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Guest Editorial

Needed: Clinical Research in Mood Disorders

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Mood disorders are among the leading causes of morbidity and disability worldwide. They are also associated with increased risk of mortality due to physical complications. Much research has been carried out to map susceptibility genes and to understand the pathophysiology of the illness. Yet, progress has been slow. This is partly explained by the obvious complexity of brain function and mood regulation; however, another reason for the lack of progress may be clinical. This month's "In Review" section is dedicated mainly to clinical research in mood disorders. Not surprisingly, many of the issues addressed by these reviews have been studied before and have produced controversial findings. As the papers in this issue demonstrate, large samples and careful scrutiny of relevant factors are needed to arrive at unequivocal conclusions.

This issue also allows us to introduce the work of the International Group for the Study of Lithium-Treated Patients (IGSLI; http://www.igsli.org): all 5 papers are from the IGSLI centres. The group, established in 1988, has collaborated over the past 15 years on several large-scale projects, such as studies of mortality among patients treated with lithium and molecular genetic studies of responders to lithium.

Dr Bruno Müller-Oerlinghausen and others have reviewed the data on mortality, and on suicide risk in particular, in patients with bipolar disorder (BD). They point to various methodological problems that are difficult to control for in studies of mortality and suicidal behaviour. Nevertheless, the data published in the last 2 decades argue convincingly that lithium significantly reduces the risk of suicide (and cardiovascular death). The authors estimate that, in Germany alone, lithium prevents approximately 250 suicides yearly. The actual number could be much higher, given that lithium is currently underused in the treatment of mood disorders.

Lithium has fallen out of fashion; yet, its utility is not restricted to the treatment of BD. Dr Michael Bauer argues that lithium is an important augmentation strategy in the treatment of unipolar major depression. First reported by De Montigny and others in 1981 (1), lithium augmentation is recognized as a useful, but infrequently used, treatment modality. In a review of published studies, Bauer and others found a response rate to lithium of 45%, in stark contrast to a response rate to placebo of 18%.

Systematic clinical observations and careful consideration of relevant variables are critical in clinical research. A case in point is the paper by Dr Christopher Baethge and colleagues. These authors illustrate clearly how interpretation of research findings depends on underlying assumptions. For several years, the research (as well as clinical lore) has been stressing the need to treat patients with mood disorders early to reduce the risk of treatment resistance and poor outcome. However, it is the most severely ill patients who are more likely to be treated early and in whom the change in frequency or severity of episodes is most dramatic. Less severely ill patients, who may wait longer before receiving treatment, appear to do as well on lithium, but the difference is not as dramatic (naturally, this is not an argument for delaying prophylactic treatment). The theoretical implications of these findings are intriguing: bipolar illness may be associated with functional and structural changes resulting from cumulative damage during episodes of the illness. As well, lithium has attracted

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attention for its potential neuroprotective effect. Intuitively, it can be hypothesized that early treatment should be associated with better outcome. As Baethge and others show, treatment delay is not random and independent from illness severity. Is it possible that patients treated early and late start their treatment with a similar cumulative load of the illness? Conversely, is it possible that, at least in a subgroup of patients, the neuroprotective effect is not the key to the response?

Dr Martina Ruzickova and colleagues expand on an observation first made several years ago, when clinicians noticed an association between major psychiatric disorders and diabetes or insulin resistance. As Dr Ruzickova's paper shows, patients with comorbid diabetes seem to suffer from a more severe form of the illness, poorer outcome, and higher rates of complications. Whether this is a consequence or a correlate of insulin resistance cannot be decided from cross-sectional data; it remains to be tested in a prospective design. Is it possible that a subgroup of patients with bipolar illness is susceptible to insulin resistance through genetic or other pathophysiological mechanisms? What implications would such a finding have for clinical management?

Finally, the paper by Dr Dorian Deshauer and colleagues examines one of the fascinating themes in the literature on affective disorders: dysregulation of the hypothalamo–pituitary–adrenocortical (HPA) axis, and results of the Dexamethasone Suppression Test (DST) in particular, had been viewed as diagnostic tests for depression—a view followed later by disappointment and skepticism. Yet, the existence of HPA dysregulation in mood disorders is real. As the same authors have shown recently, the positivity of the DST varies over time, and thus, the DST may not represent the most suitable diagnostic test but rather a state-dependent measure (2). Conversely, abnormal response of salivary cortisol levels to awakening may be a trait that is easily measurable.

These papers have a common theme. They address topics explored by researchers over several decades. Still, as these papers show, there is much to learn about even the very basic clinical aspects of these conditions. Research in mood disorders has been and will be dependent on our definition and understanding of the illness. This becomes particularly difficult when even the diagnostic criteria change over the span of only a few years. Yet, only with better understanding of such factors as variety of phenotypic expressions, clinical course, comorbidity, nature of treatment response, or heterogeneity of depression or BD will we be able to integrate research findings and create a meaningful concept of mood disorders. It is no small task, but our patients deserve it.

References

1. De Montigny C, Grunberg F, Mayer A, Deschenes JP. Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. Br J Psychiatry 1981;138:252–6.

2. Deshauer D, Grof E, Alda M, Grof P. Patterns of DST positivity in remitted affective disorders. Biol Psychiatry 1999;45:1023–9.

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