Why do so many drugs fail at the last hurdle?

Is there a serious procedural flaw in drug research?

By Michael. Kelly

As the decade of the Brain drew to a close at the end of 1999, neurologists and researchers working on Parkinson's disease (PD) had reason to be pleased with progress achieved. During the decade, significant advances were made in identifying various genetic mutations implicated in familial PD and with the fortuitous discovery of the otherwise tragic MPTP/MPP+ link, rewarding avenues opened up in linking a limited number of PD cases to environmental factors. It appeared then that it would be only a question of time until various factors would convergence to explain the root causes of PD.

Now, more than a decade later, a more cautious attitude prevails Despite extensive efforts on a broad front, progress has been slow and though there were some promising advances, especially in 2009 and 2010, it appears that PD is not ready to yield up its secrets just yet.

An unexplained aspect of PD drug research in the 2000-2010 period is the consistent string of failures to get drugs through the final stages of testing and approvals procedures (phase II and III) with proven tangible benefit for patients.

The table below lists 10 drugs that have failed in trials over the past decade. What is especially striking is that practically all were in either Phase II or Phase III clinical trials, *viz.* the latter stages of testing. The question arising is: why were they permitted to get so far? Why were they not weeded out at an earlier stage? As they must have provided promising results in animal testing, the applicability of animal models used becomes an issue.

It is not only the fact that 10 drugs were abandoned, a more disquieting aspect is that essentially no new drug that could be classified as a 'new chemical entity' became available over the decade. With due regard for the efforts involved in pursuing work on the various dopamine agonists coming to market in the time period, it may be said that these mainly represent improvements on existing therapeutic possibilities and are not major advances as such. The only other drugs of any consequence approved for use in the period were rasagiline, an MAO-B inhibitor and a homologue of selegiline, and rotigotine, a transdermal dispensing patch, delivering a non-ergoline agonist.

With across the board failures at such an advanced stage and the virtual absence of new drugs, the question arises as to whether there are fundamental flaws somewhere in the research chain. It is somewhat unlikely that the situation described arises as a result of pure chance.

The amount of time and resources involved in getting a 'new chemical entity' through all the various developmental and testing stages is very considerable. The costs involved are stated to run anywhere between €400 million and €800 million. The figures are controversial, but clearly the sums are enormous. Naturally not everything starts with a new chemical entity. Nevertheless the development and testing costs, most of which arise in Phase II and III, still can run into the hundreds of millions. The time scale runs from anywhere between 8 and 12 years, sometimes longer in the case of chronic illnesses such as PD, requiring long test times or a phase IV type follow up.

In view of this capital burn, one begins to appreciate the magnitude of sums that have had to be written off in the case of the 10 drugs listed and the risks associated with embarking on development of a new drug.

Drug failures and withdrawals

	Action	*Sponsor*	*Terminated*	*Comment*
GDNF – ref 2	Neurotrophic factor	Amgen	End 2004, phase II	UPDRS scored
Sarisotan – ref 3	Dopamine agonist	Merck KG Darmstadt	Mid 2006 Phase III	Not filed for approval
Istradefylline – ref 4	Adenosine antagonist	Kyowa	Mid 2009 Phase III	Sensitivity of evaluation tool questioned
Spheramine - ref 5	Cell therapy	Bayer Schering	Mid 2008 Phase IIb	Bayer dropped development
Cere 120 -ref 5	Gene therapy	Ceregene	End 2008 Phase II	No improvement UPDRS scored
E2007 Parampanel – ref 5	AMPA agonist	Eisai	End 2007 Phase III	No improvement
GPI 1485 – ref 5	Neuroimmunophilin ligand	Symphony Guildford	Mid 2006 Phase III	No improvement
CEP 1347 – ref 5	Kinese Inhibitor	Cephalon	Mid 2005 Phase II/III	Ineffective Cep stopped
Pimaverserin- ref 6	Anti-psychotic	Acadia Pharma	Mid 2009 Phase III	Ineffective Psychotic Continuing motor trial
Safinamide – ref 7	Multiple action MAO B inhibitor	Merck Serono Newron	End 2010 Phase III	Failed primary endpoint. Ongoing

In addition to the drug tests referred to above, some considerable effort over many years has gone into evaluating the neuroeuroprotective properties of various substances. These are substances showing a potential to slow down, arrest or, in the ideal case, reverse neurodegenerative processes. In the main, they act by scavenging free radicals, atoms or groups of atoms with one or more unpaired electrons that can cause considerable damage to tissue. They are sometimes regarded as the primary cause of senescence.

After many trials and large sums of money spent, no substance with proven neuroprotective properties has been identified to date. Q10, Vitamins C and E, polyphenols of various types, all have shown marginal or no benefits, despite promising or good *in vivo* (animal) and *in vitro* (test tube or cell culture) potential.

By way of example, the Schults trial of Q10, one of the best known of its kind, using UPDRS as assessment, while giving some indications of a neuroprotective effect, still left a large amount of uncertainty, demonstrated among other things by the large error bars in the data published. There are still many unanswered questions about the bioavailability of Q10 which normally exists as a solid substance.

Where might the problem be?

An explanation may be provided by one or by a combination of any of the following factors:

- Use of inappropriate or inadequate evaluation tools. It would appear that given the heterogeneity and variability of symptoms associated with PD, scoring a trial using e.g. the Unified Parkinson's Disease Rating Scale (UPDRS) is wholly inappropriate, all the more so when the trial period is short. The UPDRS is too blunt an instrument to measure subtle changes in slow progression

- choice of model used, possibly only for weeks or months, inadequate to reflect human disease progression taking place over many years

- flawed trial design, inappropriate selection of participants, numbers too small to yield reliable results, false positive or negative outcomes as a result of small trials, poor statistical power

- variable bioavailability, fluctuations in transfer across blood-brain barrier

As part of the testing and approvals procedure, an animal model is selected, based on the assumption that the model comes sufficiently close to duplicating a human system. The difficulty arises in selecting a model that will react in the same way as a human would or would exhibit a similar pathogenesis. This is especially true of the neurodegenerative diseases, many of which take years or decades to unfold. In Pd, with age as the greatest risk factor, the life span between humans and conventional models such as rats (2-3 years) or mice (2 years) is striking.

When research projects become complex and get sub-divided into compartments such as basic research, applied research, clinical observation and what might be termed research management, the ensuing specialisation gives rise to a situation where the project personnel in the different compartments do not have a good knowledge or appreciation of each others work

The concept of translational research has been developed in order to establish a bridge between laboratory and clinic. This approach has succeeded up to a point but is difficult to apply in practice.

Whatever the reason for the outcomes described, pressure is increasing to get to grips with this unsatisfactory situation. Pharmaceutical companies and all the various bodies sponsoring research may have deep pockets but resources are not infinite. From a patient standpoint, perspectives on the pharmacological front are sombre, especially those who have made an effort to participate in trials. They would have been hoping for a more positive result.

Drug Trials- a synopsis

Pre-clinical studies: a substance selected for testing may emerge from evaluation of hundreds or perhaps thousands of compounds, some with similar morphology, followed by in-vitro cell culture and isolated animal organ tests. This is followed by animal testing to determine efficacy, toxicity and generate pharmacological data.

Phase 0: On healthy humans**,** non therapeutic doses to establish pharmacological properties

Phase I: On healthy humans to determine destabilisation mechanisms, tolerability. Small numbers, relatively short test period

Phase II: test on patients to evaluate therapeutic effects, dosage levels, size ranges from 50 to 500 patients, length variable, typically 6 months

Phase III: Test in a defined dosage level on much larger numbers, hundreds or even thousands. For drugs used in chronic conditions, long term trials are necessary to determine effectiveness tolerability and habituation.

Phase IV: post introduction surveillance aimed at identifying any long term problems.

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