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The Perils of Alzheimer's Drug Development

Lon S. Schneider and Debomoy K. Lahiri

Departments of Psychiatry, Neurology, and Gerontology, University of Southern California Keck School of Medicine, Los Angeles, CA- 90033; Departments of Psychiatry and of Medical & Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN-46202, USA

The present commentary is based on the thoughtful commentary by Becker and Greig (2008) in the August issue of *Current Alzheimer Research*, who describe a broken Alzheimer's disease drug development system. Their theme is that it is not the drugs that fail clinical trials but potentially sponsors and investigators who fail the drugs. They argue that “many current problems encountered in Alzheimer's disease drug development can be avoided by changing practices associated with drug development.” According to the authors, we fail to give candidate drugs a fair shake by not finding the right dose, not evaluating patients properly, not using quality controls over our data, not effectively modeling the disease, and not using effective research designs. They say sponsors and investigators fail drugs every which way.

It is hard to argue that mistakes are uncommon in AD drug development and easy for us to cherry pick and choose favorite miscues. Becker and Greig with the help of a colleague at the investment firm Rodman and Renshaw identified 100 failed AD drug programs within which according to their analysis 30 compounds possibly showing initial efficacy failed in phase 3. They imply that some of these compounds could possibly have succeeded in phase 3 and been marketed. Given the various errors in development they express concerns that we can not know with adequate certainty whether drugs are failing or investigators are failing drugs.

This broad indictment is hard to counter because there are examples for the truth of every point Becker and Greig raise. One or another drug development program has fallen short on one or more of the authors' critical points (Schneider 2008a). In particular, they example the development programs for two drugs - metrifonate and phenserine – that they knew well as researchers, consultants or original inventors. Metrifonate was developed by the large pharmaceutical company Bayer, and phenserine by a defunct boutique biotech, Axonyx.

There are other views however

Critics can look at the same drug development programs and see things differently. Whereas Becker and Greig see the failure of the cholinesterase inhibitor metrifonate as one of pharmacokinetics and inappropriate dosing others might see it as due to toxicity and commercial non-viability (López-Arrieta and Schneider 2006). Did the world need another cholinesterase inhibitor, especially one that potentially caused respiratory depression?

Phenserine, on the other hand, is an easy target as perhaps an example of an unsuccessful drug development program (Schneider 2008b). It is a cholinesterase inhibitor that although demonstrated pre- clinically to have neuroprotective properties was developed in paradigms for symptomatic treatments. The company's development program could serve as the poster child for how not to develop an AD drug. Their errors are well documented in their financial filings (e.g. Axonyx Form 8-K, SEC file 0–25571, March 11 2005, Form 10-Q, June 30, 2006).

A brief list follows

They spent much time in phase 1 with healthy subjects and not the Alzheimer's patients who would potentially benefit. They did not explore doses and find a proper dosage range. They completed only one phase 2 trial, imperfectly modeled on the 12-week phase 2 trials of tacrine and donepezil. They used only 72 patients in this trial, employed an allocation ratio that led to twice as many patients receiving the fixed phenserine dose than receiving placebo. Despite a 25% dropout rate, imbalances in their randomized groups, and the failure to show statistical significance on their main outcomes they proceeded directly to a phase 3 trial. This decision might have been informed by statistical trends on secondary neuropsychological batteries that were mainly due to the very few placebo patients unexpectedly worsening over the brief 12-week period (while the ADAS-cog did not).

Their 6-month long, phase 3 trial, also modeled on cholinesterase inhibitor pivotal trials, used the same 10 mg daily dose as in the phase 2 trial and only a slightly higher 15 mg daily dose for a dose-ranging comparison. Rather stunningly, they used an allocation ratio of 2:2:1 that ensured that over 80% of the patients in the study received active drug and less than 76 patients received placebo. The known high variability of the ADAS-cog and small placebo sample size greatly minimized the chances for the placebo group to deteriorate and consequently the chances for a significant drug-placebo difference to be observed (Schneider 2008b). The allocation ratio certainly contributed to a measurement bias, such that the majority of the patients improved over 6 months. Moreover, it becomes a spin of the roulette wheel to show efficacy when there are so few placebo patients in a placebo-controlled trial. Making one of the authors' points, the trial was undertaken in several countries and several languages, and with inexperienced sites. It is doubtful however that excellent rater training and patient cooperation could have compensated for a trial so flawed by design. The signals seen on some CANTAB subscales in the phenserine phase 2 trial

(http://findarticles.com/p/articles/mi_m0EIN/is_2001_Oct_30/ai_79540858) were not tested for in the phase 3 trial. The more recently reported cognitive improvements in a small Karolinska Institute study by the Nordberg group (Kadir et al, 2008) continue to support some level of efficacy consistent with the cholinesterase inhibitors. Again, the early studies suggest a potential that was not optimized nor maximized in the phenserine clinical development program.

The phenserine experience also illustrates another barrier to drug development alluded to but not explicitly mentioned by Becker and Greig, and that is the lack of scale of small biotechs (Altstiel 2002). Having a drug for a new target is just the beginning but the main barriers are the costs of clinical development and the lack of available expertise and skill. Excessive reliance on outside consultants and academics – each with their own limited experience, knowledge, points of view, and interests – might doom any drug.

When drugs for Alzheimer's disease are developed under such circumstances, without appreciation for sample selection, sample size, outcomes, study conduct, and competing interests, even a truly efficacious drug would be unlikely to show efficacy. What phenserine needed was a better development program and intellectual commitment. To this extent, the authors make their case and indeed, the phenserine experience might be more typical of the work of smaller, boutique biotech companies – essentially one-trick ponies – trying to gain the financial interest of a deep-pocketed partner than of drug development in general.

The Alzheimer's disease drug development business is tough and conflicted and there are no easy solutions. It seems, however, as if both large and small companies keep repeating each others' mistakes, deriving their development program from an earlier, often unproven one, and this fact may speak more to Becker's and Greig's points. There has been a general lack of

learning in the field. One reason may be because the prior experiences of companies are kept confidential, and, clearly, companies should share their experiences.

In addition to the issues discussed above, genetics could influence outcomes of clinical trials, at least with respect to APOE genotype. For example treatment outcome of cholinomimetic drugs was claimed to be dependent on APOE genotype (Poirier et al., 1995) although a separate analysis on the data set showed a different result (Farlow et al 1998). Elan and Wyeth claimed in a scientific presentation that the cognitive outcome of their phase 2 trials of bapineuzumab, a humanized monoclonal antibody, which did not reach statistical significance on the protocol-specified analyses (<http://www.wyeth.com/news>), nevertheless, showed that patients not carrying the high-risk E4 allele had a statistically significant benefit in the trial's outcome measures, whereas E4 carriers as a group had a trend that was not statistically significant. At the safety front, too, APOE4 non-carriers fared better, the company states, although the data presented was not convincing. While adverse events were very common in both placebo and treatment groups overall, non-E4 carriers in the treatment and placebo groups tended to have similar numbers of them. The claim of a differential response to an experimental treatment based on APOE genotype is similar to that obtained in a phase 2 rosiglitazone trial (Risner et al., 2006). Neurobiologically, the finding raises the debate whether the brains of APOE4 carriers may be more vulnerable, and by extension more difficult to treat, than those of non-carriers. Yet in both studies there was observed no actual treatment interaction based on APOE carrier status and the apparent differences really rested with the apparently differing rates of placebo change, and not drug effect, and both trials, again, employed very small placebo groups that were further subdivided for analyses.

Notwithstanding all this, a formidable barrier to drug development is that we know very little about Alzheimer's disease, its pathogenesis, diagnosis, genetics and struggle with its clinical heterogeneity; we do not have full pre-clinical models on which to develop advanced therapeutic targets. Under these circumstances, demonstrating the efficacy for even moderately efficacious drugs is challenging. More rational development programs will help, but will not be sufficient. Yet, to Becker's and Greig's points, none of this is reason not to exert best efforts in AD drug development. No one argues that it is not important to develop a better clinical trials infrastructure and to train raters, but there will still remain substantial variability due to the instruments, patients, diagnoses, culture, other circumstances, and error. Indeed, trials that show small variances in their outcomes might be suspect because of the implausibility of such precision with Alzheimer's disease clinical trials (Schneider 2008b).

The fixes that Becker and Greig offer are helpful and necessary. Correcting errors in drug development, trial designs, and execution will matter greatly when effective drugs come along.

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