Editors' view

Vanishing clinical psychopharmacology

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Normally in these editorials we highlight certain papers that appear in the current issue of the journal. In the case of clinical psychopharmacology there are none to comment on, and we analyse why this is so.

This lack of papers apparently represents a long term trend. In the past year we published only 5 papers on CNS pharmacodynamics, none of which involved novel drugs. New drug registrations are in an equally poor state. In 2010 only two drugs with a broadly defined psychiatric or neurological indication were approved by the FDA, both after a history of other applications. The potassium channel blocker dalfampridine (4-aminopyridine) was approved for multiple sclerosis after it had been available as an avicide for almost 40 years. It prolongs action potentials, thereby increasing transmitter release at axon terminals. The thrombin inhibitor dabigatran was registered for prevention of stroke in patients with atrial fibrillation, an extension of the indication for thromboprophylaxis after major orthopedic surgery. The situation does not look very promising earlier in the pipeline. At the 2011 meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) there were only 13 out of 300 abstracts on psychopharmacology and none on new drugs, other than one new positron emitting tomographic (PET) imaging agent. The world conference meeting of the Collegium Internationale Neuropsychopharmacologicum (CINP) in 2010 had 8 out of 870 abstracts on human psychopharmacology, of which 4 reported on new or relatively new mechanisms of action.

To add insult upon injury both GSK and Astra Zeneca announced last year that they would cease research in psychiatric diseases like depression, bipolar disorder and schizophrenia and anxiety, leading to what initially appeared to herald a mass exit by many pharmaceutical industries from the field of central nervous system (CNS) drug development. Both companies, despite having made large amounts of money from antidepressants and antipsychotic drugs felt that the research was too risky. The CEO of GSK, Andrew Witty explained that the subjective nature

of the endpoints in psychiatry made it difficult to show that a drug was working even after large scale trials. Whilst the cynic could muse that this was not apparently what the company would say in advertisements about its marketed antidepressants, we concur with him that there is a problem. In response to these disconcerting developments, David Nutt and Guy Goodwin with the European College of Neuropsychopharmacology (ECNP) organized an invitational meeting in March this year in Nice, France, to discuss these events. A report of this meeting will be issued around this time. Many reasons were identified that are not unique to the development of psychiatric drugs, such as the increasing costs and complexity of drug development, and the growing gap between academia and industry. The experts also mentioned several methodological issues, such as the need for experimental and computational disease models and biomarkers, but this was not the stage for an in-depth discussion of scientific reasons for the apparent lack of progression. This is nonetheless something to consider, since devastating diseases like major depression and schizophrenia, the incidences of which are on the rise worldwide, are still treated with a drug armamentarium of at most limited value, based on mechanisms that were largely already known in the 1970s. Moreover, the older anti-psychotics were shown to be as effective as the newer second generation anti-psychotics [1].

These mechanisms almost exclusively entail the primary neurotransmitters and their receptors. This is familiar territory for basic and clinical pharmacology, and the main changes in psychiatric medications over the years have consisted of pharmacological modifications, such as a drug's intrinsic efficacy or selectivity or kinetic properties. It is increasingly clear however, that many psychiatric disorders are in fact due to highly complex derangements of integrated neuronal systems, which involve migration, degeneration and regeneration of nerve cells, astrocytes/microglia and neuronal networks, inflammatory and immunological factors, genetic and epigenetic processes, and probably many others. Ultimately, these pathogenic

derangements lead to abnormal neuronal communication, manifesting itself in disrupted nerve conduction and neurotransmitter release – the traditional targets for psychiatric medication, which therefore mainly have supportive or symptomatic effects. But the underlying processes involve other pharmacological factors such as neuropeptides, hormones, growth factors and other molecular biological regulators. Depression for instance has been linked to reduced activity of brain derived neurotrophic factor [2] and schizophrenia has many characteristics of a neurodevelopmental disorder [3]. Although much work needs to be done before the complexity of psychiatric diseases is fully understood, pharmaceutical companies have tried to target the modulatory factors that seem to underly psychopathogenesis, by development of what in this editorial will be collectively named 'neuromodulators, sadly, without much success thus far.

Attempts to antagonize the neuropeptide cholecystokinin have been unsuccessful in anxiety disorders [4], most trials with tachykinin or neurokinin (NK) 1 antagonists have failed in depression [5], and several anti-amyloid therapies have been unable to reverse Alzheimer's disease [6]. It is possible of course that these factors are not as important in the pathogenesis of psychiatric diseases as was hypothesized, or that use of the drug at the stage of disease was not optimal. But it is also possible and in some of these trials even likely that the neuromodulator did not even have a chance to exert its intended pharmacological activity, because drug concentrations were too low or too variable for adequate brain penetration and target occupancy. At any rate, adequate predictions of active doses and concentrations will undoubtedly increase the chance that a clinical trial will be successful, even if not all risks can be mitigated. But if the trial should fail despite optimized pharmacokinetic-pharmacodynamic relationships, we will at least have made progress in understanding the underlying disease mechanism. Currently, negative clinical trials often leave too many questions about what went wrong unanswered, with the consequence that many of the neuromodulators that initially failed in trials are still under clinical investigation.

How can clinical pharmacologists predict effective levels for drugs that affect regulatory factors, particularly when these targets are hidden inside the nervous system, and when their effects are indirect and develop slowly over time? There is no simple answer to these questions, but it is essential for the future of clinical psychopharmacology and neuropharmacology – and for drug development for neurologic and psychiatric diseases – to come up with a more or less systematic approach that leads to predictions for clinical trials. This has been the domain of clinical pharmacology for decades, so we will start with an outline of an approach that we have found useful for drugs with traditional mechanisms of action [7], before we will consider some differences and similarities with neuromodulators. For all drugs, accurate predictions of effective drug con-

centrations rely heavily on good animal models. It is up to researchers of disease processes to make sure that the disease models are relevant for human psychiatric disease, and that the biological systems are comparable between experimental animals and humans – or at least that we understand the differences well enough to interpret the findings and to avoid therapeutic failures or unexpected adverse effects. Pathogenic and pathophysiological research is of fundamental importance for the development of new treatments, and this obviously requires close involvement of clinical pharmacologists to provide the translational links to the clinic. When the disease is well understood and the animal models are predictive, target occupancy and corresponding plasma concentrations and secondary physiological effects in experimental animals provide important 'translational' information for the prediction of effective drug concentrations in humans. This is the basis for the determination of a drug's pharmacokinetic properties and the sources of variability, since (unbound) plasma concentrations drive the distribution to the brain and other target tissues. Brain penetration also depends on the activity of the blood-brain barrier, which can be difficult to translate between species particularly in case of active uptake and efflux transporters. It is important therefore to examine whether drug concentrations that are effective in animal models are also achieved in the human brain. Measurements of drug concentrations in the cerebrospinal fluid (CSF) can increase the confidence that the drug has penetrated the CNS.

However, there is also an active barrier between the brain and the CSF, and the drug can bypass the brain to reach the CSF where the blood brain barrier is less well developed (such as circumventricular organs or nerve roots). Brain drug levels can sometimes be measured directly, when the compound can be labeled with a positron-emitting moiety for PET-imaging, or with enough fluorine or phosphorus in a molecule to allow direct MRI-imaging, but for most drugs this is unfeasible. Increasingly, pharmaceutical companies will seek to develop an appropriate PET-ligand as soon as a new pharmacological target has been identified. Displacement of the PET-ligand from the target by the new compound, provides important support that the drug binds to its target. PET-studies provide estimates of the level of occupancy, but binding studies give no information about the intrinsic activity or the level of inhibition of a new agonist or antagonist. It is only by relating clinical experience to [¹¹C]-raclopride PET that we now know that 60–80% D₂-receptor occupancy is predictive for a therapeutic dose of an antidopaminergic neuroleptic. PET-studies can also show that the drug has penetrated the blood brain barrier, and how long it remains in the brain. PET-ligands can be very useful, but they are difficult to develop and to validate, and they are rarely available for the first representatives of a new drug class. For advancing knowledge about the compound, the most accessible way to show drug activity in the brain is by

measuring drug-related central nervous system (CNS) functional activities or CNS-pharmacodynamics with sufficient sensitivity and specificity.

The question is which is the most relevant neurological activity. In many disease areas, a physiological function can be reliably coupled to a specific pharmacological activity and a certain medical condition, for instance angiotensin activity, blood pressure and hypertension; or thrombin activity, blood coagulation and thrombosis. The journal is filled with many more examples that reflect the increasing knowledge in these fields regarding relationships between pharmacology, physiology and pathophysiology, and how this basically drives drug development. Such validated biomarkers are rare in neurology or psychiatry however, which is one of the reasons why these specialties seem to be lagging well behind in early drug development. Still, many neuropsychiatric drugs affect a range of different CNS functions in a dose- and concentration-related manner, particularly if the compounds affect neurotransmitter activities. This provides opportunities to demonstrate that a drug exhibits pharmacological activity, and hence penetrates the brain and affects a pharmacological target, even if the activity measured is not an essential step in the pathogenic cascade. The affected functions can often be roughly or partially coupled to the specific pharmacological mechanism, by knowledge of neurophysiological functions – for instance dopamine D₂-antagonism to prolactin release, or GABA_A-ergic activation to reduced peak saccadic velocity, and serotonergic stimulation to cortisol release. This makes these functions useful biomarkers for pharmacological effects, even if they have no clear functional relationship with psychosis, anxiety or depression. Even if the functional relationship is not clear at all, it is very likely that an evident concentration-related effect of a highly specific compound is mediated by the drug's designated pharmacological mechanism. Problems arise when there is no direct concentration-effect relationship, and this is often the case for neuromodulatory-type drugs. In this case, demonstration of pharmacological activity and predictions of effective doses can become very difficult.

A common response in drug development programs is to ignore problems that have no simple solution, and to try to determine the drug's potential effects in patients after little more than an assessment of pharmacokinetics and tolerability in healthy volunteers. The consequence is that all the cautious steps, which clinical pharmacologists take to ensure that a new drug reaches its target by selection of the right dose for the proper patient population, are largely ignored for neuromodulators where this is difficult to determine in humans. There is little doubt that this increases the chance of a negative pivotal clinical trial. In hindsight, disappointing or equivocal results of clinical trials with such drug types are often attributed to a presumed lack of sufficient brain penetration or suboptimal dosage regimens (for instance for the many failed trials with neuroprotective agents in brain trauma [8] or with

anti-amyloid agents for Alzheimer's dementia [9]), but in most cases we do not know whether this was the case. The disappointing innovation of neurologic and psychiatric therapies may be primarily due to the highly complex pathophysiology and the intermittent course and slow progression of many CNS-disorders, but drug development of neuromodulators can only benefit from a proper prediction of pharmacologically active doses and a better understanding of sources of response variability.

So how can we demonstrate that an indirect- or slow-acting compound exhibits pharmacological activity in the brain, and which dose-range is most likely to be effective in clinical trials? As for traditional neuropsychiatric medications, plasma concentrations are an important initial prerequisite for optimizing drug dosing. Demonstration of target binding and brain penetration using PET or other imaging tools can also be very informative, and many probes and ligands are in development for neuromodulatory targets. One example is the PET-ligand Pittsburgh compound B, which has become an important experimental technique to demonstrate brain amyloid load and effects of disease modifying drugs in Alzheimer's disease. Unfortunately, this is of little use in healthy subjects without amyloid accumulation. Another practical PET-tool in early drug development is a tachykinin 1 ligand, which was used for guiding the dosing predictions of aprepitant in clinical trials. When the trial came out negative in depression, it was clear that the negative finding was not due to insufficient receptor binding [10]. There are a small number of other ligands for neuropeptides and growth factors, but it will remain difficult to develop an imaging compound for each new neuromodulatory drug. It would be ideal to measure the direct physiological consequences of pharmacological modulation, but neuromodulators rarely cause direct functional changes or changes which are easily measurable. By nature, such compounds act indirectly or slowly, which usually means that their effects are undetectable in stable (healthy) conditions. It is not surprising therefore that tachykinin antagonists, which modulate the release of different neurotransmitters, have no clear dose-related CNS-effects in healthy volunteers – in contrast to the profound effects of direct agonists or antagonists for the same transmitters [11]. However, it can be expected that neuromodulators will reveal their effects, when the systems are perturbed which these drugs are designed to affect. This is the basis for disease models in animals, and the same approach can also be used in humans; either by creating a mild reversible disease model in healthy volunteers or by performing detailed studies in selected patients. Unfortunately, there is a large unmet need for validated disease models in healthy subjects, whereas psychiatric patients are often less eligible for experiments that provide reliable models for accurate dose predictions for subsequent clinical trials. However, clinical pharmacology can make use of the fact that neuromodulators act by influencing other pharmacological

processes, which can also be used to measure the drug's indirect or time-related changes. Such studies are still rare, but they are gradually being conducted. This is clearly illustrated by antagonists of endocannabinoids. These endogenous mediators affect retrograde neuronal synaptic signaling and plasticity, and may be involved in the development of schizophrenia [12]. Cannabinoid antagonists were investigated as potential treatment for this condition, before the demise of rimonabant thwarted much of this research. None of the cannabinoid antagonists that we have investigated so far has any CNS-effect in healthy volunteers even at high doses, but they almost completely suppress all effects of the agonist tetrahydrocannabinol (THC) at low doses [13]. Pharmacological challenge tests can also be used to demonstrate time-related changes. Selective serotonin reuptake inhibitors (SSRIs) have neuromodulatory effects, which are related to the delayed resolution of clinical depression during initiation of antidepressant therapy. These effects are reflected by slow adaptations of the sensitivity of the hypothalamus-pituitary-adrenal axis and thermoregulation to serotonergic stimulation, during prolonged SSRI-treatment of healthy subjects [14, 15].

Although such studies in themselves cannot be used to predict the clinical dose of a neuromodulator, they do show which dose has an effect that is in line with expectations. In several of the examples provided above, this led to dose adaptations for subsequent clinical trials. The examples illustrate how pharmacological challenge tests can be used to show indirect effects of a neuromodulator on other pharmacological systems, and how this changes over time. In the same vein, pharmacological challenge tests can also be used to pursue the progression of diseases that are characterized by time-related changes of neuropharmacological systems, such as Parkinson's or Alzheimer's disease and probably many psychiatric disorders. Such studies are currently underway as collaborative projects between clinical pharmacologists and neurologists and psychiatrists.

These approaches are largely based on fragmentary evidence and experience, and it may be argued that they are not developed well enough to reliably guide a drug development process. But this should be considered as an appeal to clinical pharmacology to contribute more actively to the development of neuromodulatory drugs (or drug combinations), by devising predictive ways to demonstrate pharmacological activity for compounds that act indirectly or slowly on complex and progressive pathophysiological processes. Many of these approaches can also be applied in preclinical phases of drug development and thus become truly translational. In this way, clinical pharmacologists can recover precious ground that may otherwise be lost. Clinical pharmacological techniques, like computational modeling of disease progression and drug effects or pharmacological challenge tests, can provide excellent collaborative tools among clinical researchers,

which is at least as important for scientific progress. So, the apparent abandonment of the field of psychopharmacology by companies and clinical pharmacologists seems unwise. Clinical pharmacology has the duty to develop and validate more quantitative measurements of CNS function and relate these to disease activity. This will reduce development risks and allow companies and investors to redirect their money and efforts towards the treatment of a group of diseases that produce a terrible burden on the lives of our patients and their families. Perhaps this is one of the cases where clinical pharmacologists, as experts in translational science and method development for the quantitative effects of drug on the CNS, can lead the field out of its current depression.

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