

SOS from CNS

Despite massive sales of drugs for psychiatric and neurodegenerative disorders, there still remains an enormous unmet medical need in these disease areas. Susan McGoldrick at QCTR Limited reports



Susan McGoldrick is Managing Director at QCTR Limited. Susan has worked in the pharmaceutical industry for over 10 years in medium-sized and small biotech companies, including a virtual pharmaceutical company specialising in developing treatments for psychiatry and neurological disorders, where she gained an in-depth knowledge of drug development. Susan has valuable experience in attending meetings and presenting data at the FDA and EMEA, filing a new drug application with the EMEA, and designing and obtaining agreement on the overall development requirements for a lead Phase III compound. Susan also has extensive expertise in financial and intellectual property management, as well as legal and contractual issues specific to the pharmaceutical and CRO industries.

Sales of pharmaceutical products approved for central nervous system (CNS) disorders reached US\$69 billion in the year to March 2006. Over the last three years, sales have increased by 20 per cent from \$55 billion to \$69 billion. However, the growth rate is slowing. Recent sales figures show a year-on-year increase of only five per cent, compared to the 10-15 per cent growth rates seen a few years ago. CNS drug sales are the largest therapeutic category in the US and account for 60 per

cent of total worldwide sales. Sales in North America, Europe and Japan, together with the growth in CNS sales from the years ending 31st March 2003 to 2006 are shown in Figure 2 (1,2).

Within the US CNS market, antidepressants are the biggest single category, with sales of \$12.5 billion. The top five selling antidepressants are shown in Table 1 (3). Although the number of US prescriptions written has increased in the last two years, total sales have declined by close to a billion dollars. This decline can be explained by Prozac (fluoxetine) and Celexa (citalopram) going off patent and cheaper generic versions being introduced.

Sales of schizophrenia drugs are close behind at over \$10 billion and have grown by 25 per cent on sales in 2003 (3). The top five selling antipsychotics are shown in Table 2(3). It is interesting to note that sales of antidepressants (\$15 billion) are close to that for the entire cancer drug market (\$20 billion). So, with these huge sales, one could assume that there is not much unmet medical need in the CNS area. Unfortunately the reality is very different.

Figure 1: Worldwide drug sales by therapeutic category

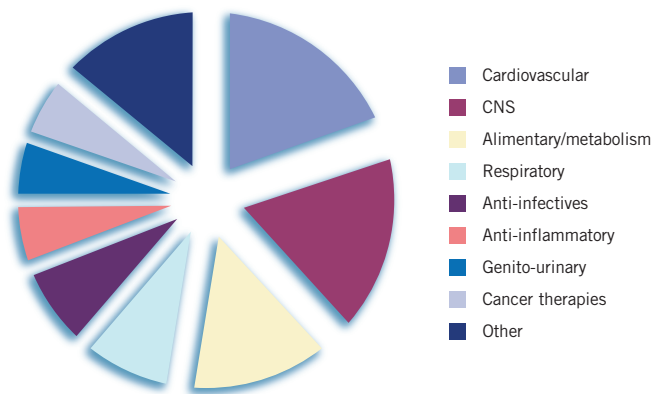
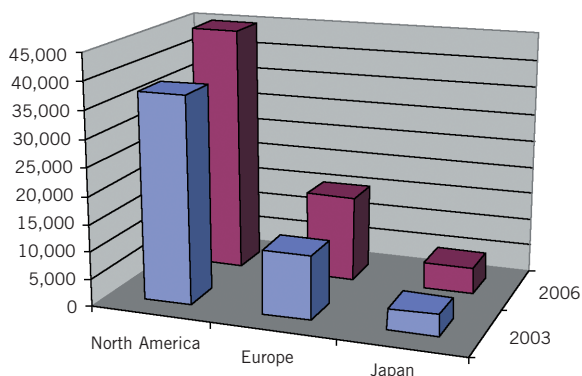


Figure 2: CNS sales in North America, Europe and Japan, together with the growth in CNS sales from the years ended 31st March 2003 to 2006



UNMET MEDICAL NEED

Within the CNS sector there are large areas of unmet medical need, with no recent advances in current therapy or medical research. CNS disorders comprise both psychiatric and neurological disorders. Within the psychiatric area, there are: mood disorders such as depression; psychotic disorders such as schizophrenia; dementia; and cognitive, personality and eating disorders. Let us look at first in detail at treatments available for one of these mood disorders.

Depression

Major depressive disorder is the most common mood disorder, with a prevalence of around five per cent, which equates to 14 million people in the US at any one time (4). A serious illness; it is not just 'feeling blue' but means the patient shows clinically

Table 1: Top five selling antidepressants

Rank	Drug	Maker	2005 US Sales	2003 US Sales	Change
1	Zoloft	Pfizer	\$3.1 billion	\$2.9 billion	+6%
2	Effexor XR	Wyeth	\$2.5 billion	\$2.1 billion	+19%
3	Lexapro	Lundbeck	\$2.1 billion	\$1.0 billion	+110%
4	Wellbutrin XL	GlaxoSmithKline	\$1.5 billion	\$0.1 billion	+1400%
5	Cymbalta	Lilly	\$0.7 billion	–	–
All	Drugs		\$12.5 billion	\$13.2 billion	-5%

Table 2: Top five selling antipsychotics

Rank	Drug	Maker	2005 US Sales	2003 US Sales	Change
1	Seroquel	AstraZeneca	\$2.6 billion	\$1.6 billion	+65%
2	Zyprexa	Eli Lilly	\$2.5 billion	\$3.3 billion	-23%
3	Risperidal	Johnson & Johnson	\$2.3 billion	\$2.1 billion	+9%
4	Abilify	BMS – Otsuka	\$1.5 billion	\$0.4 billion	+321%
5	Geodon	Pfizer	\$0.6 billion	\$0.5 billion	+18%
All	Drugs		\$10.5 billion	\$8.4 billion	+25%

significant distress affecting their ability to function and frequently there may be thoughts of suicide and suicide ideation. Treatment response is limited, with around 30 per cent of patients failing to respond to existing approved antidepressants (5,6), equating to four million patients in the US alone. This is a large number of patients for which there is no therapy that works.

In January 2006, the National Institute of Mental Health (NIMH) announced the initial results of an effectiveness trial in depression (7). Called the sequential treatment alternatives to relieve depression (STAR*D), the trial included 2,876 participants in 41 centres. In Phase I of the study, all patients took citalopram (Celexa) for eight weeks and if there was a response, continued on citalopram until 12 weeks. Around 30 per cent of participants reached remission or virtual absence of symptoms during the initial phase of the study with an additional 10-15 per cent experiencing some improvement. This meant that there were 70 per cent of patients for whom a single treatment with a standard SSRI was not enough for remission.

In the second and subsequent phases, patients were assigned to either a 'switch' phase or an 'augment' phase. In the switch phase, patients received an alternative SSRI antidepressant, or cognitive behavioural therapy (CBT); while in the augment phase patients received either an alternative antidepressant, or CBT in addition to citalopram. The Phase II results announced in March 2006 showed that one in three depressed patients in the augment phase became symptom-free with the help of an additional medication, with one in four achieving remission after switching to a different antidepressant. All the antidepressants tested – sertraline (Zoloft, an SSRI), bupropion, SR (Wellbutrin, a non-SSRI antidepressant) or venlafaxine (Effexor which targets serotonin or norepinephrine) – although representative of different classes of antidepressant, showed

similar results (8). However, that still leaves approximately 50 per cent of patients who did not achieve symptom relief by the end of Phase II, reflecting an enormous gap in medical provision.

Although the results of Phases III and IV of STAR*D are still to be made public, and the full results are yet to be published, it was somewhat disappointing to note that according to the researchers, the switch and augmented treatments could not be directly compared because of the trial design. Therefore, this trial is unlikely to result in guidance as to the optimum treatment regime for depression. Considering the trial cost the NIMH \$35 million, this would appear to be a missed opportunity.

Schizophrenia

Schizophrenia affects one per cent of the population and its prevalence is consistent across races and continents. There are around 2.4 million patients in the US and 1.2 million in Western Europe (9-11). Schizophrenia is one of the most debilitating and

poorly understood mental disorders. It has a devastating effect on those who have the condition, and on their families and friends, both because of the severe effects of the disease and because of misconceptions and stigma associated with it. Schizophrenic symptoms are categorized as: positive (hallucinations, delusions, racing thoughts); negative (apathy, lack of emotion, poor or non-existent social functioning); and cognitive (disorganised thoughts, difficulty concentrating, difficulty completing tasks and memory problems). Symptoms often present in the late teens or early 20s and it is a chronic, life-long condition. There is currently no physical or laboratory test that can absolutely diagnose schizophrenia – a psychiatrist usually comes to the diagnosis based on clinical symptoms after ruling out other conditions that sometimes have similar symptoms.

Early treatments during the 19th and early 20th Century were as diverse as the whirling chair, diabetic induced coma and the hibernation technique. Today, schizophrenia is routinely treated with the use of antipsychotics. 'Typical' antipsychotics were discovered in the 1950s, while newer, 'atypical' antipsychotics were approved in the 1980s. Despite the differences in action suggested by their naming, both types of drugs appear to exert effects via the blockade of dopamine D2 receptors in the brain (12).

In 2005, the National Institute of Mental Health (NIMH) published a study investigating the effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The clinical antipsychotic trials of intervention effectiveness (CATIE) study compared a typical antipsychotic, perphenazine (approved in 1957), with several newer atypical antipsychotics in a double blind study (13). A total of 1,493 patients with chronic schizophrenia were recruited in 57 US sites and randomised to receive olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperidal) or perphenazine.

Ziprasidone (Geodon) was included after its approval. Aripiprazol (Abilify) was not tested as it was approved after completion of the trial. The primary aim was to investigate the differences in the effectiveness of these treatments, with the time to discontinuation being the primary outcome variable.

After 18 months, 75 per cent of patients had discontinued treatment, owing to either inefficacy or intolerable side effects, with 50 per cent having stopped treatment after six months (13). The average time on drug was short: around five months for quetiapine, risperidone and perphenazine, and nine months for olanzapine.

If, however, the time on drug during which patients are achieving a reduction in their symptoms is investigated, the picture is even more dismaying. On average, patients had a response (defined as a reduction in the positive and negative symptom scale (PANSS) of 2 points) for only two months on perphenazine, quetiapine, risperidone or ziprasidone. Olanzapine produced a slightly better result at three months of efficacy. However two to three months of improvement in symptoms was all that was experienced by chronic schizophrenic patients whilst on treatment. So here again is a huge problem for which there is no adequate solution.

In terms of side effects, there were different but serious adverse effects with both the typical and atypical antipsychotics. Older antipsychotics, such as perphenazine, often caused tardive dyskinesia, a distressing movement disorder. The new atypicals, however, cause metabolic disorder and olanzapine in particular causes rapid weight gain, as much as 11lb per week initially and up to 26lbs in a year (14,15). This can lead to type 2 diabetes and heart disease. So it would appear that any increase in efficacy is at the expense of increased side effects.

The authors of the CATIE study conclude that: "patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs. Within this limited range of effectiveness, olanzapine appeared to be more effective than the other drugs studied, and there were no significant differences in effectiveness between the conventional drug perphenazine and the other second-generation drugs." There can be no clearer statement that there is still a huge unmet medical need for schizophrenic patients.

And it is not just schizophrenia and depression. There are many other psychiatric disorders which are inadequately treated with approved medicines or treatment regimes. Conditions such as personality disorders, eating disorders, anorexia nervosa and bulimia nervosa, post partum depression and paediatric depression are all areas where doctors have very little in their armoury of approved medicines with which to treat their patients. These are all remarkably prevalent disorders.

Neurology

In neurology the situation is not much better. Movement disorders such as Parkinson's disease have many treatments for various symptoms but nothing which alters the progression of the disease. Most of these drugs have serious side effects. Recent advances have been made with multiple sclerosis following the discovery of beta interferons, and latterly the monoclonal antibody, natalizumab (Tysabri) developed by Biogen Idec and Elan. Although Tysabri demonstrated superior efficacy in clinical trials in relapsing and remitting multiple sclerosis, slowing both progression and the rate of clinical relapse (16), there have been incidences of progressive multifocal leukoencephalopathy (PML), a rare and usually fatal brain disorder characterised by progressive damage or inflammation of the white matter of the brain at multiple locations. Having been initially approved and then withdrawn from the market, the FDA has since re-approved the use of Tysabri for relapsing remitting multiple sclerosis, but Tysabri monotherapy is generally recommended only for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

THE CHALLENGES

So why have we not progressed very far in the treatment of psychiatric and neurological disorders? Why, despite the billions of dollars spent each year on research, are there still millions of patients suffering untold misery with conditions like schizophrenia, depression and multiple sclerosis? The challenges are many. The biology of these diseases is not well known or understood. For example, the underlying biochemical abnormality in schizophrenia is still not known. There are theories that it relates to an abnormality of dopamine receptor, but the lack of efficacy of dopamine based drugs would suggest that this is not the primary cause.

Animal models and cell cultures are very poor at modelling psychiatric and neurological disorders, yet current drug discovery programmes rely heavily on these tools. If a particular disorder cannot be modelled then new chemical compounds will not be routinely tested. This may be part of the reason why we have reached a barren period for new therapies in areas such as schizophrenia.

The diagnosis is often made by ruling out other conditions and observing symptoms. The rating scales used in these disorders measure the progress of symptoms. These are subjective and not very sensitive to change, for example the doctor is asked to rate the patients' symptom as non-existent (1), mild (2), moderate (3) or severe (4). A movement of one point on a scale may not therefore appear to be much, but this would be clinically significant as it is having a major clinical effect.

Designing clinical trials to test new drugs on patients can also be challenging. Finding treatment naïve patients is very difficult. There are ethical considerations in testing an unproved therapy in a placebo controlled trial and potentially denying a 'proven'

therapy to a patient. However, after reviewing the results of CATIE and STAR*D, which demonstrate the inadequacy of existing treatments, perhaps this will become less of an issue.

THE FUTURE

Is there any cause for optimism? I think there is. Advances in functional magnetic resonance imaging (fMRI) and other specialised imaging techniques, such as spectroscopy and PET scans, allow researchers the chance to visualise not only the structure of the brain but also its function. With these advances researchers can begin to understand the various diseases and the underlying biochemical disorders that cause them. This could then lead to new receptor targets and new therapies. There are a number of fMRI studies currently being undertaken by investigators in the areas of schizophrenia and bipolar disorder which are being funded by the NIMH.

Greater understanding of the disorders may, in turn, lead to greater differentiation within disorders as subtypes are identified. There may be biological reasons why certain subtypes respond to one type of drug and not another, and this may ultimately bring us to personalised medicine. The revision of the *Diagnostic and Statistical Manual of Mental Disorders (DSM – IV)* may start this differentiation with the publication of *DSM – V*, which is expected in five years' time.

The rating scales are gradually being improved. There is increasing use of computerised cognitive testing in various disorders, which has the advantage of being objective and reduces the issue of investigator rating bias. The tests are also very sensitive. This increased sensitivity in testing means that trial times can be reduced and a signal of a drug's effectiveness can be detected in a much shorter timeframe.

CONCLUSION

Mental health and neurodegenerative disorders remain an area of huge unmet medical need. Perhaps it is similar to the position of cancer patients 30 years ago where, because there were so few treatments, very often a cure was not thought to be possible. Therefore no one talked about having cancer – it was referred to in hushed tones, if at all. Then there was a realisation that things had to change, research was funded by governments and large charities and curing cancer became a national priority. As a result, advances were made in medical research and cures for cancer are now a realistic possibility.

Seeking mental wellness should now be a similar priority. The US Government would appear to have recognised the need and hence the funding for 'real world' studies such as CATIE and STAR*D. However, there has to be a next step, which is to improve on these current therapies. Mental illness remains a stigma and in many cases is still not openly discussed, but it is remarkably prevalent. It is debilitating and, whilst not immediately life threatening, causes untold misery and heartbreak to the patients and their families. A 'cure' is at least

decades away, if possible at all in some conditions. However, effective management of symptoms so that patients can return to work or continue to enjoy a high quality of life in their later years should still be a realistic goal. The ultimate goal would be the identification of 'at risk' individuals and the prevention of onset of symptoms. The rewards for a pharmaceutical company which could provide this would be immense. ♦

The author can be contacted at

info@qctr.co.uk

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