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Extended-Release Carbamazepine Capsules

A Viewpoint by Philip B. Mitchell

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Academic and pharmaceutical industry interest in bipolar disorder has undergone an amazing renaissance in recent times. Long gone are the 'Cinderella' days when this was regarded as a highly uncommon disorder, for which the only recognised treatment was the effective, yet unpatentable, lithium. Recent epidemiological studies report life time prevalence rates for bipolar disorder of up to 4%[1] and high rates of disability.[2]

The last 10–15 years have seen the introduction into the market place of a growing array of new 'mood stabilisers' (a term that persists despite increasing limitations).[3] This period saw the recognition of mood stabilising properties of compounds that prior to then were utilised mainly for epilepsy (valproate and lamotrigine) and schizophrenia (the atypical antipsychotics olanzapine, risperidone, quetiapine and aripiprazole). To date, no novel compounds designed primarily for use in bipolar disorder have reached the clinical arena, reflecting the frustratingly slow elucidation of the causative underlying molecular defects, which is perhaps surprising in view of the high heritability of this condition.

The first reports of the antimanic properties of carbamazepine (in the immediate-release formulation) appeared in the 1970s and 1980s from the initial observations of the Japanese psychiatrist Okuma,[4] and the first controlled studies by the US researchers Ballenger and Post[5] at the National Institute of Mental Health. While immediate-release carbamazepine has been approved for marketing in some countries outside the US, the clinical trial data supporting its use in acute mania were sparse, probably reflecting the very limited industry involvement, with the trials largely being undertaken by academic centres.[3] There were only two double-blind, placebo-controlled, monotherapy trials in acute mania. Despite comprising a total of only 31 subjects, both found carbamazepine to be effective. Three controlled, active comparator studies found no difference between carbamazepine and lithium, but again there were substantial limitations in trial design and sample size.

It is against this background of the immediate-release carbamazepine studies that the full significance of the extended-release preparation trials can be appreciated. Although at one level, carbamazepine is certainly not a new compound for bipolar disorder, the new trials convincingly confirm its efficacy in the acute treatment of mania. The two pivotal studies of the extended-release capsules utilised state-of-the-art methodology and have recruited healthy sample sizes, allowing the capacity for regulatory approval internationally. The studies also indicate advantages of the extended-release capsules in terms of reduced dose frequency and acceptable tolerability, but the more significant message is the solidifying of carbamazepine as one of the well supported medication choices for those patients suffering from this serious and disabling disorder. ▲

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