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Bipolar Network News

Meeting Highlights:

Third European Stanley Foundation Conference on Bipolar Disorder
Freiburg, Germany, September 12–14, 2002

For the past seven years, two international scientific meetings on bipolar disorder have alternated on a yearly basis. The International Conference on Bipolar Disorder takes place in Pittsburgh, and the European Stanley Foundation Conference on Bipolar Disorder took place this year in Freiburg, Germany, from September 12–14. Highlights from the European Conference symposia and poster presentations are given here. Dr. Robert Post (Editor-in-Chief) attended the meeting and gave a presentation, and summarizes the key points below:

Bipolar Research in Germany

Dr. J. Walden and Dr. H. Grunze chaired a symposium based on the work of the German Society for Bipolar Disorder. Dr. H. Möller and Dr. A. Erfurth began with a discussion on the nature of the antidepressant switch phenomena (the use of antidepressants causing an episode switch into hypomania or mania). Dr. Möller indicated that the switch rate in his series of 158 inpatients in Munich was 25% (10% switching to mania and 15% to hypomania), in the context of treatment with mood stabilizers. If antidepressants were used without mood stabilizers, the switch rate increased from 26% to 56%. Tricyclic antidepressants (TCAs) were much more likely to be associated with manic and hypomanic switching compared with serotonin selective re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and other second-generation antidepressants. Interestingly, low thyroid stimulating hormone (TSH) was associated with an increased switch rate. Dr. Möller ended his presentation by stating that clinicians should not be "too generous in avoiding" the use of antidepressants in the treatment of patients with bipolar illness.

Dr. Erfurth reviewed data of Dr. Mundo and colleagues (2001; *Arch Gen Psychiatry* 58 [6]: 539–544) indicating that the antidepressant switch rate was higher (63%) in those patients with the short allele of the serotonin (5-HT) transporter protein gene than in those with a long allele (29%). Dr. Erfurth noted Dr. Henry's study (2001; *J Clin Psychiatry* 62 [4]: 249–255) indicating that lithium reduced episode switching, but anticonvulsants did not, which is somewhat contrary to other clinical reports. Other risk factors for antidepressant-induced switching noted by Dr. Erfurth were a bipolar II diagnosis versus bipolar I disorder (in particular, women with bipolar II); psychotic depression; and patients with rapid cycling (four of four patients switched in his experience).

- *The use of antidepressants in conjunction with a mood stabilizer remains widely endorsed in the U.S. and European guidelines on treatment of bipolar depression. Lamotrigine (Lamictal®) also has become a widely endorsed alternative. Given the increased rate of switching on TCAs compared with the second-generation antidepressants, and the high lethality of these older antidepressants in overdose, it would appear that the older TCAs (even the better-tolerated secondary amine variety such as desipramine [Norpramin®] and nortriptyline [Pamelor®]), should no longer be considered first-line treatment for bipolar depression. They should generally be avoided in favor of other antidepressant modalities which are less likely to be associated with a switch into hypomania or mania, and are better tolerated, particularly in overdose.*

Dr. Michael Bauer presented data on the effectiveness of supraphysiologic (extremely high) doses of levothyroxine (T_4) in bipolar depression augmentation. Considerable open-study clinical data suggest that between one-half and two-thirds of patients will have a clinically robust response to the addition of high doses of T_4 in the range of 300–500 µg/day (which is usually sufficient to increase the free thyroxine index by 150% or more). Over 60 patients have been studied in clinical trials using high-dose T_4 treatment. Dr. Bauer is leading a collaborative group that intends to test 300 µg of T_4 in a double-blind, randomized, parallel-group study compared with placebo to more clearly define the efficacy of supraphysiologic T_4 augmentation.

Dr. J. Walden presented evidence from an open on (drug)-off (placebo)-on (drug) German study of 10 patients with acute mania showing that levetiracetam (Keppra®) may be a useful adjunct to haloperidol (Haldol®). Most patients showed minor relapses in the "off" phase and re-response in the second "on" phase. In contrast, ethosuximide (Zarontin®), an anticonvulsant with particular efficacy in petit mal or absence epilepsy, did not appear to be as clinically effective using the same design.

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Meeting Highlights

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The Bipolar Spectrum

Dr. J. Angst presented a lecture on a broader definition of the bipolar spectrum. Dr. Angst emphasized the lack of recognition and underdiagnosis of bipolar illness which is convergent with his and many others' data. He found that on closer examination, and using a broader definition of bipolar II disorder, 25% of patients with unipolar major depression may have been bipolar II. Other investigators have found similar rates, ranging from 40–60%.

Dr. Angst proposed that the rate of switching into mania or hypomania with a given antidepressant treatment was related to the degree of efficacy of the antidepressant as revealed by percentage of responders. Thus, he postulated that electroconvulsive therapy (ECT) would be the antidepressant treatment most likely to produce mood switches, followed by TCAs, SSRIs, and then placebos.

Dr. Angst followed a group of people beginning at age 19 or 20 for more than 20 years, with six separate interviews. According to DSM-IV criteria, 0.5% were bipolar I patients, 0.4% were bipolar II, and 21% were unipolar depressed patients. However, using the broader spectrum of including patients with less than four days of hypomania, he found that the diagnostic distribution in this same cohort was again 0.5% for bipolar I, but increased to 5.3% for the bipolar II diagnosis, and reduced the unipolar depressed category to 17.1%. Including the patients with unipolar depression who also had some hypomanic symptoms (5.7%) brought the possible total of bipolar II patients to 11% versus 11.4% with pure unipolar depression. *[See sidebar, left]*

- *This large underdiagnosis of bipolar II patients by DSM-IV criteria has a tremendous clinical impact, because patients with bipolar II disorder, particularly those with recurrent brief hypomanic and recurrent brief depressive patterns, have a very high rate of suicide. In addition, there is wide agreement that the pharmacotherapy for bipolar II (requiring a mood stabilizer) is different from that of unipolar major depression, indicating that a substantial proportion of presumptively unipolar patients are receiving inadequate or inappropriate treatment.*

The data of Dr. Angst are highly convergent with those of Hirschfeld et al. (2003) in their epidemiological survey of 85,000 households, who found that approximately 5% of the individuals were classified as having a bipolar spectrum disorder, versus the usual rate of 1% commonly reported. Disappointingly, the vast majority of these individuals were not in any kind of treatment, and of the small percentage who were correctly diagnosed as bipolar, almost all were being treated inadequately with antidepressants without concurrent mood stabilizers. This epidemiological survey used the Mood Disorder Questionnaire (MDQ) as the screening instrument. The MDQ has been validated as a reliable screening instrument (Hirschfeld et al., 2003; *Am J Psychiatry* 160 [1]: 178–180). On the internet, go to www.ndmda.org to take the MDQ.

Clinical Trial Design

In a workshop on methods and research designs in bipolar illness, Dr. E. Vieta presented data strongly supporting the need for placebo and placebo-controlled trials in establishing drugs as effective. Dr. Vieta cited two acute mania studies of olanzapine (Zyprexa®) where the placebo response rate ranged from 24% in the three-week study to 43% in the four-week study.

Dr. R. Licht presented the contrasting view that placebo-controlled trials designed for drug approval and registration are not the best type of trials to optimally inform clinical decision-making. One of the principle factors that make placebo-controlled trials less than ideal is that nonrepresentative samples are included, i.e., patients who are the most ill, suicidal, or with substantial substance abuse comorbidity are excluded. Also, placebo-controlled trials do not adequately answer the question that most needs answering: if a patient fails to respond to drug A, what is the next best option, and is drug B preferable to drug C? Dr. Licht noted, for example, that of 164 patients screened for participation in an acute study of antimanic efficacy, only 17% of that population was ultimately included in the study (Licht et al., 1997; *Br J Psychiatry* 170: 264–267). These patients were less severely ill, and thus differed from the more severely ill patients who were not studied.

- *Dr. Licht pointed out that for acute antidepressant effects, only one drug, lamotrigine, is currently being proposed for registration in contrast to the ten or more drugs listed for mania. Similarly, proof of efficacy in long-term prophylaxis is currently limited only to lithium, with approval for lamotrigine soon to be requested.*

Dr. J. Geddes suggested that an alternative trial design using large but simple strategies could help supplement the acquisition of data and more precisely establish the risk-to-benefit analysis of any drug, which is what clinicians and patients need to know in making decisions about acute and long-term treatments. Patients need to know what is their risk for relapse, what are the chances that the drug will be effective, and what is the likelihood of harmful side effects occurring from the drug. Dr. Geddes and colleagues have established a collaborative clinical trial in England comparing randomized prophylaxis with lithium monotherapy, valproate monotherapy, and the two drugs in combination. The outcome measures require minimal paper work and it is hoped that this study can be completed in a clinical practice setting very similar to those routinely done for cancer chemotherapy clinical trials.

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Bipolar Network News

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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 prepublication 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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Based on the data in over 20,000 patients of Dr. L. Kessing, Dr. Geddes stated that it would be important for patients with one prior episode to know that their yearly risk of relapse is 10–15% per year. However, for those with three or more episodes, the yearly risk of relapse is 30–50%. In studies of over 800 patients in randomized clinical trials of lithium prophylaxis, it is estimated that lithium decreases the risk of relapse by about one-third; it reduces manic episodes by approximately 40% and depressive episodes by approximately 25%. The risk of harm from hypothyroidism is 4.4% and is a side effect that can readily be managed with thyroid augmentation. Thus, in this scenario, lithium would markedly reduce the risk of relapse in someone with multiple episodes, and this effect would be even more clearly discernible than in individuals with just one prior episode.

- *As noted in previous issues of the BNN, the risk of relapse is only one component of the risk associated with the illness. Illness recurrence may be associated with substantial social, economic, and employment losses, and even hospitalization, as well as the possibility of more catastrophic occurrences such as suicide. These risks also need to be factored into any risk-to-benefit equation and are rarely appropriately assessed by clinicians and patients in a hurried office visit.*

Bipolar Disorder and Suicide

Dr. Z. Rihmer gave a talk on suicide. He reported that the suicide rate in Hungary was 46 per 100,000 individuals per year (the highest rate among all countries) just two to three decades ago; this rate has been reduced to 32 suicides per 100,000 individuals per year, which although still high, is substantially reduced. Dr. Rihmer postulated that this reduced suicide rate correlated with a six-fold increased use of antidepressants, particularly the SSRIs, because factors often associated with suicide were increasing in Hungary (rising unemployment, decreasing wages, increasing alcoholism and divorce), which would have been expected to increase the suicide rate.

There are now similar data from other countries indicating that wider use of antidepressants is associated with a lower suicide rate. Dr. J. Angst has reported that those bipolar patients who were in treatment had a markedly lower suicide rate compared with patients with bipolar illness who were not in treatment (Angst et al., 2002; *J Affect Disord* 68 [2–3]: 167–181). Dr. Rihmer noted that 90% of all suicide victims have an Axis I psychiatric diagnosis and that mood disorders, alcoholism, and schizophrenia are among the highest diagnoses. Of those individuals who make a prior suicide attempt, 10% will ultimately die by suicide in the first ten years thereafter. Approximately 19–42% of patients who commit suicide have made a prior suicide attempt, indicating that attempts are one of the best correlates and predictors of subsequent suicide. Dr. Rihmer presented data suggesting that the risk of suicide in unipolar patients was 16 times greater than the risk to the general population; the risk for bipolar I patients was 1.3 times greater than that of the general population, whereas, surprisingly, the risk for bipolar II patients was 22 times higher. Dr. Rihmer speculated that the increased risk of suicide in bipolar II patients is related to their underdiagnosis, subsequent undertreatment, increased incidence of anxiety-related comorbid diagnoses, the high creativity of the population, and a marked "contrast effect" from hypomania to severe depression occurring on a recurrent basis. Other risk factors for suicide in bipolar illness are a family history of suicide, prior attempts, increased comorbid Axis I, II, and III diagnoses, aggressive personality features, stressful life events, lack of adequate treatment, and inadequate long- and short-term health care access.

[See sidebar, right]

ECT and rTMS

Dr. L. Grunhaus presented data collected from 131 patients at Sheba Medical Center in Israel that ECT was equally effective in unipolar and bipolar depression, but there was only a 50% response rate (50% improvement) in the bipolar patients and a 30% remission rate (as indicated by a Hamilton Depression Scale score of #8).

Dr. O. Dolberg reported significant improvement with 10 Hz repetitive transcranial magnetic stimulation (rTMS) at 90% of motor threshold (MT) over the left prefrontal cortex in 20 patients with bipolar depression as an augmentation to valproate treatment; a sham (inactive) treatment was included in the study for half of the patients. Active rTMS was significantly superior to sham rTMS. Response to treatment was greatest after two weeks, with no further improvement following an additional two weeks.

- *These data provide evidence from another controlled study that 10 Hz rTMS is an effective antidepressant modality, although several other studies have not been able to replicate the phenomenon. A meta analysis by Grunhaus et al. revealed that rTMS studies using long durations, higher intensities, and greater numbers of stimulations have reported greater degrees of antidepressant effect compared with those with less robust rTMS parameters.*

Dr. K. Ebmeier reported a replication of earlier findings that the distance from the skull to the cortex is directly related to the MT used in rTMS studies. The frontal cortex appears to be even further away from the outside of

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There are many similarities between the risk factors for suicide attempts noted by Dr. Rihmer and those found by Leverich et al. (*J Clin Psychiatry*, in press) in the Stanley Foundation Bipolar Network. Leverich et al. found that prior suicide attempts were associated with the occurrence of early childhood stressful life experiences, more concurrent loss of confidants and social supports, more than ten prior depressive episodes, inadequate access to health care resources, high levels of cluster B Axis II comorbidity, and a family history of suicide and alcohol abuse. Moreover, having made a prior suicide attempt was a marker for a more severe course of bipolar illness assessed prospectively by clinician ratings, indicating that these patients continued to be more treatment-refractory in the initial year of Network follow-up and naturalistic treatment. Increased medical comorbidity was also a risk factor for a prior suicide attempt, because this, in conjunction with inadequate health care access, may have increased demoralization and hopelessness beyond that already experienced from the primary affective disorder.

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the skull than the motor cortex, suggesting the importance of correcting stimulation parameters based on MT for the degree of distance that rTMS will have to traverse across the scalp, skull, and cerebrospinal fluid before the brain is reached. Dr. Ebmeier also reported a study of Shajahan et al. (2002; *Prog Neuropsychopharmacol Biol Psychiatry* 26 [5]: 945–954), utilizing 99mTc- hexamethyl-propyleneamine single photon emission computed tomography (HM-PAO SPECT), that medio-prefrontal cortical stimulation was able to increase activity bilaterally to the ventral striatum and unilaterally to the caudate, replicating earlier findings by Strafella et al. (2001; *J Neurosci* 21 [15]: RC157) that 10 Hz rTMS over left prefrontal cortex increased dopamine release unilaterally in the dorsal caudate as measured by [(11)C]raclopride receptor occupation.

- *These studies, in addition to a growing list of preclinical studies indicating neurochemical effects of rTMS similar to other antidepressants, begin to provide a physiological rationale for the proposed antidepressant effects of rTMS. These studies suggest an impact of prefrontal rTMS on the basal ganglia, which has been postulated to be involved in depression, along with alterations in prefrontal cortex and various limbic and paralimbic regions.*

Dr. M. Nitsche reported on a potential novel approach to extracranial brain stimulation, called transcranial direct current stimulation (tDCS). This technique, using low-level direct current in the range of one to several milliamperes, has an effect on the brain in proportion to the duration of time of its application. It is estimated that about 50% of the current reaches the brain. Dr. Nitsche performed a variety of studies in animals which indicated that motor cortex thresholds and visual cortex activity could be changed in the appropriate direction by tDCS.

An initial study of Costain et al. (1964; *Br J Psychiatry* 110: 786–789) found statistically significant antidepressant effects of DCS compared with the sham condition, and this has been replicated in some, but not other studies. DC studies were widely conducted in Russia for a variety of indications including treatment of depression, several psychiatric illnesses, headache, and others. Safety studies remain to be conducted prior to further clinical testing of the antidepressant potential of this technique by Dr. Nitsche and colleagues which they estimated will begin in another year.

Dr. M. Garcia-Tolo reviewed the mixed literature on the therapeutic success of rTMS in depression and presented preliminary positive data from an ongoing study using a novel approach to rTMS in medication-resistant patients. The scientific literature has generally suggested that high frequency rTMS over the left prefrontal cortex is effective, and low frequency rTMS over the right cortex is effective. Dr. Garcia-Toro et al. decided to use 30 trains of 1 Hz rTMS over the right prefrontal cortex, followed by 40 trains of 20 Hz rTMS over the left prefrontal cortex, to optimize the treatment. They also decided to attempt to individualize the laterality of this approach depending on the degree of neural activity measured at baseline by SPECT. Based on the data of Kimbrell et al. (1999; *Biol Psychiatry* 46 [12]: 1603–1613) that high frequency rTMS was most effective in depressed patients with low basal activity and that 1 Hz was most effective in those with hyperactivity, they would lateralize accordingly.

The initial analysis of this high and low lateral prefrontal cortical stimulation with active rTMS showed an improvement of 13.7 points in the Hamilton Depression Scale ratings compared with only 2.7 points of improvement with the sham condition. In addition to the bilateral differential frequency stimulation, this study was unique in adding the treatment to existing medications in treatment-refractory patients, further suggesting the eventual utility of this modality in clinical treatment. *[See sidebar, left]*

As reviewed in *BNN* Vol. 7, Issue 2, three randomized studies have suggested equal efficacy of 10 Hz rTMS and ECT in non-psychotically depressed patients. Further controlled studies to find the optimal parameters and confirm efficacy will be needed before rTMS is finally recognized as a clinically useful antidepressant modality. In this context it is noteworthy that more than 40% of the studies of fluoxetine (Prozac®), one of the most widely used antidepressants, failed to show statistical significance. rTMS should not have to outperform this standard, particularly when many studies are underpowered (low sample size) and may be seen as having too weak parameters.

Complex Combination Therapy

Dr. R. Post gave a lecture on complex combination therapy and remission of bipolar illness. A number of studies have revealed that our best drugs—lithium, carbamazepine, and valproate, either alone (monotherapy) or in combination therapy—are often inadequate to achieve clinically relevant improvement in a very substantial subgroup of patients. Even with the exploration of lamotrigine and a variety of other anticonvulsants and atypical antipsychotics in the Stanley Foundation Bipolar Network, many patients remain highly affected by their illness, despite being treated with an average of 4.1 medications per year.

Dr. Post noted that in the intramural program of the National Institute of Mental Health (NIMH), a tertiary referral center for those with refractory affective illness, the number of medications needed for treatment optimization at discharge (in order to achieve acute mood stabilization) increased from 1 in the 1970s to 3.3 in the late 1990s and to approximately 4 in 2000-2001. This need for a greater number of medications was associated with patients with a progressively earlier age of illness onset, more time depressed prior to NIMH admission, and a greater frequency of rapid cycling.

Dr. Post presented a series of cases in which mood stabilization was finally achieved in inpatients or outpatients after the use of five to nine

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medications. He suggested the need for the development of new strategies in order to define the best treatment algorithms for the large group of patients with treatment-refractory bipolar illness. In the absence of guidance from a controlled clinical trials literature, it appears necessary to invoke a sequential clinical trials drug add-on approach with careful titration of dose against total side-effects burden, rather than following any particular pre-set expected dose or blood level range of a given drug. In this way a number of medications can be used with very different mechanisms of action, and yet with a minimal total side-effects burden. According to Dr. Post, it appears most important to now focus on clinical and biological predictors and correlates of clinical response in order to more readily define which drug is best for which patient earlier in the course of clinical therapeutics. Likewise, it appears crucial to engage larger numbers of patients in clinical trials in more typical clinical treatment settings using clinician-friendly research designs in order to begin to acquire the systematic literature needed for constructing optimal algorithms. Dr. Post and Dr. W. Nolan also emphasized the utility for the patient of keeping a careful mood calendar (life chart) on a daily basis, such as using the NIMH-Life Chart Method (see previous *BNN*).

Cognitive Therapy

A clinically important study was presented by Dr. D. Lam; he reported on the 1-year outcome of a randomized, controlled study of cognitive therapy for relapse prevention in bipolar disorder. One hundred and three bipolar I patients were randomized into a cognitive therapy group or a control group in addition to taking their usual medications, which had been ineffective in producing remission. The cognitive therapy group received, on the average, 14 sessions during the first six months and two booster sessions in the second six months, while the control group received treatment as usual in regular psychiatric follow-up. Over the 12-month period, the cognitive therapy group had significantly fewer bipolar episodes, days ill in an episode, and number of hospital admissions, as well as significantly higher social functioning. There was significantly less fluctuation in manic symptoms in the cognitive therapy group, who also coped better with manic symptoms when they did occur. The findings support the conclusion that cognitive therapy specifically designed for relapse prevention in bipolar illness is a useful adjunctive treatment modality. *[See sidebar, right]*

Poster Briefs

Dr. G. Akkerhuis and Dr. W. Nolan, as part of a clinical trial of 120 bipolar patients randomized to **omega-3 fatty acids**, reported two cases in which lithium-associated psoriasis was improved during active omega-3 fatty acid treatment.

Dr. M. Bauer et al. reported similar numbers of **mood switches** in bipolar patients who were (n=21) and were not (n=17) taking antidepressants along with their mood stabilizing medications.

Dr. P. Cavazzoni et al. re-documented that bipolar patients have an increased vulnerability for **extrapyramidal symptoms** (EPS) compared to patients with schizophrenia. This finding was observed only for patients treated with the typical antipsychotic haloperidol and, most importantly, was not observed with the atypical antipsychotic olanzapine.

Equal efficacy rates of the antidepressants **venlafaxine** (Effexor®) and **paroxetine** (Paxil®) were found in 60 patients with bipolar depression by Dr. M. Comes et al., but more patients switched moods on venlafaxine (13%) than on the SSRI paroxetine (3%).

The preliminary success of **quetiapine** was reported by Dr. R. D'Souza and colleagues in an open study of 26 rural patients with bipolar disorder and amphetamine abuse; mood symptoms improved and the craving and use of amphetamines was reduced.

Dr. P. Morselli and Dr. R. Elgie revealed the preliminary findings from the BEAM survey, a 93-item bipolar disorder questionnaire mailed to 3,450 members or friends of 12 patient advocacy groups in 11 European countries. A total of 1,760 questionnaires were returned with responses. A few of the preliminary findings were: (1) a **mean age of onset** of symptoms of 25.6 years; (2) **first diagnosis** occurring at a mean of 31.3 years (a delay of 5.7 years); (3) sixty-five percent (65%) of patients reported a family history of affective disorders, including bipolar disorder in 35% and major depression in 44%; and (4) three-quarters of the patients felt that the availability of more information would help them manage their illness better. The delays in the onset of instituting treatment of bipolar disorder thus mirror, to a lesser extent, those observed in the Stanley Foundation Bipolar Network (Suppes et al., 2001; *J Affect Disord* 67 [1–3]: 45–59) in which an average of ten years' delay was seen between first symptoms and first treatment.

A double-blind, randomized, placebo-controlled trial of **omega-3 fatty acids** was conducted by Dr. S. Frangou and Dr. M. Lewis in 75 bipolar patients with depression for 12 weeks. They reported positive effects of both the 1 gram and 2 gram (per day) doses of the omega-3 fatty acid ethyl-EPA as an adjunctive treatment. There was no difference in efficacy between the 1 gram and 2 gram doses.

Dr. M. Hillegers and colleagues found that both **life events** and **familial loading** (presence of bipolar

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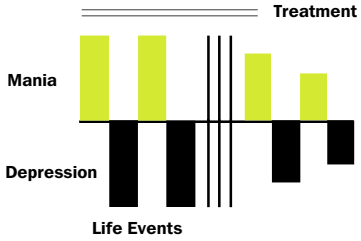
The data of Dr. Lam supplement a rapidly growing literature database indicating that a variety of psychotherapeutic strategies (ranging from individual educational work to cognitive-behavioral approaches to family systems psychotherapy) are significantly more effective on a variety of therapeutic outcomes than a control group or treatment as usual. It is no longer a hypothetical construct or presumed supposition, but a proven set of findings that patients with bipolar illness should receive appropriately targeted psychotherapy in addition to their pharmacotherapies. Significant effects of psychotherapy have also been demonstrated in unipolar affective disorders and a range of anxiety disorders, and therefore these new data in bipolar illness are greatly welcome and help support the contention that these modalities should be a standard part of bipolar illness treatment.

Life Chart Highlight

Response to omega-3 fatty acids in bipolar illness?



- **What are omega-3 fatty acids?** Omega-3 fatty acids are long-chain polyunsaturated fatty acids, essential for neuronal function in the body. Neuronal cell membranes are primarily composed of phospholipids and cholesterol. Phospholipids contain saturated, polyunsaturated, and monounsaturated fatty acids. The brain has a large concentration of polyunsaturated fatty acids, especially DHA and EPA. Omega-3 fatty acids cannot be formed in the body, and therefore we must get them from our food intake.
- **What foods have omega-3 fatty acids?** Good sources of omega-3 fatty acids include wild game, oily fish (such as mackerel, bluefish, and salmon), flaxseed, soybean oil, and walnuts.
- **Is it safe to take fish oil or omega-3 fatty acid supplements?** It's important to remember that for psychiatric treatment purposes, you should first consult with your physician before adding any new treatment. The clinical trial studies noted here and listed on page 8 used omega-3 fatty acids as an additional treatment to the medication patients were already taking; we don't have any good data that omega-3 fatty acids used alone will be beneficial.

Background

An initial four-month, double-blind study of omega-3 fatty acids by Dr. A. Stoll and associates in 1999 (*Arch Gen Psychiatry* 56 [5]: 407–412) suggested that 9.6 grams of a mixed product of omega-3 fatty acids (with both eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) was more effective than placebo (olive oil) in preventing mood episodes in treatment-refractory bipolar patients. A small (n=20) four-week, double-blind, placebo-controlled study of 2 grams of the ethyl ester of EPA (E-EPA) in patients with major depressive disorder by Nemets et al. (2002; *Am J Psychiatry* 159 [3]: 477–479) found highly significant benefits of the addition of E-EPA compared with placebo after four weeks. A larger double-blind, placebo-controlled, dose-ranging study was recently completed by Peet and Horrobin (2002; *Arch Gen Psychiatry* 59 [10]: 913–919); doses of 1, 2, or 4 grams per day of E-EPA or placebo were given to 70 patients with persistent depression in addition to their usual medication. The 1 gram per day E-EPA group showed a significantly better outcome than the placebo group on all three rating scales.

Six double-blind, placebo-controlled studies of omega-3 fatty acids have been conducted with schizophrenic patients. One study was negative, but the other five were moderately to strongly positive in their assessment of the benefit of omega-3 fatty acids.

Case Report

The Stanley Foundation Bipolar Network (SFBN) has recently completed recruitment of more than 120 patients who were randomized to 6 grams of E-EPA or placebo for 4 months, followed by an 8-month open continuation phase. Preliminary analyses of the double-blind phase of this study did not suggest overwhelmingly positive results, but more detailed analyses remain to be performed (Keck et al., 2003, unpublished data). One also needs to ascertain whether apparent responders continued to respond in the open phase of the study as suggested by this case report.

As illustrated in the life chart (Fig. 1), this patient had substantial cycling and residual depression despite multimodal treatments of her illness. When omega-3 fatty acids were started in an open fashion (Fig. 2), the patient achieved almost a complete remission for the first time in many years, which persisted for the next two years of follow-up (Fig. 2). The question remains as to whether the patient's remission was directly related to omega-3 fatty acids, was a natural course-of-illness phenomenon, or possibly merely a continuation of previously partially effective agents which gradually induced the remission. More detailed analyses of the latest SFBN randomized study and other studies that are now in progress will hopefully provide more definitive answers.

One possible explanation for the divergent findings in the literature are the initial suggestions of Dr. D. Horrobin and colleagues that lower doses of E-EPA in the range of 1-2 grams per day may be more beneficial than higher doses, which appear to have a paradoxical effect on levels of arachidonic acid in the cell membranes of blood elements. Dr. Horrobin believes that increasing arachidonic acid in the body is crucial to the efficacy of the omega-3 fatty acids. In the dose-ranging study of 1, 2, or 4 grams of E-EPA per day versus placebo in schizophrenic patients (Peet and Horrobin, 2002; *J Psychiatric Res* 36 [1]: 7–18), the 1 and 2 gram doses increased arachidonic acid levels, whereas the higher dose (4 grams) decreased these levels. Thus, the possible lack of promising effects in the latest SFBN randomized study (Keck et al., 2003) may be due to a higher dosage (6 grams) used.

An alternative explanation has been suggested by Dr. J. Hibbeln. He and his colleagues conducted the negative study of 2 grams of E-EPA in patients with schizophrenia and found no overall positive effects. However those who had the intended increases in membrane DHA (thought to be the active endogenous component of omega-3 fatty acids) showed significant improvement over placebo. In contrast, those who did not achieve this effect of increasing DHA with the omega-3 fatty acids showed clinical worsening compared with placebo.

Thus, there may be subgroups of patients who will or will not be particularly responsive to a given E-EPA treatment depending on whether the intended membrane changes are achieved. The SFBN will be proceeding to test this hypothesis and see if it is replicated in patients with bipolar illness. Based on the data of Dr. Hibbeln, we would predict that the

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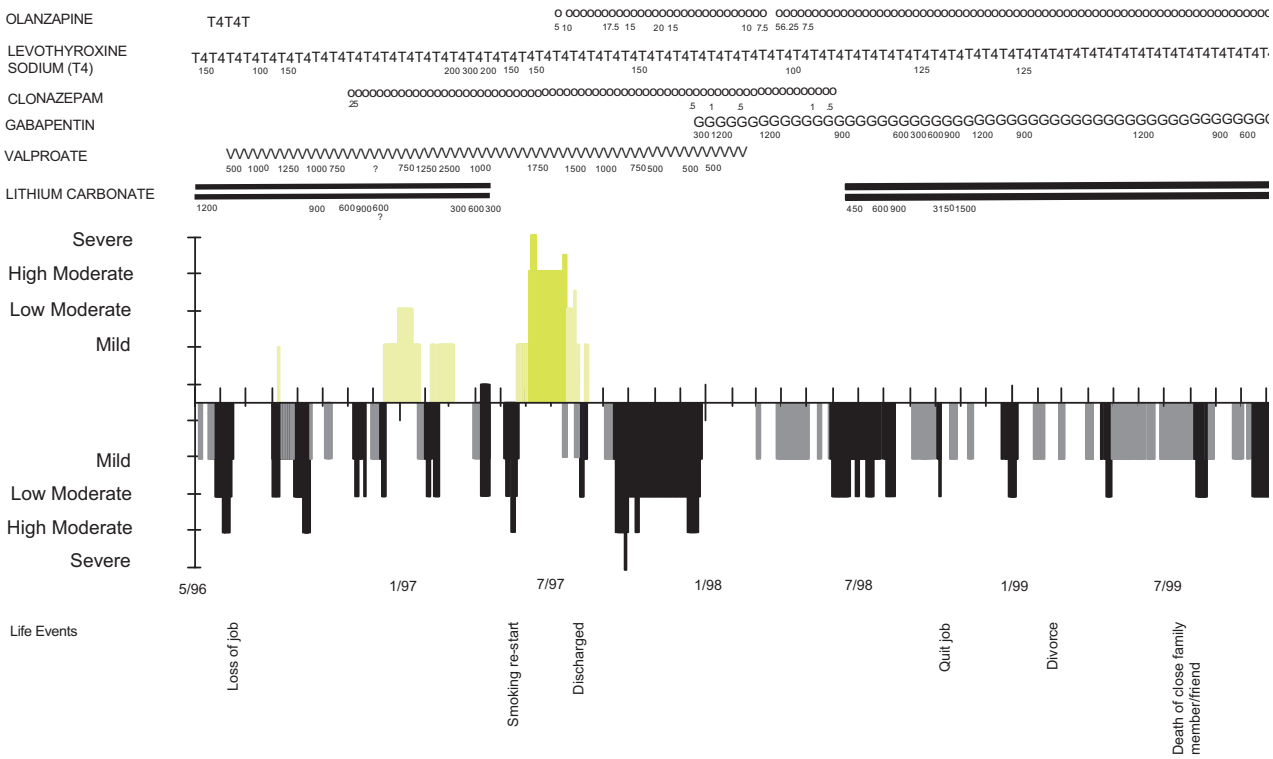

Figure 1: Life chart showing considerable cycling and inadequate antidepressant response to olanzapine, T_4, gabapentin, valproate, and lithium.

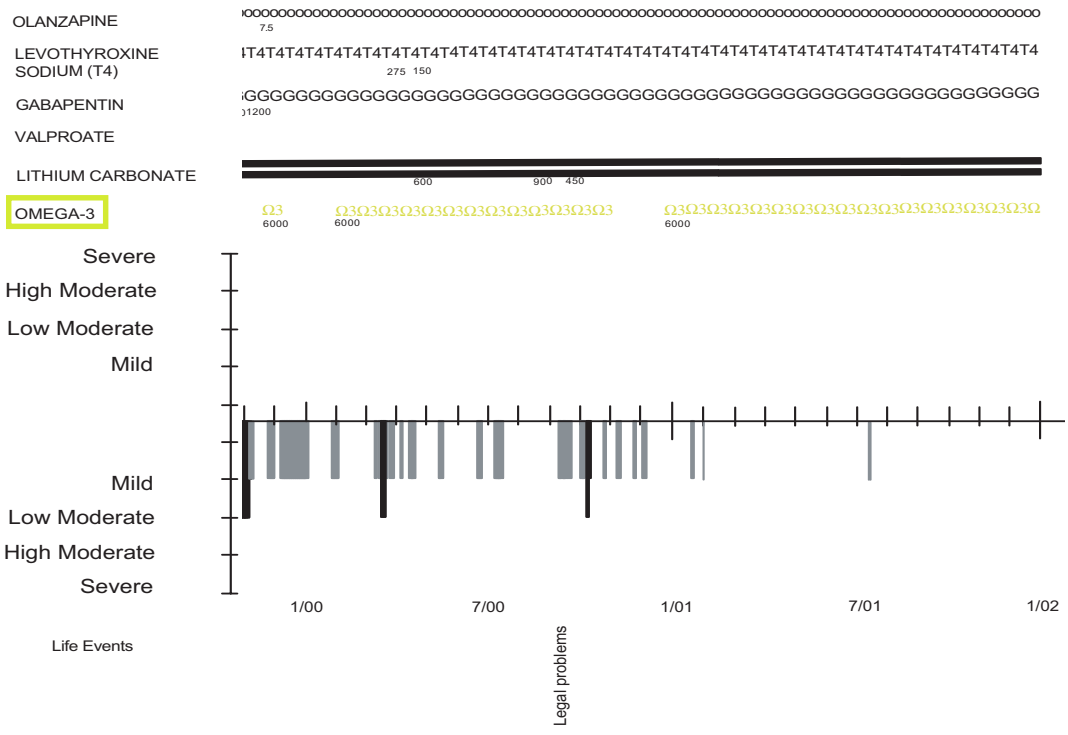

Figure 2: Life chart showing complete remission achieved with the addition of 6 grams per day of omega-3 fatty acid treatment (E-EPA).
*Note change in timeline scale between two life charts

Life Chart Highlights

(Continued from page 6)

patient illustrated in the life chart would have an increase in her blood cell membrane levels of DHA and/or arachidonic acid.

Treatment Implications

As the scientific field has not conclusively determined the optimal use of omega-3 fatty acids in mood disorders, how should a particular physician and patient team consider the use of this agent? We give the following suggestions based on personal opinion only; these opinions are highly provisional, and patients and their doctors should check both the existing and future literature for new data and revision of these suggestions.

It is important to note that all of the positive studies in psychiatry have been reported with the use of omega-3 fatty acids as an adjunct, and considering using omega-3 fatty acids alone in the treatment of bipolar illness would not (at this time) appear wise. On the contrary, the use of omega-3 fatty acids alone may lead one to avoid prescription medication approaches with known treatment efficacy.

It would appear that use of lower doses of pure E-EPA than employed in the study of Keck et al. (6 grams) would be more effective. Most of the positive studies with omega-3 fatty acids used 1 or 2 grams of E-EPA. When using a mixed preparation of EPA and DHA, perhaps also attempting to achieve a daily dose of EPA in this lower range would be appropriate. The course of illness over one to two months should be examined for treatment response, as in some studies it takes time for supplemental omega-3 fatty acids to change membrane composition.

More definitive studies in the scientific literature have indicated that omega-3 fatty acids are effective for cardiovascular health and perhaps in the treatment of rheumatoid arthritis. None of the studies in psychiatry or in these other medical areas revealed life threatening side effects of which we are aware.

Thus, the risk-to-benefit ratio of using omega-3 fatty acids would appear to be relatively favorable, as it is possible that there could be positive effects either on the affective components of the illness (less likely) or on the secondary health benefits in other medical areas (more likely). Aside from the negatives of cost, inconvenience of taking a large number of gel capsules per day, and mild gastrointestinal (GI) side effects associated with these preparations in some patients, there appear to be few other major negatives to considering the use of this approach as a possible augmentation strategy. ■

What is the relationship between omega-3 fatty acids and mood disorders?

Depression: A number of studies have found a lower level of omega-3 fatty acids in depression. A comparison among a number of countries in 1998 found a strong correlation between high fish consumption and a lower prevalence of major depression (Hibbeln 1998; *Lancet* 351 [9110]: 1213).

Schizophrenia: Dr. Horrobin has proposed the membrane phospholipid hypothesis as the cause of schizophrenia, which suggests that there is an accelerated loss of some essential fatty acids from phospholipid neuronal membranes in schizophrenic patients. There are many reports suggesting that the metabolism of both omega-3 and omega-6 fatty acids is disrupted in schizophrenia.

Bipolar Disorder: Bipolar disorder has been linked to overactivity of cellular and synaptic function. Large doses of omega-3 fatty acids are incorporated into the cell membrane and can inhibit neuronal signal transduction, in a way similar to lithium and valproate, two treatments known to be effective in bipolar illness (Stoll et al.).

Summary of adjunctive omega-3 fatty acid studies in mood disorders

Bipolar Disorder

Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial

Stoll, Severus, Freeman, et al. (1999)

Arch Gen Psychiatry 56: 407–412

Patients: 30 **Dose:** 9.6 grams/day

Results: Omega-3 fatty acid group had significantly longer period of remission than placebo group after 4 months

Major Depression

A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs

Peet and Horrobin (2002)

Arch Gen Psychiatry 59: 913–919

Patients: 70 **Dose:** 1, 2, or 4 grams/day

Results: The 1 gram/day group showed significantly better outcome than the placebo group on all rating scales after 12 weeks

Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder

Nemets, Stahl, and Belmaker (2002)

Am J Psychiatry 159: 477–479

Patients: 20 **Dose:** 2 grams/day

Results: Sixty percent (60%) of patients on omega-3 fatty acid treatment achieved a significant reduction in depressive symptoms after 4 weeks

Schizophrenia

A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia

Vaddadi, Courtney, Gilleard, et al. (1989)

Psychiatry Res 27: 313–323

Patients: 48 (39 with schizophrenia)

Dose: 0.54 grams/day gamma-linolenic acid; 4.32 grams/day linoleic acid

Results: Fatty acid treatment produced highly significant improvements in total psychopathology scores and schizophrenia subscale scores

Omega-3 fatty acid supplementation in schizophrenic patients

Mellor, Laugharne, and Peet (1996)

Hum Psychopharmacol 11: 39–46

Patients: 20

Dose: 1.71 grams/day EPA; 1.14 grams/day DHA

Results: After 6 weeks, significant amelioration of both schizophrenic

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Meeting Highlights

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disorder in a family member) have a strong independent effect on the liability for mood disorders, and that the effect of life event load was stronger in the case of high familial loading, in 140 adolescent offspring of parents with bipolar disorder.

Dr. L. Kessing et al. reported that in a case register study in Denmark, a **number of life events** were associated with an increased risk of being admitted to a psychiatric ward for the first time for a manic or mixed episode. Suicide of a relative, especially a mother or a sibling, showed large predictive effects, whereas the death of a relative by causes other than suicide had no effect. These data derived from a cohort of 1,565 patients and 31,300 control subjects provide further support for the previous observations of funereal mania, i.e., patients becoming manic for the first time at a funeral.

Dr. R. Kupka et al. found that clinical **correlates of rapid cycling** included nonresponse to lithium prophylaxis in 76% of rapid cycling patients versus 47% of nonrapid cycling patients; female gender and the bipolar-II subtype were also significant correlates.

An increase in **deep white matter lesions** using magnetic resonance imaging (MRI) in 41 euthymic patients with bipolar disorder (regardless of age) was reported by Dr. A. Lloyd and colleagues. The risk factors associated with these lesions are not clear, nor are the potential consequences of having such lesions. Several meta-analyses found increased white matter lesions in bipolar patients compared with other psychiatric groups and controls, further implicating bipolar disorder as a central nervous system illness.

Dr. P. Mortensen and co-investigators in Denmark used data from the Danish Psychiatric Central Register of 2.1 million people to investigate **risk factors** for bipolar disorder. They found a risk of bipolar disorder associated with a family history of bipolar disorder as well as other psychiatric disorders in parents and/or siblings. Early parental loss, and particularly maternal loss, were also associated with bipolar disorder, further indicating both experiential and familial variables influencing the onset of the illness.

Dr. W. Nolen et al. reported on the **correlates** of one year **prospective outcome** in 258 bipolar patients in the Stanley Foundation Bipolar Network as rated by clinicians. Increased severity of mania in the follow-up year was associated with a history of comorbid substance abuse and more than 10 prior manic episodes, as well as poor prior occupational functioning at study entry; increased severity of depression was associated with more than 10 prior depressive episodes and poor occupational functioning; and an increased number of episodes was associated with a positive family history of drug abuse, prior rapid cycling, and poor educational functioning.

In a study in the Netherlands of 132 13–23 year-olds with bipolar parents, Dr. C. Reichart and colleagues found that **psychopathology** of these bipolar offspring was not highly elevated compared with that of the general population of The Netherlands. In offspring where there was increased risk, it appeared to be manifest in depressive rather than bipolar disorders. Dr. Reichart's study is in contrast to studies reported by Chang et al. (2000; *J Am Acad Child Adolesc Psychiatry* 39 [4]: 453–460) and other U.S. investigators showing a high incidence of bipolarity in the offspring of bipolar patients; Dr. Reichart believes that less frequent use of psychomotor stimulants and antidepressants for attention-deficit hyperactivity disorder (ADHD) and early depressive symptoms in children in The Netherlands may be a factor in this contrasting rate of bipolar disorder in high risk families, but many other factors could account for these findings as well.

Dr. G. Sachs et al. reported that **quetiapine** as an adjunct to mood stabilizer treatment was significantly more effective than placebo in acute mania. The mean dose was 500 mg/day. These data begin to confirm, as expected, that all of the atypical mood stabilizers will be found to be effective in the treatment of acute mania either as monotherapy or adjunctive therapy. New data on aripiprazole in monotherapy support this contention as well.

Dr. M. Tohen and colleagues found **olanzapine** to be significantly more effective than lithium in preventing relapse into mania in bipolar disorder. More patients also remained on olanzapine throughout the year, indicating that it was better tolerated. There were no differences between lithium and olanzapine in the prevention of depressive relapses in this 12-month clinical trial.

Dr. Tohen also reported on a two-year follow-up study of bipolar patients after hospitalization for a first manic episode. After two years, 97.5% achieved **syndromal recovery** (i.e., were no longer manic), but only 73% recovered symptomatically and 60% had no new episodes. Strikingly, only 36% showed functional recovery to occupational or residential status before the manic episode, indicating long-lasting consequences of a manic episode.

- *These findings should be considered in the risk-to-benefit ratio when deciding whether to start prophylactic treatment to prevent future episodes.*

A single-blind, randomized, prospective clinical trial of **group psychoeducation** in remitted (euthymic) bipolar I patients (N=25) compared with no psychoeducation (N=25) resulted in a significantly reduced number of total recurrences and depressive episodes at the end of two-year follow-up, as presented by Dr. C. Torrent et al.; only 60% with psychoeducation relapsed, compared to 92% without. The investigators felt

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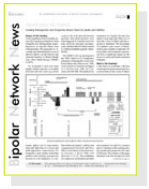
Did you miss the Life Chart issue (BNN Vol. 8, Issue 1)?



The Life Chart issue contains forms and instructions for completing a retrospective and prospective life chart for adults, and for children with bipolar symptoms.

We still have some extra copies to give out.

Call (301) 435-2529, request the life chart issue, leave your name and address, and we will send you a copy if we still have any remaining.

You can also go to the web address (see p. 11) and download the issue.

Meeting Highlights

(Continued from page 9)

that the effect of psychoeducation went beyond simply enhancing treatment adherence.

Dr. V. Sharma et al. found that in an ongoing prospective study of the course of bipolar disorder during **pregnancy**, women with bipolar disorder had fewer relapses or recurrences of mood episodes during pregnancy and more relapses or recurrences during the immediate postpartum period, implying that pregnancy has a protective effect on the course of bipolar disorder, but the relapse rate is very high during the postpartum period.

In another study, Dr. Sharma and coinvestigators reported that sleep loss, anxiety, and depression were risk factors for **postpartum psychosis** in bipolar women compared with nonpsychotic controls. Those in the psychosis group had significantly longer labor durations and more nighttime deliveries.

Dr. O. Yazici and colleagues conducted a study on controlled **lithium discontinuation** in bipolar patients with a good response to long-term lithium prophylaxis of at least five years. Despite careful monitoring, 32% relapsed in the first month, 46% in the first seven months, and 62% in the first year, indicating the high risk of relapse despite long-term stability when lithium prophylaxis is discontinued. Rapid discontinuation within two weeks or a gradual discontinuation over two to twelve weeks made no difference in the relapse rate in this prospective study.

- *These data further stress the importance of maintaining successful lithium prophylaxis, not only for continued episode prevention, but also for decreasing the risk of suicide (Tondo et al., 2001; Acta Psychiatr Scand 104 [3]: 163–172) and preventing lithium discontinuation-induced refractoriness (Maj et al., 1995; Am J Psychiatry 152 [12]: 1810–1811).* ■

Omega-3 fatty acid studies

(Continued from page 8)

Schizophrenia (cont.)

symptoms and tardive dyskinesia

A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia

Fenton, Dickerson, Boronow, et al. (2001)

Am J Psychiatry 158: 2071–2074

Patients: 87 **Dose:** 3 grams/day

Results: No differences found between groups in symptoms, mood, cognition, or global impression ratings after 16 weeks

Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia

Peet, Brind, Ramchand, et al. (2001)

Schizophrenia Res 49: 243–251

Patients: 55 (study 1); 30 (study 2)

Dose: 2 grams/day EPA or DHA (study 1); 2 grams/day EPA (study 2)

Results: Significant improvement in positive and negative symptoms after 3 months on EPA versus DHA or placebo in study 1; EPA patients had significantly lower scores after 3 months on the positive and negative syndrome scale than those on placebo in study 2

Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia

Emsley, Myburgh, Oosthuizen, et al. (2002)

Am J Psychiatry 159: 1596–1598

Patients: 40 **Dose:** 3 grams/day

Results: After 12 weeks, the omega-3 fatty acid group had significantly greater reduction of positive and negative symptoms than placebo group

A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenia symptoms

Peet and Horrobin (2002)

J Psychiatric Res 36: 7–18

Patients: 115 **Dose:** 1, 2, or 4 grams/day

Results: Greatest improvement in symptoms seen in patients on clozapine and all three doses of omega-3 fatty acids, with greatest improvement in the 2 grams/day group

Abstracts

The Maudsley Bipolar Disorder Project: a double-blind, randomized, placebo-controlled trial of ethyl-EPA as an adjunct treatment of depression in bipolar disorder

Frangou and Lewis (2002)

Bipolar Disorders 4: 123

Patients: 75 **Dose:** 1 or 2 grams/day

Results: Both doses of omega-3 fatty acids improved depression scores on rating scales; no change in mania ratings

Case Reports

Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes

Puri, Richardson, Horrobin, et al. (2000)

Int J Clin Pract 54: 57–63

Patients: 1 **Dose:** 2 grams/day

Results: Dramatic reduction of positive and negative symptoms, as well as a reversal of cerebral atrophy after 6 months of treatment

Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient

Su, Shen, and Huang (2001)

Eur Neuropsychopharmacol 11: 295–299

Patients: 1 **Dose:** 6 grams/day

Results: Dramatic improvements with omega-3 fatty acid monotherapy treatment during pregnancy for 12 weeks

Eicosapentaenoic acid in treatment-resistant depression

Puri, Counsell, Richardson, et al. (2002)

Arch Gen Psychiatry 59: 91–92

Patients: 1 **Dose:** 4 grams/day

Results: Patient with 7-year history of unipolar major depression showed no depressive symptoms after adjunctive omega-3 fatty acid treatment for 9 months

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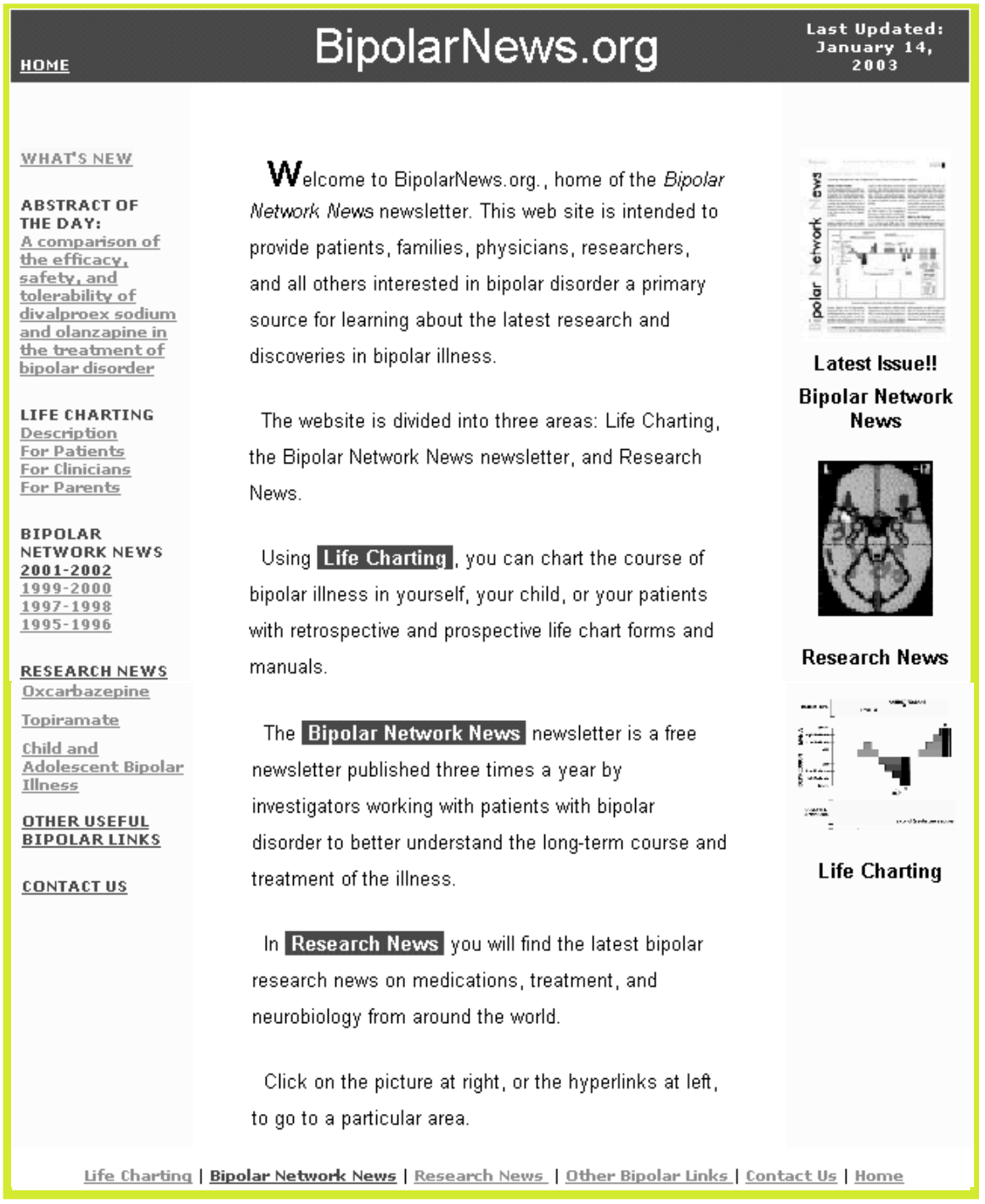

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