weeks to adequately discern effectiveness.

As summarized by Kowatch at this meeting, one can no longer consider the treatment of childhood-onset mania to lack a systematic clinical-trials database, and clinicians should think about beginning appropriate pharmacological as well as family psycho-educational therapy early in the course of childhood-onset mania. Family support, education, and clinical management techniques are a necessary part of the treatment plan in the vast majority of children. Ideally this combination of pharmacological and family interventions would lead rapidly to symptom improvement and eventually to remission, and as a consequence, preserve the child's family, social, and educational development and relationships, thus producing a more benign course of illness than that achieved in less systematic interventions, i.e., what is currently seen with "treatment as usual."

Bipolar Network News

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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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Provisional Status of Efficacy, Tolerability, and Utility of Treatments for Pediatric Mania*

(where utility is a rough subjective integration of efficacy, practicality, and long-term tolerability)

*To be modified as further data become available

Drug	Evidence in: ADULTS				CHILDREN			
	Acute		Prophylactic		Mania	Problems	Tolerability	Utility
	Mania	Depression	Mania	Depression				
Mood stabilizers								
Valproate	+++F	+	++	++	(++)	Weight gain, Polycystic ovarian syndrome	B+	B+/A-
Lithium	+++F	++	+++F	+++	++F	Weight, DI, Thyroid, Acne, Requires blood levels	B	B+
Carbamazepine	+++F	++	++	++	(++)	Rash, Rare bone marrow suppression	C+	B
Oxcarbazepine	++	+	?	?	(+/-)	Hyponatremia, Sedation	B	B-
Lamotrigine	0	(++)	++F	+++	(0)	Rare severe rash	B	D
Atypical Antipsychotics								
Aripiprazole	+++F	++▪	+++F	+/-	+++F	Akathisia, Minimal weight gain, GI upset	A-	A
Clozapine	+++	++	+++	++	+++	Seizures, Drooling, Weight gain, Requires white blood cell monitoring	C	C
Olanzapine	+++F	++▲	+++F	++	+++F	Weight gain +++, sedation	B-	B-
Quetiapine	+++F	+++F	+++▪F	+++▪F	+++F	Weight gain ++, sedation	B	A-
Risperidone	+++F	+	++	+	+++F	Prolactin increases, Weight gain ++	B	B
Ziprasidone	+++F	?	++	?	+++F	Minimal weight gain, Increases QTc (but not clinically problematic)	A-	A

F	FDA approved, FDA approval pending	( )	Ambiguous data	▪	Adjunctive	
+++	Strong evidence, placebo controlled RCT	+	Some evidence of likely effectiveness	?	Unknown effect	
++	Substantial evidence, multiple series	+/-	Minimal evidence	0	No effect	

A Preliminary Treatment Algorithm for Mania in Children and Adolescents Derived From Consensus Guidelines, Kowatch et al. (2005) and Update (2008)

Step 1: Atypical Antipsychotic (A.A.) or Mood Stabilizer (M.S.)

e.g. Aripiprazole (Abilify)/Ziprasidone (Geodon)/Quetiapine (Seroquel) or e.g. Valproate (Depakote)

If Good Effect:	If Inadequate Effect:	If Poor Tolerability:
Continue Drug**	Add other class of drug Continue both drugs**	Switch within drug class

Step 2: Add other drug class (M.S. or A.A.)
Step 3: Include Lithium
Step 4: Add Combination within class (e.g. Lithium plus Valproate)
Step 5: Add an Atypical to Step 4
Step 6: Switch Atypical
Step 7: Switch M.S. to Carbamazepine

** Add low dose stimulant (amphetamine/methylphenidate) for residual ADHD or symptoms

If Good Effect:	If Poor Effect:
Continue	Switch type of stimulant

Researchers Frustrated by Media Attacks On The Field

During the meeting, members of the Childhood and Adolescent Bipolar Foundation (CABF) led a discussion of media attacks on researchers of childhood-onset bipolar disorder. Examples given suggested that the media often abdicate their role as providers of unbiased information and instead create sensational stories to sell papers in this time of increased competition for dollars. These examples included deliberate distortions, such as splicing together separate comments from two different interviews of a doctor conducted weeks apart in order to twist their meaning or, in another instance, quoting an individual who was never contacted by the media.

Much press scrutiny has fallen on combination treatment of bipolar disorder in children, especially following the possibly erroneous citation of a published statement by Tom Insel, Director of the National Institute of Mental Health, which suggested that combination treatment in childhood bipolar illness is unwarranted and that no data support this type of treatment. Many recent studies have indicated that combination therapy is, in fact, required in a large majority of children.

Investigators in the meeting pointed out that other serious medical illnesses in children, including cancer, rheumatoid arthritis, diabetes, and heart disease, are routinely treated with large numbers of drugs in combination, with little or no reaction from the press, because these are considered "legitimate illnesses," as opposed to psychiatric illnesses, which are often depicted as suspect by the news media. Some in the press fail to realize the extent of the impairment caused by bipolar illness, probably due to ignorance, stigma and the desire to create sensational stories.

Most investigators agreed that attempts at educating reporters already intent on creating controversy by coaxing an investigator into saying something that could be twisted into a negative quote were not likely to be effective. The suggestion of media training for investigators was also rejected, because no amount of media training would be effective in the face of reporters solely interested in the creation of a preconceived story line.

A suggestion from the audience that appeared potentially useful was proactively contacting groups of reporters who might be interested in new findings. However, the problem of distinguishing these individuals from others more hostile to the field remains to be worked out.

There was consensus among the group that when an individual investigator is attacked, it would be helpful to have an advocacy group, such as parents from CABF, who could intervene and make clarifying comments, because once an investigator becomes a "target," attempts at defending him- or herself only add to the controversy.

Hopefully, both individuals in advocacy and in the clinical science of childhood-onset bipolar illness research and treatment could be identified and established as unbiased and available resources for clarifying issues raised in the press. An audience member suggested that the American Academy of Childhood and Adolescent Psychiatry (AACAP) might provide such leadership and commentary, but this idea was met with disapproval by members of the meeting, indicating that so far the organization has failed at this mission. It remains to be seen what other group could fill this role.

Treatment

Updates on New Treatment Studies for Bipolar Disorder in Children and Adolescents

Aripiprazole Effective in Bipolar Disorder With Comorbid ADHD

Luis Rohde from the Federal University of Rio Grande do Sul, Brazil first-authored a study entitled, "Aripiprazole in children and adolescents with bipolar disorder comorbid with ADHD, a randomized clinical trial." The researchers found that aripiprazole in average doses of 14 mg/day was more effective than placebo in 43 patients randomized to either aripiprazole (n=18) or placebo (n=25). The data are highly consistent with a larger industry-sponsored trial of aripiprazole (Abilify) that led to FDA approval of the drug for child- and adolescent-onset bipolar disorder.

The children ranged in age from 8 to 17 and had diagnoses of either bipolar-I or bipolar-II. In addition, 75% had comorbid ADHD. The researchers found highly significant decreases in the Young Mania Rating Scale (YMRS) score in the patients taking aripiprazole compared with those taking placebo, with an effect size that is considered meaningfully large (ES = .80). There was a significantly higher percentage of response, 90% on aripiprazole compared to 50% on placebo, and a higher rate of remission, 70% on aripiprazole as opposed to 30% on placebo, but no significant differences in ADHD symptomatology were observed.

Aripiprazole was generally well tolerated, with few patients dropping out of the study due to intolerable side effects, although a number of side effects were more prominent on aripiprazole than placebo, respectively. These included somnolence or drowsiness (47.1% vs. 16.7%), tremor (29.4% vs. 8%), sweating (35.3% vs. 12.5%), coughing (47.1% vs. 25%), sleepiness (53% vs. 25%), and sialorrhea or drooling (35.3% vs. 8.3%). While patients gained 1.2 kg weight on aripiprazole during the seven-week study, this was not significantly different from the 0.72 kg increase on placebo. The researchers noted that this weight gain on aripiprazole was substantially different from the 3.66 kg increase in weight when children and adolescents were treated with olanzapine for only three weeks in a study by Mauricio Tohen of Eli Lilly and Company and colleagues that was published in Archives of General Psychiatry (2007).

Valproate Found Effective for Aggression in Adolescents Independant of Its Anti-Manic Effects

Joseph Blader, PhD of Stony Brook SUNY School of Medicine presented the poster, "No evidence that changes in manic symptoms mediate reductions in aggression associated with valproate treatment."

Valproate, which is effective in acute mania in adults, has not conclusively been found to have the same effectiveness in childhood and adolescent acute mania. Open randomized data suggest that valproate is effective in children with bipolar-I manic symptomatology, but these findings have not been replicated in a large, industry-sponsored randomized controlled clinical trial.

Now, regardless of valproate's efficacy on manic symptoms in children, there is much evidence that in children without bipolar disorder, the drug is an effective treatment for aggression and behavioral dyscontrol.

Valproate in a preparation of divalproex extended release at a mean dose of 585 mg/day was more highly effective than placebo in reducing aggression in children with ADHD and comorbid either ODD or CD at ages 6 to 13. Fifty-three percent of those randomized to divalproex responded, as opposed to 14% randomized to placebo. Divalproex improved the odds of remission nearly seven-fold over placebo. Blader and his team of investigators concluded that in children with chronic aggressive behavior who did not have bipolar-I disorder, reduced aggression on valproate is not a function of a reduction in manic symptomatology.

These findings mirror that of several other studies, in particular a placebo-controlled trial by researchers at Columbia, who found marked improvement in aggression and dyscontrol with valproate compared with placebo in children who did not meet strict criteria for a bipolar disorder. Together, these and other data indicate that valproate is an effective treatment for aggressive symptomatology whether or not it proves effective in childhood mania.

Diagnostics

Severe mood dysregulation

Severe mood dysregulation (SMD) is at the most controversial end of the bipolar spectrum. It is characterized by chronic irritability and aggression without the classic bipolar symptom of euphoria, and most individuals suffering from SMD have little family history of bipolar disorder. SMD is a disabling illness, but clinicians are unsure about its relation to other mental illnesses, especially as to whether it belongs in or out of the bipolar spectrum. There are also questions about how it should be treated.

Ellen Leibenluft of the National Institutes of Health (NIH) described criteria for SMD in 2003. Symptoms include high levels of chronic irritability, with increased reactivity to negative emotional stimuli that is manifested verbally or behaviorally at least three times per week. It also includes hyper-arousal, with greater than three characteristics including insomnia, agitation, distractibility, racing thoughts, flight of ideas, pressure of speech, or intrusiveness. SMD is also characterized by anger and sadness at least half the day, which is noticeable to others most days. Chronic or non-episodic symptoms must be present for at least 12 months without symptom-free periods.

The main symptoms that appear to distinguish SMD from BP-NOS, according to Leibenluft's 2003 criteria, are the exclusion of cardinal bipolar symptoms (as per Barbara Geller and colleagues, 1998), such as elevated or euphoric mood, grandiosity/inflated self esteem, or episodically decreased need for sleep. Another criterion excluding an SMD diagnosis was any distinct episode of manic symptomatology that lasted greater than one day.

No Evidence of Lithium's Effect on SMD

At the conference, Daniel Dickstein, Ken Towbin, and Daniel Pine, members of Ellen Leibenluft's research group, presented the talk, "A randomized double-blind, placebo-controlled trial of lithium in youths with severe mood dysregulation (SMD)." Dickstein et al. found that lithium was no more effective than placebo in treating SMD.

However, there are several caveats to the interpretation of this study, the first of which is the small and highly selective sample of children who met the criteria for SMD. Investigators screened some 700 children, with 60% of them emerging with bipolar diagnoses. Of the 196 patients screened for SMD, 104 were found not to have

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Treatment of Severe Mood Dysregulation Undetermined

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the diagnosis. Of the 45 who were brought in for inpatient assessment, 20% no longer met the criteria, suggesting a high rate of spontaneous remission upon hospitalization without further psychopharmacological intervention. Of the 25 patients left, 14 were randomized to lithium and 11 to placebo, and 2 of those on lithium dropped out eventually, leaving only 23 participants who completed the study.

"It is unfortunate that most industry- and government-sponsored studies are terminated after the initial controlled phase of the trial is completed, losing a valuable opportunity to assess followup clinical responsivity. Further followup studies on this population of children with SMD might have helped point the way to which treatments they would ultimately respond."

Similarly, Melissa Brotman (also of NIH) found only 3.2% of individuals in a community sample met Leibenluft's criteria for SMD categorization.

Another caveat to this study is the amount of lithium used. The minimum therapeutic level of lithium is considered to be 0.8 to 1.2 mEq/L. In this study, while patients' mean serum lithium level was 0.82 mEq/L at week six, the levels only exceeded the minimum during 3.4 of the weeks on average. Several investigators have indicated that higher serum levels may be required in youth in order to achieve the same brain levels or intracellular levels of lithium as seen in adults.

Other investigators have observed that lithium decreases myoinositol in the brain and increases N-acetyl aspartate (NAA), a marker of neuronal integrity. These changes were not found in the children studied, further raising the possibility that physiologically effective lithium levels were not obtained. None of the expected lithium-induced alterations on the Young Mania Rating Scale (YMRS) were observed in the study, either.

While some might be tempted to interpret this study as evidence that SMD is not part of the bipolar spectrum because it did not improve with lithium, there is an additional caveat. A rich literature shows that lithium decreases aggression in adults, and an equally robust literature indicates that in most randomized controlled trials, lithium beats placebo for reducing aggression and behavioral problems in conduct-disordered youth. Even if SMD were not in the bipolar continuum, one would expect lithium (if the dose and size of the trial were large enough) to be effective in this group with severe mood dysregulation based on its general properties of inhibiting aggression and behavioral dyscontrol in those with non-bipolar presentations.

Despite the evidence that children diagnosed with SMD lack the incidence of bipolar illness in first-degree relatives that one would expect if SMD were part of the bipolar continuum, Leibenluft suggested during the presentation that some neurobiological findings are not definitive in excluding SMD from the bipolar continuum. In particular, facial emotion recognition deficits that appear specific to bipolar illness are also found in the subgroup of patients with SMD. Also, amongst neuropsychological and brain imaging findings in the SMD group, some parallel those in bipolar patients while others differ.

The presenters questioned whether SMD was a bipolar subtype because of the lack of discrete episodes observed. The illness also differs from ADHD because of the significant mood symptoms evident, and from oppositional defiant disorder (ODD) because it encompasses more complex behavior than just rule defiance.

Is SMD Just ADHD Plus ODD?

In a poster presented by Joseph Biederman et al., a group of investigators from Massachusetts General Hospital suggested that the category of severe mood dysregulation (SMD) is an amalgamation of ADHD and ODD. The poster, "Is severe mood dysregulation (SMD) ADHD + ODD? A ten-year prospective study of boys with ADHD with and without comorbid ODD," stated that the early diagnosis of ADHD plus ODD was associated with an increased risk for the diagnosis of ADHD, ODD, and major depression at four and ten years of follow up. However, childhood ODD was not associated with an increased risk for bipolar disorder in the follow up interval. In children with ADHD, ODD and conduct disorder, there was an increased familial risk for depression but not bipolar disorder.

The authors concluded that these results were consistent with the work of Brotman et al. (2006), who found that SMD is a risk factor for early adult depressive disorders. They suggest that SMD may not be sufficiently distinct from the diagnosis of ADHD plus ODD to warrant a new diagnostic term, citing similarities in outcomes across both groups of patients. SMD might merely be a "nuanced" form of ADHD with comorbid ODD.

Treatment for SMD Not Yet Delineated

A critical issue that remains to be further clarified is to what medicinal interventions those with severe mood dysregulation might respond. When this editor (R.M. Post) asked participants in the conference for clinical vignettes or experience as to what was likely to be effective, even based on non-randomized clinical trials, there were no positive suggestions. Instead, Leibenluft suggested that her group would conduct clinical trials with antidepressants and psychomotor stimulants to see whether individuals with SMD, who might emerge in the ADHD/depressive spectrum, might respond to these more classical treatments for those with ADHD and depression. An audible groan from the audience followed this suggestion, indicating that most felt these irritable, hyper-aroused children with prominent, consistent anger and sadness might be further dysregulated by these treatments.

It does not necessarily follow that because there is an increased risk for later depressive disorders, antidepressants would be an effective treatment for these children (along with psychomotor stimulants). Many, including the Biederman group, have reported that antidepressants may destabilize behavior in those in the bipolar spectrum, and whether this occurs or not in those with SMD or the similar condition of ADHD plus comorbid ODD remains to be clarified.

Even open clinical vignettes about treatments to which this group appeared to respond prior to the conduct of the controlled clinical trials seemed to be unavailable, and controlled trials may not yield answers to this question for several years.

It is unfortunate that most industry- and government-sponsored studies are terminated after the initial controlled phase of the trial is completed, losing a valuable opportunity to assess followup clinical responsivity. Further followup studies on this population of children with SMD might have helped point the way to which treatments they would ultimately respond.

Further Findings on the Diagnosis of Pediatric Bipolar Disorder

Diagnostic Instability In Bipolar Children Predicts Poorer Outcomes

Gabrielle A. Carlson of Stony Brook University School of Medicine gave a presentation on "Diagnostic stability, comorbidity, and early age of onset and ten year outcomes of hospitalized bipolar patients." She analyzed the diagnosis history of 272 individuals between 15 and 50 years of age first hospitalized in a community sample for psychosis between 1989 and 1995 in twelve Suffolk County N.Y. hospitals. She found that only 30% of individuals retained the same bipolar diagnosis from their first visit to 6-month and 24-month follow up, and then again at ten years follow up.

Carlson also found that the 3⁄4 of the respondents who had definite or probable childhood psychopathology were 3.5 times more likely to have inconsistent bipolar diagnoses than consistent bipolar diagnoses. **Those who showed more childhood psychopathology and had inconsistencies in their bipolar diagnoses also had the least favorable outcomes at the ten-year follow up period.** The absence of childhood psychopathology was associated with diagnostic clarity and a consistent bipolar diagnosis over the ten-year course.

These data show once again that those with early onset childhood psychopathology often have the least favorable outcomes over their course of illness and into adulthood. This is quite clear for both childhood-onset recurrent unipolar depression and bipolar illness; those with the youngest ages of onset have a more pernicious course of illness compared with those with adult onsets. Thus, the data speak to the importance of early intervention in these types of affective and psychotic symptoms in an effort to prevent this adverse prognosis with more effective treatment from the outset.

Maternal Reports Of Pediatric Bipolar Disorder Are Reliable

Joseph Biederman and colleagues presented a poster titled, "How informative are maternal reports of pediatric bipolar disorder in the absence of corroboration by the youth?" These investigators concluded, "Even in the absence of endorsement by the youth, maternal reports of mania identified a severe clinical picture of mania that was largely indistinguishable from concordant cases [in which both the mom and the child agreed]." This study speaks to the importance and validity of maternal reports of psychopathology, which often trump those of the child.

Childhood-Onset Bipolar Disorder Differs in Different European Countries

Recent literature from Europe highlights differences in the prevalence of childhood-onset bipolar disorder in different countries around the world. There is a relative absence of observed childhood-onset bipolar disorder in the United Kingdom, Ireland, the Netherlands and Germany, while the illness is prominent and widely recognized in the U.S., and a high incidence is also now reported in Norway, Spain, Italy and Turkey.

Potential reasons for the discrepancy in the incidence of childhood-onset bipolar disorder on different continents and within the European community deserve further attention and study with appropriate epidemiological investigations. This might lead to the identification of the relative protective factors present in the British Isles, the Netherlands and Germany compared with vulnerability factors in the U.S., Norway, Spain, Italy, and Turkey.

At the Pediatric Bipolar Disorder Conference, Aditya Sharma of Sir James Spence Institute at Newcastle University gave the report, "Surveillance of pediatric disorder in United Kingdom and Republic of Ireland." Investigators found little evidence of pediatric bipolar disorder in these locales.

Inmaculada Escamilla and others from Clinica Universitaria of Navarra gave a presentation on the illness in Spain, describing the longitudinal course of pediatric bipolar disorder in a Spanish sample. They found that children ages 12 or younger spent 50% of follow up time in an episode, while those over 12 spent 44.6% of the time. Children with younger age of onset of symptoms fared worse. At the end of follow up, only 39.5% of the children had achieved partial remission or recovery. These data disappointingly parallel many other investigative groups including Geller et al., Birmaher et al. (2006), and DelBello et al. (2007) indicating a considerable difficulty in achieving sustained mood stabilization in children treated naturalistically either in the U.S. or now in Spain.

Cesar Soutullo and others from the University of Navarra gave another presentation on the clinical characteristics of bipolar illness in a sample of Spanish children and adolescents. These children closely resembled those described in U.S. clinics. The most frequent mood alteration at the time of diagnosis was irritability. Bipolar disorder was associated with severe impairment and had high levels of comorbidity that required complex treatment. Like data reported in many clinics in the U.S, the Spanish study results showed that almost half of the sample required at least three medications to control their symptoms.

Number and Severity of Symptoms Differentiates Childhood Bipolar from ADHD

This editor (R.M. Post) presented the poster, "The number and severity of dysfunctional symptoms differentiates prepubertal onset illness from ADHD." The research group completed a new series of analyses of children with onset of bipolar illness prior to age nine, in order to age-match them closely with a sample of children with ADHD, as diagnosed by Bob Findling at Case Western Reserve. Not only were measures of decreased sleep and increased brief and extended periods of mood elevation very early differentiators of who would emerge with a bipolar (as opposed to an ADHD) diagnosis, but also the sheer quantity of dysfunctional symptoms in bipolar illness markedly exceeded that found in ADHD.

The classic attentional symptoms of ADHD, including hyperactivity, decreased attention and impulsivity did not differentiate the two diagnoses at any point over the child's age or symptom trajectory, but affective symptoms did begin to differentiate the bipolar children from those with ADHD after age seven. These symptoms included periods of sadness, withdrawal, suicidal thinking, and somatic concerns.

Barbara Geller of Washington University in St. Louis and colleagues recently reported a high incidence of psychotic symptoms (either hallucinations or delusions) in about 75% of those with childhood-onset bipolar illness (either prepubertal- or adolescent-onset). Thus, psychotic symptoms, along with suicidality, homicidal threats, and the manic symptoms of mood elevation and decreased sleep, should be considered indications of the possibility of bipolar disorder rather than uncomplicated ADHD.

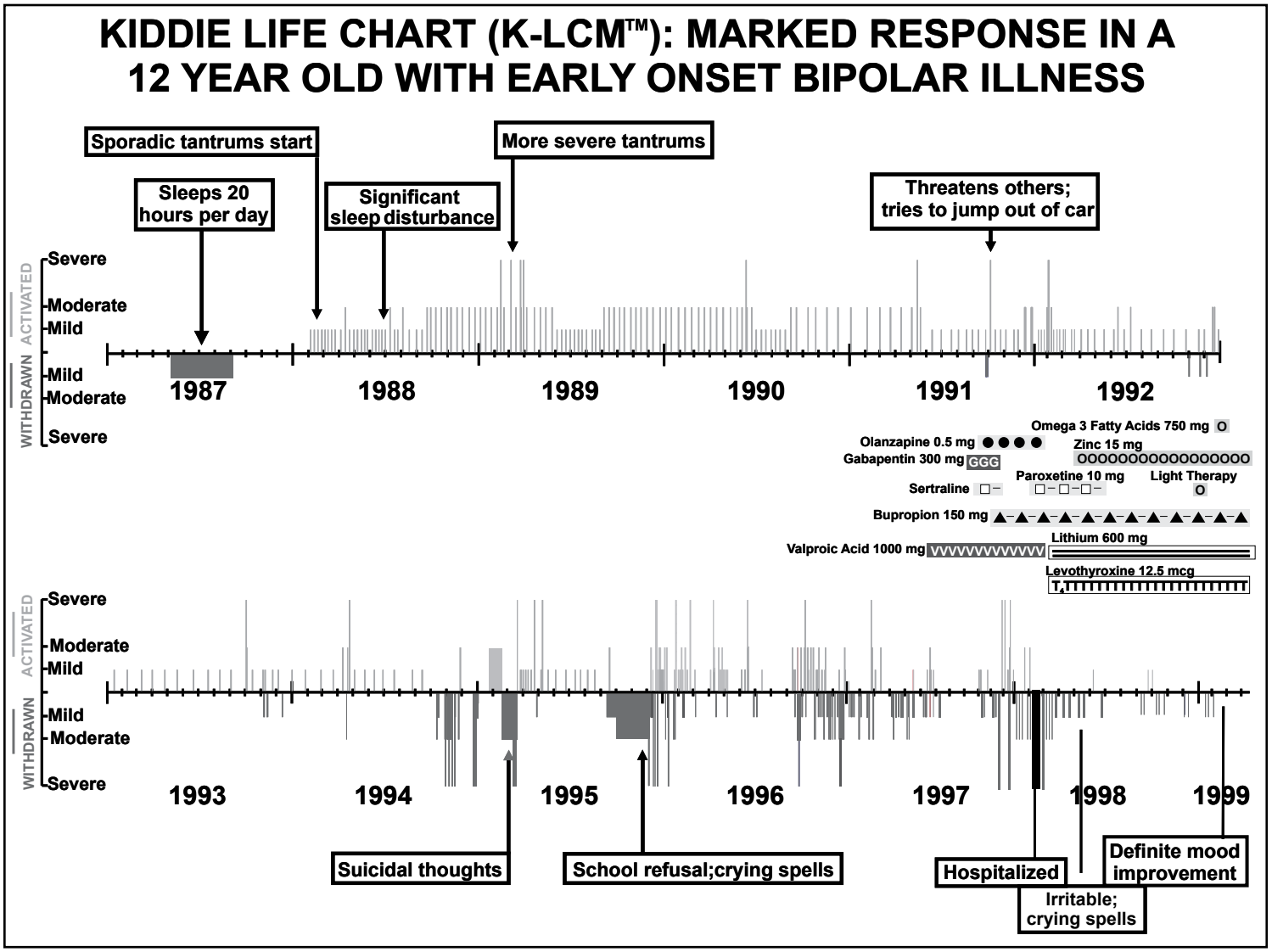
This distinction is important because psychomotor stimulants, which are the first-line treatment for those with ADHD, should be deferred in bipolar patients until mood stabilization is achieved with drugs such as atypical antipsychotics or lithium and anticonvulsants, according to consensus guidelines (see Kowatch et al., Journal of American Academy of Child and Adolescent Psychiatry, 2005 and 2007. Also see summary on page 1).

Life Chart Case Demonstration:

Late Diagnosis Of Bipolar Disorder At Age 10 After Years Of Affective Dysregulation: Good Response After Two Years Of Clinical Trials

A life chart can be used to record daily activated or inhibited symptoms and responses to treatment. Over time, the observation of trends may help with diagnostic assessment and consultation. This particular figure shows the patterns from the life chart of one individual with childhood onset bipolar disorder.

Life charts for adults and children are available on the BNN website, www.bipolarnews.org.



The course of illness graphically depicted on this children's version of the LCM illustrates a number of key points in the approach to childhood-onset bipolar disorder.

1) Despite years of extreme affective and somatic dysregulation, including aggressive threats to others, suicidal thoughts and actions, both the diagnosis of childhood-onset bipolar illness and the initiation of treatment were extremely delayed. The patient would likely have met criteria for a diagnosis of bipolar-NOS (not otherwise specified) early in life, and in 1994 would have met criteria for bipolar II disorder with more extended periods of depression and a hypomanic episode lasting for more than a month.

2) After periods of profound lethargy and sleeping more than 20 hours/day in her first year of life, decreased amount of sleep became apparent from 1988 onward. This is often one of the earliest signs of pre-pubertal-onset bipolar disorder, along with brief and extended periods of mood elevation, which this patient did not consistently show until 1994.

3) Her severe tantrums, beginning in 1989, consisted of inconsolable aggressive behavior and screaming which might last for several hours, and indicated poor frustration tolerance. Severe tantrums are not a specific characteristic of bipolar illness, but extreme irritability and poor frustration tolerance are seen in very high percentages of bipolar patients, in contrast to less severe difficulty in these domains in about 50% of children with uncomplicated ADHD.

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4) Because of the initial lack of mood elevation and euphoria, some investigators would have labeled her early in life with a diagnosis of severe mood dysregulation (SMD), according to the criteria of Leibenluft et al., or ADHD with oppositional defiant disorder, as suggested by Biederman and colleagues, rather than bipolar disorder.

5) The beginning of long periods of depression in 1994, with prolonged crying and school refusal, should have heightened suspicion of a bipolar disorder diagnosis. The extreme mood instability and activated behavior rapidly alternating with the inhibited behavior associated with each depressive burst could also have signaled the onset of bipolar disorder.

6) After 1994 she clearly manifested bipolar disorder, showing more prolonged and consistent episodes of both depression and hypomania with brief bursts of more full-blown mania as well. Discrete longer episodes of depression and mania may only emerge after a prolonged period of bipolar-NOS with rapid mood alterations (Birmaher et al., 2006).

7) She appeared to have an initially good response to valproic acid (Depakote) in 1997, but major mood oscillations continued, despite the addition of the serotonin-selective antidepressant sertraline and then bupropion, along with a brief trial of gabapentin and then olanzapine.

8) In 1998 she began to do well on a regimen of lithium carbonate and bupropion along with small doses of levothyroxine (T4 or Synthroid, 12.5 mcg/ml) and began also to utilize zinc (15 mg), and later, omega-3 fatty acids. Her behavior normalized markedly and she did well in school after being hospitalized for a major depression earlier in the year.

9) The development of more protracted periods of depression and suicidal thoughts after age 7 is highly consistent with the retrospective data of Luckenbaugh and colleagues who saw that those who had pre-pubertal-onset of bipolar illness (prior to age 9) did not begin to have consistent periods of depression that differentiated them from those with ADHD until after approximately age 7.

10) These data are also consistent with the view of Birmaher and colleagues that about a third of youngsters with bipolar illness present with BP-*not otherwise specified* subtype (BP-NOS) because the duration of their manias do not meet the four day minimum for BP-II or the one week of mania required for BP-I.

11) However, Birmaher and colleagues saw that those with BP-NOS were impacted heavily by their mood disorder, and, in fact, took more than twice as long to achieve mood stabilization as those who had more classic BP-I and BP-II presentations.

12) In addition, after several years of clinical follow up, they observed that some 30% of BP-NOS children converted to a BP-II or BP-I diagnosis, suggesting that the BP-NOS presentation with chronic extreme mood instability may not only be an important subgroup of patients with this diagnosis, but also an earlier precursor to some cases of longer-lasting BP-II and BP-I hypomanic and manic episodes, as seen in this figure.

In Birmaher's experience, it required some nine months for the BP-I and BP-II children to achieve acute mood stabilization while those with a BP-NOS presentation required more than 2-1/2 years before this improvement occurred. These data are at least partially consistent with the lifechart, indicating that a number of clinical trials may be required before appropriate pharmacotherapy is achieved.

13) A clear take-away message from this case presentation is that while the illness can be extremely disabling and even life-threatening (due to the prevalence of suicidal thoughts and acts such as jumping out of moving cars), it can also be improved dramatically by medications, although this often requires a considerable amount of time and often, a number of medications in combination.

Findling and colleagues have presented controlled clinical trial data that children with bipolar illness who were stabilized on the lithium/valproate combination appeared to require both drugs in a very high proportion of instances. This was evident upon their attempts at randomized blind discontinuation to either drug in monotherapy. They observed that some 50% to 66% of patients subsequently relapsed during treatment with either lithium or valproate monotherapy. However, the majority of patients then re-responded when the combination of lithium plus valproate was reinstated. This patient responded to lithium in conjunction with other agents, and whether she would have done better and held her responsivity for a longer period of time on a combination of lithium plus valproate remains open to speculation. Moreover, as we noted in "Kowatch" on the front page of this newsletter, there are now considerable data suggesting that all of the atypical antipsychotics are effective not only in adult mania, but in childhood and adolescent mania as well.

Filling out a retrospective monthly kiddie NIMH-LCM (Life Chart Method) like the one illustrated in the figure and continuing to rate progress on a daily basis will provide invaluable longitudinal documentation of a child's illness and response to treatment. Ultimately, these kinds of longitudinal data will put an end to the major controversies about the diagnosis of bipolar disorder in children, because a sufficient longitudinal perspective usually yields unequivocal evidence for or against the diagnosis.

As described elsewhere, an inherent advantage of the kiddie LCM is that it deals only with the severity of activated versus inhibited symptomatology, without necessarily claiming that it is specific manic or depressive symptomatology. Exactly when a severely ill child actually crosses the threshold to achieve a bona fide DSM-IV diagnosis of BP-I, II, or NOS is a bit arbitrary, and likely does not represent a discrete event but rather a series of symptom categories on a continuum of intermittency, severity, and duration.

Use of the kiddie LCM will circumvent many diagnostic difficulties and controversies. Moreover, it will assist in the evaluation of the effectiveness of a given treatment regimen, which most treating clinicians agree typically requires a combination of treatments rather than just one drug in monotherapy. Assessing the impact of each drug as it is added, in terms of its contribution to the overall profile of efficacy and/or side effects, is facilitated with use of the kiddie LCM.

Family, Education and Therapy Briefs

Family Environment and Suicidality

Tina Goldstein of the University of Pittsburgh Medical Center presented a poster entitled, "Family environment and suicidality among bipolar youth." Researchers found that those with current suicidal ideation reported greater conflict with their mothers, lower levels of family adaptability and more family stress during the previous year. Together, these findings indicate the importance of engaging the entire family in the therapeutic process for bipolar children, as has been recommended by many investigators.

Psychoeducation for Families

Mary Fristad of Ohio State University presented the poster "Direct and mediated effects of psychoeducation on outcome for children with mood disorders." She and her research group found that family psychoeducational interventions were highly effective in improving the outcome of children with bipolar disorder. These data, along with other consistent findings, begin to make a strong case for the critical importance of family, group, and individual psychoeducational efforts in approaching this illness.

Neurobiology Briefs of Clinical Interest

Facial Emotion Labeling Deficits Found in Bipolar Youth

Melissa Brotman of the Mood and Anxiety Disorders Program of the National Institute of Mental Health (NIMH) gave an oral presentation, "Facial emotion labeling deficits in youth at risk for bipolar disorder." She and other investigators in a group led by Ellen Leibenluft found that deficits in facial emotion labeling were highly evident in patients with pediatric bipolar disorder. The deficits did not occur in patients with major depression and anxiety disorders, those with ADHD and conduct disorders, or in normal controls.

Brotman created a series of pictures depicting facial emotion that were gradually "morphed" by a computer to become increasingly difficult to recognize. Subjects were shown the series of faces, and investigators measured at what point in the morphed sequence the subjects stopped being able to accurately identify facial expressions. She found that both bipolar children and those at high risk (with a bipolar parent or sibling) showed greater deficits on facial recognition of emotional expression compared with controls. This test could be used to study whether at-risk individuals with the largest deficits in facial emotion recognition (along with other neurobiological and clinical markers) go on to develop the illness. Should such findings emerge, the task could be used in conjunction with other neurobiological markers to assess vulnerability to the illness, and perhaps to initiate earlier treatment.

BDNF Levels Low in Children with Pediatric Mood Disorders

Ghanshyam Pandey of the University of Illinois at Chicago gave a report on "Brain-derived neurotrophic factor (BDNF) in platelets of pediatric patients with mood disorders." BDNF is a peptide secreted by neurons that is critical for long-term learning and memory in addition to neuronal growth and survival. He found highly statistically significant ($p < .001$) reductions in both BDNF protein and BDNF mRNA in children with bipolar disorders compared with children in a control group.

Pandey's data are highly consistent with a large body of evidence indicating that serum BDNF is reduced in adult patients during depressed and manic episodes, usually in proportion to the severity of the episode. There are also significant data that show increases in oxidative stress measured in the blood of adult patients with bipolar disorder, and increases of cytokine and other inflammatory markers in children with bipolar illness. These findings together indicate the possibility of using biological markers to assist in earlier diagnosis and treatment.

Cortical Thinning in ADHD with Bipolar

Nikos Makris presented a poster on "Thinning of both attentional and affective cortical networks in comorbid ADHD/bipolar disorder." The cortex is the part of the brain responsible for higher level social, cognitive and integrative functioning. These researchers and others have previously shown cortical thinning or delayed maturation of the cortex in multiple areas of brain associated with attentional and executive circuitry in children with ADHD.

In those with bipolar disorder and comorbid ADHD, additional areas of cortical thinning included the insula, the orbital frontal cortex, and the frontal-temporal regions, which had previously been closely associated with affective dysregulation. It is not yet known why this happens.

This study and the deficits in facial emotion recognition reported elsewhere suggest the importance of treating children with ADHD and comorbid bipolar disorder for their cerebral dysfunction and introducing appropriate psychotherapeutic and rehabilitative treatment strategies.

Neurobiology

Images of Brain Development Could Aid in Diagnosis

John Gabrieli of the Massachusetts Institute of Technology gave a plenary presentation, "Development of the mind in the child's brain: evidence from MRI." This talk on the development of the normal child's brain revealed differing rates of cortical development in areas of brain corresponding to different types of high-level visual specialization. These include object recognition in the lateral occipital complex, facial recognition in the fusiform face area and recognition of places in the perihippocampal place area.

Judy Rapoport and Jay Giedd of the National Institute of Mental Health (NIMH) have also emphasized the differences in development of various parts of the brain as well. They found that the cortex develops several years more slowly in subjects with ADHD than in normal controls. The new findings will allow for better comparison and identification of normal versus pathological brain functioning, with helpful implications for diagnosis and treatment.

The brain dramatically changes its landscape throughout development. In children and adolescents, there is a decrease in gray matter and an increase in white matter. The central nervous system is remodeled with added inhibitory synapses (as opposed to excitatory synapses) and enhanced connectivity with other regions of the brain. The increasing white matter (myelin sheaths that surround neurons' main axon terminals) is instrumental in conducting and conveying new information.

Gabrieli (and Rapoport) found that stimulant drugs enhanced performance in both normal subjects and those with ADHD by increasing functioning of the prefrontal cortex. However, in some measures, such as the degree of brain activation during impulse control tasks, while both groups did better on methylphenidate (Ritalin) than off, their regional brain function diverged in opposite directions. In both the caudate and putamen, key areas of the brain involved in motor control, controls showed fewer pixels activated on the drug, while those with ADHD showed greater numbers of pixels activated. Gabrieli suggests that Ritalin may have a normalizing effect in the ADHD group, because the increases in activity in areas of brain with the drug were very similar to the absolute numbers of pixels activated in the controls in their baseline state.

In a response inhibition "go/no-go" task (where some symbols require an active response like pressing a button and others require withholding that response), Gabrielli showed that several areas of the brain were correlated with response inhibition, but that ADHD patients failed to use some areas of brain used by the controls, or used the other side of the brain.

Gabrieli made the case that brain imaging might be at the threshold of providing clinically meaningful information upon which one could act therapeutically. He used an example from the evaluation of children's reading skills. Teachers using standard reading measurements were fairly accurate in identifying children who were poor readers, with a correlation coefficient of .57. Similarly, brain activation scans predict poor reading ability with a modest correlation coefficient of .55. However, when teachers' predictions and evidence from brain scan are combined, the two together yield a much higher correlation coefficient of .81.

Given such an accurate ability to predict, the two measures could be used together to initiate effective remedial approaches to reading with a high degree of assurance that the children most in need had been identified. We look forward to similar advances in the area of clinical therapeutics of bipolar disorders.

Neurobiology

Two Strategies for Genetic Progress in Bipolar Disorder:
Searching for novel genes v. indentifying gene profiles of responsive patients

In a plenary presentation, Mark Daly of Massachusetts General Hospital reviewed progress to identify genes involved in polygenic illnesses in other branches of medicine where the findings have contributed to a new understanding of pathophysiology and have suggested alternative approaches to treatment.

Daly cited examples of macular degeneration, Crohn's disease, and type II diabetes as illnesses in which new genetic findings have been revealed. This was made possible through the combination of multiple data sets to create a very large N (number of subjects). The size of the data set allowed for a robust picture of the role of multiple single nucleotide polymorphisms (SNPs), or common gene variations, in the population.

Progress was made in the field of psychiatric illness when a spontaneous deletion that occurs in chromosome 16p11.2 was found to account for 1% of autism. Interestingly, this gene is not specific for autism; its presence carries a ten-fold increased risk for ADHD, dysthymic disorder, schizophrenia, bipolar disorder, pain syndromes, and mental retardation, suggesting that it represents a broad risk factor for psychopathology. Researchers also found that the structural protein Ankyrin G and a subunit of the l-type calcium channel were involved in bipolar disorder.

Daly predicts that the accumulation of a large sample size in the study of childhood-onset bipolar illness could lead to similar progress identifying new physiological pathways to the disease, which could ultimately lead to new treatments. He made the point that even though each gene contributes only 1 or 2% of the vulnerability to the illness, treatments targeted at a given gene can have unexpectedly large therapeutic effects. However, it will likely take a decade or more before any such findings lead to new therapies for the illness.

This editor (R.M. Post) raised an alternative strategy previously suggested by David Cox of drug company Pergalen. Cox helped drive the technological innovations that made sequencing the entire human genome rapid and relatively inexpensive. Currently, it costs about $500 to sequence the entire human genome. However, Cox has been pointing out for several years that focusing on particularly relevant parts of the genome could produce clinically relevant information even more quickly and inexpensively.

Cox suggests that by analyzing an array of 50 to 100 SNPs that have been implicated in bipolar illness and related neuropsychiatric disorders like depression, schizophrenia and ADHD, researchers could determine how a subject might respond to a specific treatment. For example, if a researcher ran a trial of lithium and analyzed an array of SNPs in each individual in the study, the results might show whether responders' SNP profile differed from that of non-responders. Thus, instead of searching for the single SNP that might explain vulnerability to an illness, researchers could analyze an array of common SNPs and gain clinically relevant information more quickly.

This strategy would be particularly helpful for bipolar illness, where there are not only several categories of effective drugs, such as anticonvulsant mood stabilizers, atypical antipsychotics and antidepressants, but also multiple drugs within each category. Defining which patients are most likely to respond to which of the available treatments would be of great clinical value.

Cox had emphasized that the technology is currently available to determine subjects' SNP profiles. All of the actions of a given SNP would not need to be determined, only whether its presence or absence in association with other SNPs was related to a likelihood of response to a given treatment.

He gave a cogent illustration from the field of lung cancer treatment. A treatment is now available that yields complete remission in a high percentage of subjects in a particular subgroup, but that subgroup comprises a minority of all those with lung cancer. People in the subgroup have an alteration in a receptor for neurotrophic factors that makes cells particularly likely to grow and reproduce. The new drug would appear ineffective in the entire population of patients with lung cancer, but when patients with the specific receptor defect are identified and targeted, the drug appears extraordinarily effective. Genetic developments in psychiatry may not result in as robust a prediction as in this example, but even a slight increase in response prediction could be helpful.

Already, multiple studies have indicated that those with a short form of the serotonin transporter are less likely to have positive antidepressant effects to serotonin-selective antidepressants. We also know that children with unipolar depression and adults with bipolar illness who have the short form are more likely to have suicidal ideation than those with the long form. Incorporated into an array of common gene variations (SNPs), these types of results could readily be applied to prediction of individual clinical treatment response.

Another benefit to the SNP profiling strategy is the possibility of determining an individual's vulnerability to serious side effects that are risks with some drugs. This has already proven feasible in the case of carbamazepine. A gene alteration has been linked to an HLA antigen that often causes a serious rash in Asiatic populations on the drug.

One obstacle to overcome in the SNP profiling strategy is the clinical methodology. Cox recommends that in each large clinical trial assessing responders and non-responders to a given agent, a limited SNP profile be completed. However, a large consortium of government and private industry is necessary to combine available SNP profiling techniques with available patients in clinical trials.

Despite the possible benefits of this approach, a commitment to the strategy and a means of organizing private monies, the pharmaceutical industry, and governmental funds towards this purpose may be difficult to accomplish. This editor approached an American College of Neuropsychopharmacology subcommittee on government/industry interactions with the idea, but no mechanism for forming such a consortium was identified, and the proposal was essentially tabled.

In addition, at the Pediatric Bipolar conference, Mark Daly expressed little enthusiasm for a shift from gene discovery toward Cox's SNP profiling strategy, even if it would lead to more rapid clinical therapeutic advancement in the field of bipolar disorder research.

One can only hope that eventually a scientific body will recognize the utility of Cox's approach and shift the investigative paradigm from searching for new genes that may or may not yield new targets for therapeutics to assessing an array of genes for more immediate clinically valuable results.

Not only would this approach aid in the assessment of individual patient response to individual agents, but with a robust enough SNP profiling, it could also identify those at high risk for early onset of illness, or those at high risk for more pernicious course of illness, and lead to earlier treatment for people in those groups. A process for rapidly acquiring information that could prevent much morbidity and disability should not be discarded lightly.

Traditional molecular genetics approaches and personalized medicine approaches should not be viewed as either/or strategies, but ones that are highly complementary. However, without a specific goal of organizing a methodology for clinical trials and assessing individual clinical responses to link them to such gene profiling, the promise of rapidly identifying the most effective treatments for a given individual will not be readily achieved.

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