Where Will New Drugs Come from to Treat Neuropsychiatric Diseases?

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A new report from PhRMA (medicines in development for mental illnesses) highlights the statistic that 1 in 4 American adults suffer from some form of mental illness and that this costs the US economy more than $317 billion annually. It also points out that 200 medicines are now in clinical development for mental health indications. Sadly most of these medicines are not new but are variations or re-formulations of medicines we already use and the number of really new approaches to mental illness is very small.

A recent article in *Nature*[1] states that 13% of the global burden of disease is attributable to mental, neurological and substance abuse disorders, surpassing both cardiovascular disease and cancer. To make matters worse, at a time when the need for drugs to treat mental health problems has never been greater, many of the larger companies in the pharmaceutical industry have been making dramatic cuts in their worldwide research investment in this area[2] . Part of the reason is the difficulty of developing such drugs. Companies have decided that psychiatric diseases are too complex to allow profitable drug development [3]. The required clinical trials depend on soft behavioral endpoints in the main and there are no established biochemical surrogate markers to inform such studies[4].

The time taken to develop CNS (Central Nervous System) drugs is longer than for other therapeutic areas (phase II and III take an average of 8.1 years and some drugs have taken as long as 18 years to develop) and the rate of success is lower (only 8.2% of CNS clinical drug candidates become available for use in patients).

The drugs that we currently use did not arise from an understanding of the disease process so they do not necessarily point to where we should look next for new treatments.

These partially effective drugs that we use to treat disorders such as depression and schizophrenia were derived from inspired empirical research in the 1950s[5]. This theme of research lasted nearly 40 years. Although it involved much virtuoso medicinal chemistry, it did not help us understand why patients suffer from depression and what really happens in their brains to cause the disorder. There is a similar situation with the treatment of schizophrenia. .

The key drugs for treating a number of severe and hitherto untreatable neuropsychiatric conditions were introduced by empirical methods. They have been of enormous benefit to more than a generation of patients but have left drug discovery scientists with a dilemma as to how they produce improved treatments without a clear understanding of disease pathophysiology. The best clues we have at present have come from the actions of drugs rather than from disease mechanisms. For example, blocking the effects of glutamate at the cation channel coupled receptor sensitive to N-methyl-D-aspartate (called the NMDA receptor for short) with agents such as phencyclidine or ketamine produces symptoms that resemble those seen in patients with schizophrenia. Agents that can modulate the actions of glutamate in the brain by acting at what are called metabotropic glutamate receptors (mGluRs) are currently being evaluated as potential treatments for schizophrenia[6].

Another example is the realization that the monoamines thought to be implicated in depression have their secretion controlled by a variety of peptide neurotransmitters. Also, blockers of some neuropeptide receptors, such as the NK1 receptor at which substance P has its actions in the brain, have animal pharmacology that resembles that of known antidepressant drugs such as the SSRIs. This has led to clinical trials of NK1 antagonists as treatments for depression[7]. In both the examples given, early clinical studies looked promising. But, it has so far not been possible to get robust phase III clinical data that would support registering one of these drugs as an approved treatment.

It is therefore necessary to go back to basics and to try to understand the anatomical and biochemical basis of the diseases that we need to treat. Studies on post-mortem brain samples taken from patients dying with neuropsychiatric disease have been conducted for many years but have not generally been helpful. Biochemical changes found after death may not necessarily reflect the situation in life. Even when anatomical changes are examined, there is a problem in obtaining age-matched control samples that allow differentiation of age and disease related changes. Also, as little data is available on subjects who have not been treated with drugs, there is always the possibility that the changes seen are drug rather than disease-related.

However, we are now in a new research era based on advanced imaging techniques[8] and genetic studies that hopefully will lead to new and better treatments. As a result the clock has been reset . Although much of the pre-existing research on antipsychotic and antidepressant drugs will not be helpful in this endeavor, we may at last be on the way to understanding the causation of these important diseases.

The use of magnetic resonance imaging (MRI) has allowed patients to serve as their own controls and in-life anatomical measurements can now be made at the time of diagnosis and then followed over many years. For example, a study on twins from families with a high risk of either schizophrenia or bipolar disease showed that decreased white matter volume and thinning of particular areas of the cerebral cortex was associated with the presence of genetic risk factors[9]. It has also recently been shown that when individuals with a high genetic risk of schizophrenia use cannabis, they are likely to show a loss of volume in a brain area called the thalamus, which may help explain why some but not all cannabis users are at risk of developing the symptoms of schizophrenia[10].

The use of functional MRI (fMRI) allows relative activity of brain areas to be studied and parallel NMR (Nuclear Magnetic Resonance) spectroscopy allows some brain biochemistry parameters to be measured in-life. MRI techniques are non-invasive and can be applied to healthy control subjects with minimal ethical concerns, such that it is also possible to obtain control data from non-afflicted family members of the patients being studied.

The use of positron emission spectroscopy (PET) is generally restricted to patients as this technique involves administration of drugs or chemical probes labelled with short-lived radioactive isotopes. PET makes it possible to get a window on what is happening to specific populations of receptors and to transmitter systems in designated patients. Such studies have confirmed that there are abnormalities in the dopamine neurotransmitter systems in the brains of patients with schizophrenia but that these defects appear to be mainly presynaptic, affecting dopamine synthesis and release processes which are unaffected by current D2 receptor blocking treatments[11]. It is also clear that genetic association and copy number studies point to glutamate system hypofunction in schizophrenia and this is driving research, especially in the area of new animal models that can be used in drug discovery[12]. However, the genetic picture remains complex. We know that although some families have a genetic makeup that gives a high risk of schizophrenia or bipolar disease, there are also sporadic cases where there is no clear genetic association. It is likely that there is a genetic factor in at least 60% of schizophrenics but environmental risk factors also play an important part[13].

At present up to 1000 genes have been suggested to be involved in the aetiology of schizophrenia and this clearly does not point to an easily addressable drug discovery target! Much re-investigation of the genetics of schizophrenia is in progress using the most up-to-date techniques which allow sequencing of large regions of the genome. Hopefully new knowledge will soon emerge to help us understand what is needed to allow discovery of a new generation of drugs[14]. It has also been claimed that for the first time it is possible to find a biological signature for schizophrenia in serum which should assist in the early diagnosis of the disease[15].

The problem remains as to where the research to discover new drugs will be conducted. In some cases when companies announced that their internal research efforts were to be terminated they revealed that they have put alternative plans in place. For example, Astra-Zeneca has retained a skeleton group to work with researchers outside the company and to license promising therapeutics from other companies and Novartis has substituted a genetics research group for the traditional CNS drug discovery effort that is being terminated. There is undoubtedly an expectation that the gap left by the big companies pulling out will be filled by a mixture of research done by academic groups and by the small biotech companies.

Although much creative early stage research is

going on in this challenging arena, it is unlikely that anyone but the large pharmaceutical companies has deep enough pockets to perform the late-stage clinical trials needed to show that new therapies are effective.

Given the low rate of success in the recent past and the current risk- averse behavior of the large pharmaceutical companies, there is a possibility that exciting new agents taken to the point of first study in human subjects by academic groups or small companies will then struggle to find funding for late stage clinical trials. Although there is a certain amount of government and charity grant money available on a competitive basis to supplement venture capital funding of early stage clinical testing there is no alternative funding for expensive late-stage studies. Until this issue is resolved then the future of neuropsychiatry drug discovery and development at best remains uncertain.

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