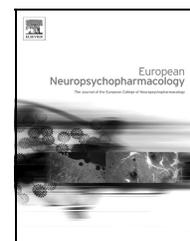




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ECNP SUMMIT REPORT

ECNP Summit on the future of CNS drug research in Europe 2011: Report prepared for ECNP by David Nutt and Guy Goodwin[☆]

In early March 2011 the European College of Neuropsychopharmacology (ECNP) hosted a summit to consider the implications and consequences of the abrupt withdrawal of a number of major pharmaceutical companies from key areas of neuroscience research and development in brain disorders and psychopharmacology in particular. This paper presents the recommendations of the summit plus details of the background and analyses of the problem. It will be widely circulated within Europe and elsewhere.

1. Recommendations from the meeting

1. Work on ways to increase investment.

- 1.1 Provide a detailed response to the current EC consultation on research priorities for FP8, emphasising the costs of brain disorders and the relative underinvestment in these, the need to build infrastructure; mitigating the loss of research expertise; training the next generation of brain researchers.
- 1.2 Give strong support to the European Brain Council (EBC)-led proposal to make 2014 the European Year of the Brain. This initiative will explain the workings of the normal brain and the ways it goes wrong to the European public. It will explain the scale of the costs that brain disorders produce to society and help them understand the value of research and treatment for the vast numbers of those afflicted.
- 1.3 Consider incentives to companies and others working on new and especially novel drugs for brain disorders. Options might include extending patent life for the first in a new class and removing the six-month efficacy data requirement until after the drug is licensed to make Europe equivalent to the USA.

[☆] Disclaimer: With respect to European Medicines Agency (EMA) associated participants the views that have contributed to this document were personal and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or any of its Committees or Working Parties. Moreover, the report reflects the conclusions of the ECNP chairmen/rapporteurs, assisted by helpful feedback from participants but it is not a consensus agreed in every detail by every participant.

2. Enhance research.

- 2.1 Provide tools to improve academic brain research. Ideas ECNP will explore include:
 - Hosting a network for psychopharmacology research: 'the medicine chest'. This would include databases of tool research compounds for human studies, including tracers for positron emission tomography (PET). Companies will be encouraged and helped to make such tool compounds available for research; particular emphasis will be given the issue of insurance.
 - Developing 'open-source' databases for compounds that companies are no longer working to develop. This might include an 'eBay-like' option for other companies to bid for unwanted compounds.
 - 2.2 Set up and/or recognise special centres of excellence in central nervous system (CNS) experimental research and brain imaging where sophisticated early phase trials can be conducted, experience accumulated, new researchers trained and skilled employment positions provided.
 - 2.3 Work with US colleagues on initiatives in the same arena, such as the new National Institute of Health (NIH) translational medicine institute.
 - 2.4 Create access to clinical trial databases to allow individual patient data meta-analyses to answer critical questions relevant to patient selection and trial design.
3. **Review the regulatory process:** to encourage more and better trials in psychiatry. Points to be reviewed should include:
- 3.1 Exploring discrepancies between psychiatric and neurologic drug development pathways.
 - 3.2 Optimising the child/adolescent trial requirements.
 - 3.3 Exploring alternatives to placebo-controlled designs and improved signal detection.
 - 3.4 Clarifying requirements regarding the add-on approach to drug development.
4. **Empower patients:** work with patient organisations, particularly in relation to stigma, trial outcome measures and funding sources.

To work on these goals the group will meet regularly to monitor progress. A small steering group with representatives from all sectors will lead this process, and subgroups for specific areas will be set up.

2. Background

The well-reported pull-out of pharmaceutical companies from neuroscience research that has occurred in the past year is a major concern to researchers, clinicians, patient groups and ECNP. The pharmaceutical industry has been a core partner for science, research, and innovation in the development of improved treatments in medicine. Industry is a major investor in neuroscience and the obvious provider of skilled employment for science graduates in Europe; its move away from the field is a direct blow to knowledge-based economies across the continent. Finally, this is particularly critical for the mental health domain. Within the total range of disorders of the brain, neuropsychiatric illness has become *the* health care challenge of the 21st century in Europe. Highly prevalent disorders such as depression, anxiety and addiction are responsible for by far the highest proportion of the region's total disease burden, mainly due to early onset, illness-related work disability, social role failure and premature death. Furthermore, current available treatment options are imperfect – the withdrawal of research resources is a withdrawal of hope for patients and their families.

Participants at the ECNP Summit included high-level representatives from major pharmaceutical companies, including many that have decided to discontinue major parts of their CNS programmes, representatives from the biotechnology sector, the European Commission's (EC) Research and Innovation Directorate-General, the European Medicines Agency (EMA), patients' organisations and academia, as well as the heads of other European and international organisations involved in the research and treatment of brain disorders, including the director of the US National Institute of Mental Health (NIMH). The meeting was a closed one to allow full and frank discussions without unnecessary attribution of individual comments. This paper summarises the rapporteurs' conclusions from the meeting and the ideas generated for ways to minimise the potential damage to the field and keep the hope alive for future CNS drug development.

3. The current problem

The identification of reliable targets for improved pharmacological treatment in psychiatry and neurology is particularly complex and challenging. This means that the costs of drug discovery and development no longer easily translate into returns from the market for prescription medicines under current conditions. A range of specific factors influencing companies directly in their strategic decisions were identified:

- 1) With an average of 13 years, the time to develop a medicine for a psychiatric indication is longer than that for other disease areas. This may grow even longer because, for some innovative new treatments such as disease-modifying agents in Alzheimer's disease, Phase 2 trials could now take up to four years.
- 2) The failure rate of medicines in psychiatry and neurology is higher than that for other disease areas and many medicines fail late in the development process – at Phase 3 or even at registration – leading to particularly high financial loss.
- 3) Moves within western countries, especially the USA, to sue companies for any adverse event related to the use of

prescription medicines add to costs, reduce investor confidence and restrict sales. Consequent marketing decisions may have nothing to do with the scientific research and development or the clinical need in a particular CNS therapeutic area.

- 4) It is widely believed that small biotechnology firms might fill the vacuum in early phase research after the withdrawal of big companies. However, their efforts can only contribute to early phase research, not full development: the funding of such projects from venture capital sources is typically short term (at most 10 years, and often with conditional options to pull out much sooner), not supporting the full cycle of development and commercialisation costs. Moreover, the availability of venture capital in Europe remains uneven.
- 5) Different companies perceive the balance of risks in the overall equation in different ways. There appears to have been a shift in many large companies away from scientist-led towards MBA-led management and this may oppose the ethos of long-term investment based on strong underpinning science.

It is difficult to avoid the primary conclusion that companies are pessimistic about the commercial promise of the current science base in CNS. Secondary concerns relate to the environment in which science and industry must function.

3.1. Deficiencies in the science that underpins drug discovery?

For almost 20 years the genetic revolution, linked with high throughput computational chemistry and biotechnology, has promised to redefine drug discovery. The precision of genetic data seemed to pave a royal road to target discovery. Molecular genetic studies of the human genome and of the major diseases have dominated the biomedical research agenda for both academia and industry. There remains a remarkable consensus that this is still the right course, while the time needed to achieve large-scale and reproducible successes appears to have been underestimated. Human genetic association studies have been confidently predicted to identify targets whose neurobiology can be quickly understood and become the objective for functional modification by novel drugs. This approach has yet to succeed. Predictive and prognostic biomarkers for psychiatric disorders are largely nonexistent and the poor predictability of the pre-clinical models for both psychiatry and neurological diseases is only now being addressed by the development of experimental human models.

Most psychiatric medicines have been discovered by guided or "well-educated" serendipity. A highly rational approach to drug discovery, removing clinical intuition and the close proximity of experienced clinicians to patients in early clinical trials will work against chance discoveries. Moreover, as the recent analogous experience of the financial markets would tend to suggest, the existence of an overwhelming consensus driving research in a single direction may come with additional risks.

3.2. Is society prepared to value and pay for mental health research?

There is an unspoken (maybe almost unconscious) range of prejudices still frequently directed at the problem of brain disorders. While this is often highlighted as the stigmatising

attitudes of society towards patients, there is an equally important prejudice against the science that is done in the mental health field. Thus, there is a widespread misconception that there has been little progress in understanding the causes, pathophysiological mechanisms and treatment of psychiatric and neurologic illnesses over the past decades. This is probably particularly the case for innovations in the pharmacological management of mental disorders. The argument is regularly heard that biomedical approaches to psychiatric disorders are simply not appropriate and are driven corruptly by the agenda of industry. Alternatively, new treatments may be deemed not to have improved sufficiently on older and cheaper medicines, whatever the evidence of their greater acceptability.

If the new treatments we have seen in recent years are generally not valued appropriately, it should not be surprising that health care systems are reluctant to prioritise payment for them. Such decisions are not rational because the same systems do prioritise very expensive and not always very effective treatments for cancer.

The low value attributed to mental ill-health as a treatment target helps also to explain why the investment for improved treatments of mental disorders is substantially lower than for other indications. The shortfall in total investment is also in sharp contrast to the high total disease burden, exceedingly high indirect costs and remarkably lower direct treatment costs.

3.3. The regulators' dilemma: has the bar for psychiatric medicines been raised too high?

It is recognised that regulators face a difficult dilemma: on one side they need to get really new and valuable medicines to the patients, on the other side they are under pressure to ensure that effectiveness (efficacy and safety) and optimal use of medicines in real clinical practice are assured before granting (and maintaining) authorisation.

Placebo controlled clinical trials of monotherapy continue to be required for registration of most new medicines in psychiatry. In the past decade there has been a remarkable difference in the number of registrations of drugs for epilepsy (ten registered) in comparison with one for major depression. There is no reason to believe that this reflects a true difference in the quality or quantity of the underpinning innovative research. The new medicines for epilepsy do not result from breakthrough discoveries about the aetiology and pathology of the disease. However, they are commonly accepted on the basis of add-on strategies for treatment in epilepsy, whereas these are not encouraged in depression. We will continue to work in consultation with EMA to define appropriate patient populations and add-on/augmentation trial designs.

There has been understandable concern that medicines tested in disorders in adults may be used inappropriately to treat children. In response, the EMA's demands for studies in children and adolescents have enlarged. The need for safety data from observational studies appears entirely reasonable to help protect children from adverse effects not obvious in adults, but the extension of this demand to require placebo-controlled proof of efficacy is clearly to ask the impossible in many indications. Some disorders are so rare in children that it would take almost every case in Europe to provide enough cases for a study to be conducted in a reasonable time, if the

relevant ethics committees would allow placebo-controlled studies in the first place. It would be regrettable if companies have decided not to develop drugs in some adult indications because the requirement for studies in children is so difficult.

The generic rise of disproportionate regulatory processes at every level in the research enterprise is also a potent barrier to efficient research, not just in the mental health field, of course. The problems that have been caused unnecessarily by the EU Clinical Trials Directive are widely acknowledged and under review. However, the imposition of disproportionate checks, controls, duplications and 'ethical' excesses has been epidemic in the last decade. A basic example is perhaps the requirement for double entry of data, which nearly doubles this cost yet in quality centres has been shown to contribute almost nothing to scientific accuracy or patient safety. Regulation with the potential to harm research badly needs justification on the basis of evidence of risk, not the assumption of risk. Many of these problems may appear individually trivial, but because they have multiplied ceaselessly, they have become crushingly important.

The regulatory burden falls particularly on investigators, but the patient representatives also questioned the undue emphasis on safety which they felt was, from their perspective, excessively paternalistic and had the potential to deny them choice in new treatments. They should be more involved in the discussions around benefit/risk profiles of currently available and new medicines.

3.4. National health technology assessments — an obstacle?

Following European-level approval and registration of a medicine, health technology assessments provide a further series of 27 individual state hurdles that companies have to surmount once they have achieved centralised approval. The delays eat up patent life and threaten profitability of new products. The reasons appear implicitly or explicitly to be economic: health systems are prepared to prevent or delay access of new medicines to their markets simply to save money, even though the costs of medicines rarely exceed 5% of direct costs of treatment. New legislation aimed at harmonisation between member states should address this important issue.

3.5. The risk of declining research capacity for brain diseases

The analogy with antibiotics was highlighted, where some 15 years ago research stopped because of regulatory recommendations for drugs with improved efficacy; this objective proved impossible to attain. When companies pulled out, the research base died. However, the growth of antibiotic-resistant bugs made different drugs – even if they were not more efficacious – an acceptable and worthwhile, indeed necessary, target. Special arrangements have had to be made on an international scale to resurrect research expertise in this area.

The analogy with antibiotics is not exact, of course, but it illustrates that the consequences for brain research of

pharma company withdrawal may be very serious. We must not lose the capacity for drug discovery and development in brain disease.

4. Ways forward

This is a global problem and links with USA are now especially important since many of the large pharmaceutical companies are based there. The NIMH shares our sense of how critical things may become for the field. It was agreed that there was scope for a multi-pronged approach that involved all the community and multiple stakeholders (physicians, patients, caregivers, payers, advocacy groups, policy makers, government and regulators).

4.1. The research policy dimension

Given on the one hand, the scientific challenge of improving the validity of target definition in the brain and, on the other, the true size and burden of brain disease as the growing and leading health challenge of 21st century, the field needs a concerted effort to increase resources and funding in order to address this problem and increase the probability of viable solutions.

According to the most recent data on research investment in Europe provided by the EU, key indicators suggest that the proportionate spend of GDP on research in Europe lags well behind that of other developed countries. Moreover, neuroscience research is considerably less well supported than that of other comparable diseases such as cancer (€465M out of a health research spend of €6050M).

New EBC/ECNP data on the costs of brain disease in Europe reported at the summit showed that they total more than all other diseases put together. There should be a concerted effort to rectify this under-investment in neuroscience in the FP8 programme. ECNP and EBC are committed to supplying reliable and objective data to inform all relevant stakeholders to promote concerted efforts on the European and international level.

Although the current science clearly leaves us short of our objectives in understanding and treating brain disease, there was a general sentiment that societies must agree to prioritise brain research given the looming crisis of an ageing population. This implies a shift in governments' political priorities to pay more for the research and treatment of brain disorder.

4.2. Investor confidence

To deal with the failure of investor confidence several approaches were suggested:

- The commitment and performance of companies in the neuroscience area should be published and compared. The positive impact that measurement of such performance might have on investment in brain research should not be underestimated: league tables can motivate companies.
- The patent life of drugs with psychiatric and neurological indications could be extended in proportion to the true development time and cost.

- Mixed funding models (charity/company/government) should be considered and the moral and practical obligation of society to support research in brain disorders clarified. The scope for joint initiatives between governmental and private agencies was illustrated by the recent NEWMEDS project funded under the Innovative Medicines Initiative (IMI) in FP7. This was welcomed as an example of EC research investment with pharma. A greater emphasis on pre-competitive collaborative research consortia of a variety of types could make R&D in the area of psychiatry more efficient by creating standard ways of testing medicines in healthy volunteers and sharing normative data.
- If EU competition rules could be satisfied or appropriately modified, consideration could be given to extending the IMI model to patient-based clinical trials with new compounds on which companies could work collaboratively with government funders.
- New, yet already proven, approaches to research investment and data-gathering are demonstrated by the parent and patient organisations that have raised huge sums for research in some diseases – most notably cancer but also, for example, autism.

4.3. The scientific dimension

The need for new models and approaches is needed. As an example, an approach for drug discovery/development was suggested with more emphasis on 'prototype' discovery in expert academic centres. This could add value in the early phases with a rollout to more traditional Phase 3 only when there is confidence in drug efficacy. Such an approach would have the added benefit of creating centres of excellence for training and the knowledge base in psychopharmacology that can move the field forward.

Tool compounds – for example, drugs with specific pharmacology and clinical safety but which are not in clinical development for reasons related to funding priorities – should be made available for research. A good example would be drugs discarded for Alzheimer's disease but which might be useful in other neuro-developmental syndromes or even for treating depression and cognitive symptoms across various psychiatric disorders. In addition, retesting some compounds in clinical trial designs with different entry/exclusion criteria, outcome measures and duration of study could be considered. This would require hosting of the compounds and insurance to cover adverse effects. The new NIH translational medicine institute is a promising approach that we in Europe might work with and learn from.

Big science investment is low in Europe and companies have few sites at which to do studies using expensive techniques such as PET and pharmaco-MRI. Investment by government in new centres would not only provide research but also create new hi-tech jobs and training opportunities. A European-level provision of PET tracer precursors and test compounds could be helpful.

The extensive databases held in the EMA should be explored for new insights into why trials fail – or succeed. Industry should share data on negative and failed studies and not withhold information. ECNP could seek to play the part of an honest broker in achieving this end.

Trial design could then be improved, for example by providing a rationale for sub-grouping or disease stratification. It is now widely assumed that medicines with a greater impact in sub-groups of patients are likely to be more useful than drugs showing small improvements in weak average

population effects. However, we have few established ways to stratify patient samples because of the traditional approach to clinical trials of including as wide a sample as possible to claim blanket efficacy.

Investment is required in validation of biomarkers; their role as proxy outcomes in psychiatric and neurological disorders needs clarification by regulatory authorities, as has recently been achieved for Alzheimer's disease.

Modelling psychiatric and neurological disease and treatment response in normal volunteer experimental medicine studies is a promising new development that could be supported in pan-European networks of excellence.

Other ideas include giving more emphasis to patient-centric outcomes and quality-of-life measures especially under real-world trial conditions. Two work packages in IMI are in this area.

Stigma might be reduced by changing the names of some disorders. For example, in Japan schizophrenia has been redefined as a 'neurocognitive syndrome', although translation does not capture the greatly increased acceptability this achieves in Japanese: treatment rates have improved enormously. ECNP could support national and European level initiatives to this end.

5. Conclusions

Research in new treatments for brain disorders is under threat. There is a pressing need for all interested parties to work together to minimise the damage that this will cause to the care of patients. This ECNP initiative is the beginning of a process that we hope will begin to rectify the current situation and build a strong foundation for the future.

6. Participants of the ECNP Summit

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