

POTENTIAL ANTIPILEPTIC DRUGS IN CLINICAL DEVELOPMENT: A CRITICAL APPRAISAL

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After the introduction of several new antiepileptic drugs (AEDs) in the last decade, investment of the pharmaceutical industry into development of novel AEDs has been declining somewhat, partly due to concerns with increasing competition within a limited therapeutic segment, sky rocketing development costs, and disillusion about the feasibility of identifying major therapeutic breakthroughs based on available AED discovery strategies. These pessimistic considerations, however, fade when viewed against the many arguments pointing to epilepsy as a fruitful area for drug development. First, advancing knowledge in the pathophysiology of seizure disorders is likely to lead to more rational AED design in the future. Second, because over one third of people with epilepsy remain uncontrolled by available treatments, there is a tremendous market potential for any new AED which could impact significantly on the refractory population. Third, most AEDs have found wide applications in additional indications, ranging from bipolar disorder to migraine and neuropathic pain. Lastly, novel targets for AEDs are being identified in the field of neuroprotection and disease modification. These considerations justify major efforts into the discovery and development of new agents and, indeed, at least 20 new compounds are already in clinical development. These can be broadly classified into three categories: (i) structural analogues of already available AEDs (es., eslicarbazepine acetate, seletracetam, brivaracetam, fluorofelbamate, valoctamide, JZP-4); compounds acting through innovative mechanisms and/or at innovative target sites (e.g., ganaxolone, NS 1209, talampanel, retigabine); compounds identified by random screening and/or with not yet established modes of action (e.g., losigamone, carisbamate, rufinamide, lacosamide). For some of these agents, preliminary efficacy and tolerability data are available, which will be discussed together with a critical reappraisal of discovery strategies, methodologies applied in clinical development, and therapeutic perspectives for patients with epilepsy who cannot be managed satisfactorily with current treatments.