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editorial

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Many are called, yet few are chosen. Are neuropsychiatric clinical trials letting us down?

Neuropsychiatric drug discovery and development is undergoing tough times. The recent press release from Neurocrine Biosciences (14 September, 2010) stating that the joint Neurocrine/GSK CRF1 antagonist, GSK561679, failed to show any benefit for the treatment of major depressive disorder in a Phase II clinical trial was not reassuring [1]. Following the abandonment of at least seven other CRF1 antagonists, Sanofi-Aventis's SSR 125543 is the only one still in clinical trials for depression (NCT01034995); though other psychiatric-related disorders are still being pursued with this class of compounds. Following in the wake of other failures of potential treatments for psychiatric disorders such as the NK1 receptor antagonists, for example, Pharma is becoming more and more disillusioned with psychiatric drug discovery. Notable big Pharma virtual abandonment of in-house psychiatric research, coupled with CNS casualties of recent mergers and acquisitions, has swelled the market with displaced CNS biologists.

Neurological drug hunters are not faring much better, despite the identification and tractability of more physical, rather than psychological, mechanisms underlying neurological disorders. Pharmacological treatment of Alzheimer's disease (AD), for example, has scarcely changed for over 10 years since the first cholinesterase inhibitor, tacrine, was approved in 1993. Notwithstanding the widespread use of cholinesterase inhibitors, and now memantine, their beneficial effects are limited both in terms of the number of patients responding to the treatment and in terms of the duration of the treatment itself. Because of these limitations, symptomatic treatment strategies for AD have largely been replaced by disease-modification; unless late-stage symptomatic treatment opportunities become available. However, such opportunities need be approached more cautiously considering the expensive failure of dimebon (Latrepirdine) to show clinical efficacy in a Phase III AD clinical trial [2].

There is no shortage of drug discovery targets or strategies for either the symptomatic or disease modifying treatment of AD. These strategies include further explorations of the cholinergic glutamatergic, histaminergic and serotonergic systems by manipulating receptor function, enzymatic inhibition of the production of potential neurotoxic amyloid fragments, prevention of amyloid aggregation or tau hyperphosphorylation, anti-oxidants, mitochondrial stabilisation, anti-inflammatory agents, statins, estrogens, to name just a few.

Regardless of the number of potential targets, the results of clinical trials over the past decade have not been promising. Overall, some 80% of new chemical entities (NCEs) fail during the different clinical testing phases. None of the 67 other NCEs identified by Roses and Pangalos in 2003 has been successfully registered for the treatment of AD [3]. Many of these failures may be accounted for by reasons intrinsic to the molecule, such as unexpected toxicity, or other physico-chemical limitations that become apparent when the compound is tested for the first time in human. Approximately 48% of 172 potential AD drugs in clinical

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trials up to 2006 failed in Phase I when many of these problems become apparent [4]. However, some limiting effects are predicted neither from animal studies nor in early clinical trials. A notable example is the γ-secretase inhibitor semagacestat (LY450139), which advanced to clinical Phase III before being withdrawn following worsening of clinical measures in mild-to-moderate AD patients [5]. This lack of success is worrying not only for the increasing number of patients with, or who will develop AD, their caregivers, but also for the biopharmaceutical industry and their financial backers that have invested much talent, resources and money over the years.

Genetic and molecular studies have focused attention on the presence of amyloid plaques, tau-related neurofibrillary tangles and associated inflammatory events surrounding these prominent histopathological characteristics of AD. Reduction of the amyloid load in the brains of AD patients and prevention of the production of neurotoxic amyloid particles have been the main thrust of drug discovery strategies. The hypothesis being that disorders in amyloid processing lead to neurodegeneration in AD, and that by interfering directly with this and other physical hallmarks of AD, clinically relevant behavioural improvements may be achieved. An immunotherapeutic approach to reduction of amyloid through vaccination with amyloid fragments has gained prominence with the publication and subsequent analyses of Elan AN1792 trial in AD patients. This trial was terminated because of neurological complications associated with active immunisation [6].

While robust reductions in amyloid load are observed consistently in transgenic animals [7] or the AN1792 trial subjects, long term follow-up of the cognitive state of the surviving patients, however, has yielded mixed results; that is, either a reduction in the rate of cognitive decline [8], or no difference in either survival time or cognitive decline in immunised and untreated survivors 6 years after treatment [9]. The small number of patients available for study from a clinical trial not designed to assess cognition primarily may account for these differences. The equivocal results of the AN1792 study, however, raise concern that the reduction of amyloid load may not translate to improved cognitive function, which is a fundamental clinical endpoint of any treatment for AD. These results also beg the question of the significance of improved cognitive performance in transgenic animals used to model this disorder that have been immunised after AD pathology is established [7].

Issues with actual clinical trial designs and practices are being identified, not only in the drug development process of novel AD treatments, but also in clinical trials for CNS therapeutics in general [10,11]. For example, it may well be that amyloid-related neuronal damage is already present and irreversible by the time of AD diagnosis is made requiring earlier immunisation for greater clinical benefit. In terms of AD clinical trial design, earlier diagnosis requires more precise measures of disease state and progression, that is, the use of valid biomarkers and longer duration trials. Biomarker research is an integral part of present drug discovery and development programs. Extending clinical trial duration presents its own issues.

Changes in the response to placebo treatment are a particular issue in the design of clinical trials for AD and other CNS disorders with a strong behavioural component. Placebo responses can result in failed trials in which neither the drug being tested nor its active drug comparator are different from placebo. With the present emphasis on disease-modifying drugs requiring longer treatment and observation times, the placebo response can become even more problematic. The variability of response in patients on placebo treatment increases over time, and this 'fanning out' of placebo variability will make it difficult to detect any statistically meaningful effect of new drugs now being developed to slow the progression of the disease [12].

Behavioural outcome measures are key to neuropsychiatric clinical trials. These measures are rated for clinical relevance. If these measures are associated with large variance and poor inter-rater reliability, it is very difficult to detect a significant signal from the experimental 'noise'. Sources of variability include heterogeneity in patient populations. As more and more clinical studies are being conducted in developing countries, cross-cultural and language differences become magnified [11]. Differences in the level of training both of clinical raters and subjects required to respond to a given test also contribute to high variance [13]. A common dogma in experimental design is that error variance can be successfully controlled for by increasing sample size. Increasing sample size does not address the more basic issue of the ordinal nature of clinical rating scales or the quality and competence of investigators using these scales. Increasing the number of imprecise observations will not lend any more precision or accuracy to the outcome [14]. Clearly, standardisation of the quality of clinical research sites, and of the raters employed to administer subjective clinical rating scales and evaluate the results of would require fewer subjects for drug development and reduce outcome measure variability.

Notwithstanding the need to improve behavioural outcome variability, there may be even more fundamental issues compromising the success of neuropsychiatric clinical trials such as establishing treatment doses and ranges without considering properly the pharmacokinetic and dynamic properties of the test drug. Lack of continuity throughout the drug discovery and development phases, and especially time and budget considerations, may contribute to clinical trial failures. Inadequate studies may be carried out on the basis of cost and availability of results, and it is not uncommon for an NCE to be advanced (or abandoned) on the basis of commercial rather than scientific considerations [14].

While this editorial considers reasons why changes in clinical trial conductance and design may help lessen the rate of attrition of neuropsychiatric NCEs, a related issue of the apparent inability of animal models to predict clinical efficacy is germane to this theme. Modeling aspects of various neuropsychiatric disorders in animals is integral to drug discovery. These models provide evidence of proofs of mechanism and concept, and are essential to the advancement of the compound into the clinic [15]. Nevertheless, activity in one or many animal models need not necessarily guarantee a successful drug [16], or indeed identify a red-flag impediment to further advancement [5]. Issues with neuropsychiatric clinical trial design may be one factor that could explain the lack of translatability of potential clinical efficacy on the basis of animal studies to effective clinical efficacy. However, a more fundamental consideration is that preclinical and clinical investigators speak completely different languages. Preclinical studies rely on changes in behaviour through which efficacy is inferred.

Clinicians, by contrast, are required to show human clinical improvement, usually through clinical scales self-administered or administered by raters. Closer interaction between preclinical and clinical investigators seeking a common language, perhaps through imaging or the development of language, culture and species free measures and endpoints, is helping to close the translational gap [15,16]. Integrating more objective measures of behavioural correlates throughout the experimental medicine and clinical development of an NCE is one way to reduce variability and hopefully reduce clinical trial attrition of potential neuropsychiatric drugs.

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