Pharma fears

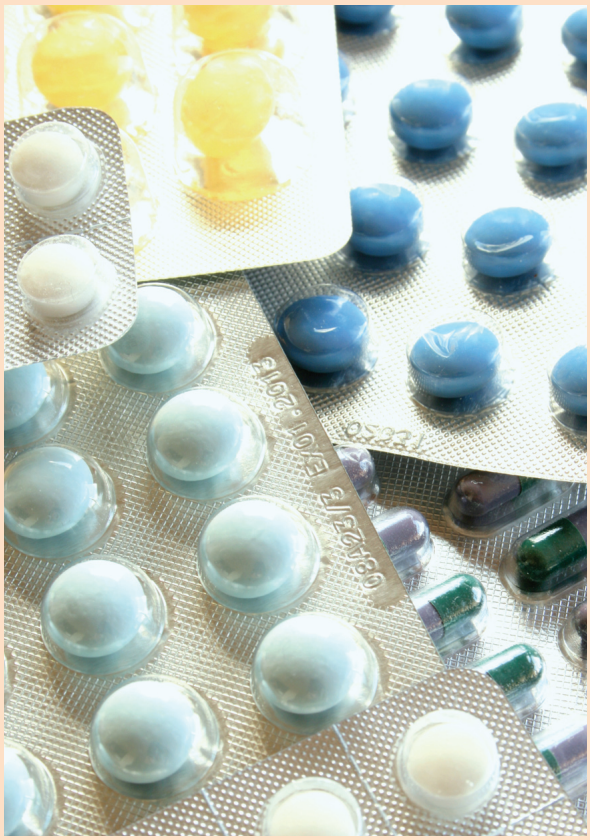
David Nutt and Guy Goodwin, of the European College of Neuropsychopharmacology, discuss efforts to protect neuroscience in difficult times...

Last year was not a good year for European neuroscience. In February, GlaxoSmithKline announced that it would be closing its neuroscience research divisions globally. A month later AstraZeneca followed suit. Since then Pfizer, Merck and Sanofi have all pulled back on research into brain disorders, and in December, Novartis announced that it too would be abandoning traditional drug discovery into neuropsychiatric treatments. Suddenly, one of Europe's great scientific success stories was in grave danger.

Given the contribution of industry to neuroscience research in Europe, a retreat on this scale raises serious questions about the future of the field. Why is this happening? And what can be done about it?[1]

These questions were the basis of a summit the European College of Neuropsychopharmacology (ECNP) held in Nice in March 2011, bringing together 60 key stakeholders from industry, academia, patient organisations, public advocacy groups, the European Commission and the European Medicines Agency to discuss the problem and map out a plan of action. The output of this meeting was published in European Neuropsychopharmacology, and it makes for uneasy reading.[2] For while research and development in many treatment areas are under pressure, as pipelines dry out and generics drastically erode profitability, the problems facing drug discovery for neuropsychiatric indications are especially severe.

It now takes over 13 years and more than $1bn to develop a brain treatment, compared to as little as five years for a new cancer drug. And as well as longer development times, the risks of failure are higher, and the failures typically occur later in the development process so are particularly expensive. This would be bad enough, but the stigma that is still attached to mental illness continues to translate into lower reimbursements in many European countries. Moreover, the sheer complexity of the brain has made the search for new drug targets extremely difficult, while the increased pressure companies are under from investors has meant the principle of serendipity that has historically underwritten most of the field's great breakthroughs can simply no longer be tolerated. So powerful are these forces, in fact, that they actually counteract the logic of the market, which in many ways is highly favourable to neuropsychiatric medicine, with



almost two-fifths of Europe's population suffering from some kind of mental disorder in any given year.[3]

It is this prevalence that adds gravity and urgency to the discovery of new and better neuropsychiatric treatments, and makes tackling the threats to ongoing research a moral as much as a public health imperative. At stake is more than the survival of a scientific discipline, but the wellbeing and quality of life of tens of millions of people. What then can be done to keep the science of drug discovery for disorders of the brain moving forward?

This is far from being an easy problem and in the face of such an enormous challenge any efforts short of European-wide governmental intervention might seem all but futile. But there are things scientists can do – and are doing – that if they will not solve the crisis will at least, hopefully, address some of its more damaging consequences.

Two initiatives being spearheaded by ECNP are examples of how the scientific community is responding to the

rapidly changing environment. The first is the 'Medicines Chest', a programme to collect tool compounds developed by the pharmaceutical industry and tested in humans and make them available to academic researchers. Even in the best of times, many potentially useful compounds sit on the shelf because their development has been stalled or discontinued. Many remain poorly documented and some, over time, disappear altogether. Clinical researchers are often unaware which agents are accessible for research purposes, how to acquire them, and the conditions under which they might be used. Now, with neuropsychiatric drug research in many companies being shut down en bloc, whole collections of compounds risk dropping out of sight – a tragic waste of decades of effort and innovation by industry laboratories.

As part of the Medicines Chest, therefore, ECNP is negotiating with pharma companies to act as a broker between researchers and industry, to make access to tool compounds much easier. This will facilitate research by providing a single point of contact for researchers and companies, supplying data sheets as well as the drug, having in place intellectual property arrangements to minimise paperwork on both sides, holding data on safety as well as research findings, and possibly providing an indemnity for researchers.

One drawer of the chest would contain compounds that can be used to explore specific questions in human pharmacology, such as receptor-selective drugs that are not currently available. Another drawer would hold imaging tracers and their precursors. Further collections might be developed in due course as, for example, preclinical tools. This could lead to new indications for old drugs, thereby rewarding their discovery, as well as helping to maintain academic expertise in translational neuroscience, so that when the sector rebuilds, the skills still exist to utilise new investment. Discussions with industry have been very positive. In the UK, AstraZeneca – in collaboration with the Medical Research Council (MRC) – has just opened up a number of its development compounds for competitive research projects in the public arena, and hopefully other companies and funders will follow suit.[4]

The second initiative has similar goals, but aims to salvage patient data. Some of the arguments for better access to existing patient data echo those of the Medicine Chest. We need to better understand the science of clinical trials just as we need to understand better the actual mechanisms of action of different drugs.

As was discussed in ECNP's summit, the presence of high placebo response rates may be adding further complexity to the already challenging task of identifying reliable targets for improved psychiatric treatments. In the case of major depression, higher response rates have clearly had a negative impact on the clinical development of new therapeutic agents, leading to delays in bringing new treatments to market, increasing costs of drug development and, in some cases, resulting in the decision to stop the development of certain compounds altogether. Analyses of patients with major depressive disorder have shown that in antidepressant trials the response rates to placebos have increased significantly in recent years, leading to a relationship between the year of publication and the response rate, and distorting the scientific process.[5]

Addressing this issue is therefore a critical challenge facing the future of neuropsychopharmacology, for industry, academia and regulatory agencies, not least because the relationship between scientific evidence and drug approval has sometimes been conflicting.

Using technology for accessing and aggregating information from disparate databases and file systems, ECNP is now working to create an electronic database of individual-patient data (IPD eDatabase) from placebo-controlled clinical trials with full metadata allowing analyses across federated databases provided by pharmaceutical companies and regulatory agencies. The database will allow analyses of clinical questions and empirical investigation of the effects of different designs and logistical issues, such as the placebo effect issue and site-to-site performance, before institutional memories fade and the data is lost.

These measures alone will not rescue neuroscience from a full-scale pharma retreat. But they do offer a model for how on-the-ground self-help can ameliorate some of its worse consequences. So far both initiatives have been funded by ECNP, but ECNP can take them only so far. It is now to be hoped that central agencies will recognise the urgency and take this campaign to the next level.

1 P Sobocki et al, 'Resource allocation to brain research in Europe European', Journal of Neuroscience 24 (2006), pp. 2691-93, 'The total funding of brain research in Europe was estimated at €4.1bn in 2005, of which public grants amounted to <€900m. Thus, industry funding accounted for 79%'

2 G Goodwin and D J Nutt, ECNP Summit on the future of CNS drug research in Europe 2011, European Neuropsychopharmacology 21.7 (2011), pp. 495-99

3 H-U Wittchen et al, 'The size and burden of mental disorders and other disorders of the brain in Europe 2010', European Neuropsychopharmacology 21.9 (2011), pp. 655-79

4 MRC/AstraZeneca: Mechanisms of Disease call for proposals. www.mrc.ac.uk/Fundingopportunities/Calls/MoD/MRC008389

5 B T Walsh et al, 'Placebo response in studies of major depression: variable, substantial, and growing', Journal of the American Medical Association 287.14 (2002), pp. 1840-47

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