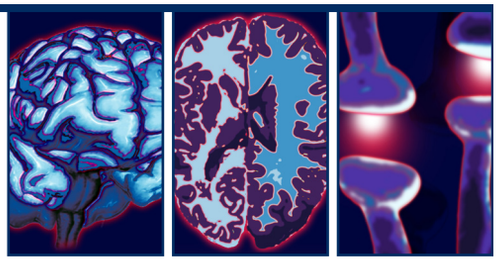

Bipolar disorder treatment research: new initiatives needed

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Q What originally led to your interest in bipolar disorder?

When I was an undergraduate I heard a talk on active dreaming sleep and the fact that rapid eye movement sleep occurred during dreaming. This led to my interest in what was going on in our mysterious brains. As an undergraduate I was a Psychology student and the whole phenomenon of learning and memory as it related to psychiatric illness was particularly intriguing. It seemed that we had a much better understanding of how the other organ systems worked, but the brain was still a complete mystery, therefore almost anything we found out about how it worked would be of potential interest.

I started at the National Institutes of Mental Health (NIMH) in 1970, working with Fred Goodwin and William E Bunney Jr on their research unit, where they were studying patients with bipolar disorder. I was very impressed from the outset with how manic a patient can be one day, then depressed the next day and even have some well intervals in between; this struck me as something that had to be a biological phenomeneon. So I continued working in the area of bipolar disorder from that point onwards.

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Q Which researchers have influenced or inspired your research?

The early work of Emil Kraeplin charting the course of illness and making graphic representations of each patient's illness was very influential in the development of our more detailed life-chart method for charting the patient's course of bipolar disorder. In addition, Jules Angst had some of the best long-term follow-up studies on the course of mood and schizoaffective disorders and was also very influential. Finally, I found Mogens Schou and his studies of how lithium affected the course of illness very inspirational.

Q What has been your biggest achievement in the field?

We were the first to study carbamazepine in a controlled fashion and from the beginning of our studies in the late 1970s we saw it was going to be an effective antimanic treatment. We used a double-blind design, where we substituted active treatment with carbamazepine for placebo. When we discontinued the drug on a blind basis people relapsed and when we started again they improved [1]. With this on–off–on design we were convinced that it had antimanic and antidepressive properties, but it was 20 years later that a drug company conducted placebo-controlled studies with a long-acting preparation called Equetro™ and it received US FDA approval [2]. The initial studies with carbamazepine helped lead the way towards studies with other anticonvulsants, such as valproate and lamotrigine. The anticonvulsants are now part of regular treatment possibilities for bipolar illness, but when we started our work the only option was lithium.

We also conducted some of the first studies with the calcium channel blocker nimodipine and demonstrated that it was effective in some patients [3]. This is of interest because in genome-wide association studies one of the well replicated findings in bipolar illness is an alteration in the L-type calcium channel, and there is also evidence of intracellular calcium level increase. With nimodipine being effective there is now a calcium 'story' emerging.

In addition, we helped start the repeated transcranial magnetic stimulation (rTMS) studies with Mark George at the NIMH and now at the Medical University of South Carolina (SC, USA). We saw that stimulation with rTMS on the left side of the brain had antidepressant effects compared with placebo and we saw different effects of high- and low-frequency stimulation in different patients [4]. Now rTMS is also an FDA-approved antidepressant treatment.

Q You head the Bipolar Collaborative Network; what are its main aims?

This network was founded in 1995, following lectures by myself and Susan McElroy (University of Cincinnati, OH, USA) about the relative lack of treatment outcomes research for bipolar illness, and we received funding from the Stanley Medical Research Institute until 2002. We had four sites in the USA and three in Europe, where we would follow patients longitudinally in great detail over the course of their illness. If the patients became ill they could enter clinical trials, either randomized or open, to investigate what would be more helpful to them. We collected data on approximately 900 patients, including data on more than 500 patients who were rated on a daily basis for more than 1 year consecutively. In this treatment outcome network all the collaborators in the network have agreed to continue working together to analyze and write up the data, even though the funding for the network has ended.

Some of the latest findings are that patients in the network from the USA had a many-fold increase of childhood-onset bipolar disorder compared with Germany and The Netherlands [5,6]. The incidence of bipolar disorder is between 1 and 3% in most countries. The adult incidence appears to be the same, but the difference is that there is a much earlier onset of illness in the USA. The average age of the patients in the Network was 42 years and 22% of the US patients experienced onset before 13 years of age compared with 2%in Europe. There was also evidence of more genetic vulnerability in the parents, more psychosocial adversity, more stressors at the onset of illness and before the last episode, more rapid cycling, anxiety

disorder comorbidity, substance abuse comorbidity, more episodes and a poorer outcome prospectively in the USA. We are now investigating some of the factors involved in why the illness appears to have an earlier onset and more pernicious course in the USA compared with Europe.

Q Do you have any hypotheses for why that may be?

Understanding the real difference in epidemiology of childhood-onset bipolar disorder is going to be critical to understanding all the factors involved. You could make the case for immigration playing a role, that is, people with more bipolar-like adventurism sensation-seeking genes were the ones who had the courage to make the crossing from Europe to the USA. This could account for the increased incidence of bipolar illness in the parents of our patients in the USA compared with The Netherlands and Germany, but you might think there would then be a similar incidence in Australia, which is not the case. Also, in the USA we found that more people with bipolar illness marry people with either bipolar or unipolar illness, resulting in both parents having affective illness, which is another vulnerability factor. Moreover, people in the USA move around on average every 6 years, more often than in Europe, and this may account for some of the assortative mating and increases in psychosocial stress that we have seen in the USA.

We found that two of the known vulnerability factors for early onset were more prevalent in the USA. There was more positive family history for bipolar illness in the parents and more childhood adversity in the USA compared with Europe. There are also data to suggest that patients with an earlier onset of bipolar illness may have a more difficult course. When these adults were younger, 30 years ago, those with childhood-onset bipolar disorder were not treated for an average of more than 15 years from the onset of illness. Even those with adolescent-onset disease were not treated for a decade. The hope would be that if we treated the disorder better and earlier it would not be such a difficult illness.

Q Why is early-onset bipolar disorder associated with delays in treatment?

The epidemiological studies of RC Kessler and colleagues at Harvard University (MA, USA) also found that the younger the onset of unipolar or bipolar illness, the longer the delay to first treatment [7]. There are many different reasons for this. One reason is that for a long period of time it was not recognized as an illness in children. Aside from the diagnostic controversy, early-onset bipolar disorder seems to be becoming more common. Part of the reason it was not recognized or treated back then was that it was probably less prominent.

I also think there is some reluctance to treat children with major mood stabilizers, such as lithium or atypical antipsychotics, and I think a big part of that is based on stigma – there is much less reluctance to treat children with epilepsy or childhood-onset rheumatoid arthritis than bipolar disorder. This can have a really adverse effect; the prospective studies of Barbara Geller (Washington University, St Louis, MO, USA) followed childhood-onset bipolar patients for 8 years and they found the children were ill for a large part of their lives and also that 37% of them were not treated with lithium or atypical antipsychotics, which are the consensus treatments for the illness [8,9]. People who were being treated in the community even after a clear-cut research diagnosis were not receiving the right medications. The patients that did receive lithium had the earliest remission rates and did the best long term.

Thus, there are multiple factors but it seems particularly problematic. We found that the delay to first treatment was an independent predictor of how poorly people did when they were treated prospectively with naturalistic treatment in our network. Those with the longest delay to first treatment were more depressed at the end, had more severe depression, more time depressed, less time euthymic, more episodes and more ultra-rapid cycling [10]. The delay appeared to have an ultimate adverse effect on the outcome. In schizophrenia, the duration of the untreated interval (DUI) is termed a

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remedial risk factor for a poor outcome, and studies of the prodrome are proceeding in an attempt to shorten the DUI, but we have not yet conducted these studies with bipolar disorder – we are more than a decade behind.

Q Are there any other treatment options available to children?

There are possible treatments, but disappointingly they are not very well studied. Omega-3-fatty acids in schizophrenia prodrome studies have been shown to prevent conversion to full schizophrenia and there is evidence of benefits in bipolar children. It would be interesting to study whether they did have an effect because the side effect profile is so benign.

Q Are criteria changing to try to aid diagnosis in children?

They are trying to deal with this better in the new Diagnostic Statistical Manual that the APA is compiling, but one of the big problems is that childhood-onset bipolar disorder is so highly comorbid with attention deficit hyperactivity disorder (ADHD) that children with bipolar disorder are being treated for their ADHD with stimulants and antidepressants, rather than with mood stabilizers first and then treating any residual ADHD. The big problem is that many of these children are receiving treatments that are either not helpful or may be counterproductive because of the comorbidity. This is an area where we need more awareness.

I believe that the controversies will continue. My hope is that it will be more explicitly stated how the criteria for adults should be applied to children. The Diagnostic Statistical Manual was written for adults and it also needs age-appropriate language for dealing with diagnosis in children.

Q What factors determine response to treatment for bipolar disorders?

I think the type of presentation makes an important difference. For example, people with a positive family history of bipolar disorder and a more classic presentation of discreet episodes of euphoric mania tend to be the best responders to lithium. Conversely, patients who do not have those typical presentations are more likely to respond to carbamazepine. Also, too many episodes before starting treatment with lithium or naturalistic treatment seem to be a risk factor for poor outcome. Comorbidity with anxiety disorder or substance abuse also appears to lower the response to treatment considerably.

There is still a substantial subgroup of patients who have a very difficult course. One of the problems is that there is very little guidance from systematic controlled literature about matching patients to the best treatment. The design of trials that result in drugs becoming FDA approved tend not to include information on clinical predictors of response, and even more importantly, when patients do not respond to a given drug, there are no follow-up studies to suggest what treatments to try next.

Q Can you describe the findings of your recent research into the complexity of treatment for a sustained response in bipolar disorder? What are the clinical implications of these findings?

We looked at patients who came into our network that were not euthymic but were having trouble with the treatment they were receiving, and then we followed these individuals naturalistically with treatment in our network. We found that it took, on average, 1.5 years before we were able to stabilize those patients and it took an average of three medications. A lot of treatment revision was required and some very complicated regimens enabled these patients to achieve remission or improve. We termed these patients responders if they had a sustained response for at least 6 months, so we are talking about people being very much improved for a long period of time. There was still a subgroup of more than 305 patients who did not have a good sustained response. When we looked at the medication they were treated with, we found they were treated just as aggressively with the same types of medication and they were exposed to a larger number of medications, seven on average. When we looked at the predictors of who ultimately did not respond, one of the big factors was having many more episodes in the past [11]. We think if you treat bipolar disorder earlier

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it might ameliorate the problem to some extent and might make the course of illness more benign. We still need a lot of work to identify the best treatment algorithms for these nonresponders.

Q What are the biggest challenges clinicians face in treating bipolar disorder?

First, there is the relative neglect of treatment research compared with the other major mental illnesses, such as schizophrenia. There are five- to eight-times more studies on schizophrenia in the USA than bipolar illness. This is partly due to the fact there is wide agreement about how to study schizophrenia and unipolar depression and what scales are best. Bipolar disorder is more complicated in terms of its pleiomorphic presentations with mania, depression, cycle frequencies of different duration and many comorbidities, making it difficult to determine the best methodology.

Dealing with the depressive side of bipolar illness is also a challenge. We have a number of good antimanic agents and can deal with that phase well, but the depressive phase carries a huge morbidity and the mortality from suicide is almost uniformly in the depressive phase. There are new data that the more depressive episodes a patient has, the more cognitive dysfunction they have and the greater the risk of dementia in later life [12]. Treating the depressive side is the biggest problem and we do not have the data to identify the best treatment options. The fact that we do not know the optimal treatment sequence for bipolar depression more than 50 years after the beginning of the new era of psychopharmacology is very disappointing.

Q How do you envisage the treatment of bipolar disorder developing in the next 5–10 years?

Unfortunately, I do not think we will catch up with the other psychiatric disorders. I would hope that, even at a slow pace, eventually we will get better clinical and biological markers of who is going to respond to which individual treatment and as we get some illness vulnerability markers, both genetic and neurobiological markers, that will enable us to start treating the disorder earlier and more consistently. As we identify the markers of response, the era of personalized medicine will eventually come into play and we will be able to choose the medications better from the outset. We also need much more precise longitudinal monitoring of the illness [13]. As an example, when patients became more involved with the treatment of their diabetes and had very good regulation of their blood sugar, late complications of the illness were much delayed. My hope would be that with more precise, consistent longitudinal monitoring, as in diabetes, we will be able to intervene more effectively and hopefully see a similar improvement in the complications of bipolar disorder.

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Financial & competing interests disclosure

RM Post has spoken for and consulted with AstraZeneca, Bristol-Myers-Squibb/Otsuka, GlaxoSmithKline, and received honoraria from them as well as Puretech, Ciba-Geigy and Janssen Cilag. He has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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