A personal approach to treatment is the key to advances in psychiatry

The search for the means to identify patients most likely to respond to specific treatments is the ultimate goal in many areas of medicine, and psychiatry is no exception. Delegates at the Latest Advances in Psychiatry symposium held in London in March heard about work within the fields of dementia, depression and addiction that may bring that goal closer to a reality. Steve Titmarsh reports.

**Therapy for the dementias**

In 20 years there are expected to be at least 1.6 million people in the UK with dementia; double the number there are now. The number of people with the disease is increasing at a greater rate in developed countries than undeveloped nations, and there are estimated to be 35 million cases worldwide. Alzheimer’s disease (AD) accounts for about two-thirds of all cases of dementia.

Professor John O’Brien from the Department of Psychiatry at the University of Cambridge described some of the developments in diagnostic criteria, drug treatment targets and modifiable risk factors that may offer patients with dementia hope for the future.

Diagnostic criteria for AD have been developed by consensus groups (DSM and ICD have never been particularly strong in this area). However, while these criteria are sensitive they are not very specific, so they fail to exclude the wide range of other dementias now recognised: Lewy body dementia, frontotemporal dementia, etc. Neither do they recognise the developments in genetics, brain imaging and other biomarkers of disease (see Table 1). In addition, they focus on late stage disease so early diagnosis, which is being recognised as increasingly important to improve treatment outcomes, is not possible. For these reasons, significant changes to diagnostic criteria, first developed in the 1980s, are being proposed to include aspects such as biomarkers.

Current drugs for AD mostly focus on the cholinergic loss seen in AD: donepezil, rivastigmine and galantamine are cholinesterase inhibitors and memantine is an NMDA receptor antagonist. It can be argued that clinical data show that these drugs produce relatively modest symptomatic improvement. However, the re-analysis of data from the Nordic study1 by NICE indicated that the greatest benefit of treatment was seen among patients classified in other studies as non-responders, who declined at a much lower rate when continued on treatment than those non-responders from whom treatment was withdrawn. Indeed, it appears that those who decline most rapidly are the ones who gain most benefit.

However, in vascular dementia there is a small but significant effect on cognition but no effect on global outcome or behaviour. In the case of frontotemporal dementia, the drugs can make symptoms worse. Similarly, in mild cognitive impairment there is no evidence of significant benefit. These aspects underline the importance of accurate diagnosis. In addition, dementia is a progressive brain disease so treating at an early stage could help preserve as much function as possible.

| Medical temporal lobe atrophy on MRI scan |
| Tempo-parietal hypoperfusion on SPECT or hypometabolism on PET scan |
| Amyloid on PET scan |
| CSF low beta-amyloid |
| CSF high tau / p-tau |

**Table 1.** Five biomarkers for Alzheimer’s disease

The amyloid cascade hypothesis is currently the dominant theory of pathological change in dementia and this postulates that altered amyloid metabolism and production precede the appearance of clinical symptoms. It was this theory that led to the development of a vaccine in the 1990s designed to prevent plaque formation. Further antibodies have been produced but have so far shown little success in improving cognition or activities of daily living. However, there is an indication that if given in the early stages there may be a benefit, suggesting again that more specific diagnosis to tease out particular patient groups and allow early treatment may help clinicians achieve optimum results from treatment.

Risk factors for developing dementia are becoming better understood and some of these parameters, such as exercise, blood pressure and cholesterol, are also being studied, particularly
in terms of effects at the early stages of disease.

**Depression still showing resistance**

Professor Sidney Kennedy from the University of Toronto, and President of the International Society for Affective Disorders (ISAD), told delegates that only around half of patients with major depressive disorder respond to first-line treatment and even after four treatments around a third of patients will still not respond. Part of the problem, Professor Kennedy said, is that psychiatrists are using a homogenous treatment for what is almost certainly a heterogeneous group of disorders. Clinicians are also hampered by the fact that there are no objective biological measures on which to base diagnosis, prognosis or treatment selection. If subtypes of major depression could be identified, it might be possible to better tailor treatment for individual patients.

As our understanding of the complex interplay between factors such as stress, inflammation and hormonal influences on the biochemical changes that are seen in depression becomes clearer, so the potential individual markers – neurotransmitters, genetics, proteomics and neurocircuitry, for example – can be identified. Those markers could then be used alongside clinical symptoms to allow clinicians to better tailor treatment to individuals. Equally, an improved definition and differentiation of the symptoms could go some way to better identify patients who might respond to a particular treatment.

Anhedonia is an example of a marker that may help guide clinicians to more targeted treatment. Anhedonia has been shown to reflect a blunted dopamine response to rewarding stimuli, particularly in the mesolimbic and mesocortical tracts, areas known to be abnormal in depressed patients. When venlafaxine is compared with agomelatine, which is known to have an effect on the dopamine system, the two show similar efficacy as measured by standard depression and anxiety rating scales but agomelatine has a greater effect on anhedonia than venlafaxine as measured on the Snaith-Hamilton Pleasure Scale (SHAPS). Professor Kennedy sees the challenge in depression as providing rapid diagnosis and the right (tailored) treatment. He is hopeful that the diagnosis and treatment process for depression will eventually resemble that for breast cancer at the hospital in which he works in Toronto, where treatment is based on the results of tests such as a mammogram, biopsy and blood tests with an answer within five to seven days. "So if it can be done in breast cancer it can be done in any of the psychiatric conditions," Professor Kennedy remarked. It may be a while before that can be achieved but it has to be the ultimate aim, he added.

The Canadian Biomarker Integrated Network for Depression (CAN-BIND) has started to work towards that goal with a study involving escitalopram. Patients will undergo neuroimaging and molecular data collection alongside clinical examination during the study in an attempt to compare the results in responders and non-responders. The aim is to identify possible markers that could be used to help decide whether escitalopram is the best choice of antidepressant in an individual.

**Addiction: pharmacology and policy**

Professor David Nutt from Imperial College, London, told the symposium that, including alcohol and tobacco, addiction is the biggest business in the world. Moreover, the illegal drug trade is the second biggest business in the world after oil.

The cost of addiction to the UK economy is around £50 billion a year with the biggest killer being tobacco, which is associated with around 80 000 deaths a year, followed by alcohol (around 7000-8000 deaths a year) and opiates (1200 deaths a year). The drugs that the government gets hysterical about – cannabis and MDMA – kill almost no one, Professor Nutt said. ‘One of the most chilling statistics I have met in medicine is that alcohol is now the leading cause of death in men between the ages of 15 and 65 years. And we don’t do anything about it.’

Unlike deaths from diseases such as diabetes, cancer, heart disease and stroke, which have fallen over the last 30 years largely due to medical intervention, deaths due to liver disease have risen two and a half times. Eighty per cent of that rise in liver deaths is due to alcohol and the rest due to hepatitis. Within 10 years, liver disease will kill more men than heart disease. ‘To deny that as a public health emergency is truly objectionable,’ Professor Nutt said.

Addiction is an amalgam of social, drug and personal biological factors and understanding...
addiction involves understanding many aspects of human behaviour. For some it provides pleasure, many people use illicit drugs to reduce suffering, and for some it gives meaning. But Professor Nutt contended that what is known about the use of drugs in relation to biological principles can be summarised on one slide (see Table 2).

One of the perplexing aspects of addiction is that the most problematic substances are actually difficult to become addicted to – people do not usually like tobacco when they first try it, for example – they have to work at getting addicted, Professor Nutt commented. But we do know that reducing use reduces harm. For example, a 50 per cent reduction in alcohol consumption (from 100g to 50g of alcohol a day) produces an eightfold reduction in harm. That’s why minimum pricing would have such a big impact on health, Professor Nutt said.

Of the newer approaches to reducing addiction, Professor Nutt sees unlearning addiction as a promising area. Fear learning in animals never goes away, but it can be overwritten with another behaviour that can be facilitated by increasing glutamate function. This can be achieved using a drug such as d-cycloserine (originally used in tuberculosis), which is patented in the USA as an augmenting drug for psychotherapy to help people overcome phobic states. The question is, could it also be used to overwrite non-addictive behaviour over addictive behaviour? Some animal and human studies suggest that this may be possible. But there appears to be a lot of variability in response to d-cycloserine, so Professor Nutt suggests that it should be used only in those patients showing the most conditioning.

Endorphins are among other drug targets that hold some promise for tackling addiction. The endorphin system is targeted by opioids: mice with the mu receptor knocked out do not become addicted. There is also some evidence from PET studies that craving for alcohol correlates positively with the number of mu receptors. That may explain the interest in the potential for opiate antagonists to be used for alcohol abuse. For example, nalmefene, a mu receptor antagonist recently licensed in Europe as an aid to drinking cessation, can be used by alcohol-dependent people when they feel they are going to lose control. So it helps to reduce the number of heavy drinking days.

Then there is the GABA system, which is probably the primary target for the effects of alcohol in the brain. It is the major inhibitory system in the brain and the one that benzodiazepines target. Alcohol binds to a different site on the GABA$_A$ receptor from benzodiazepines, so there is a theoretical possibility that an antagonist could be used to prevent the effects of alcohol in the brain.

Expression of the different GABA$_A$ receptor subtypes is region specific suggesting they have different functions. An alpha5 subtype inverse agonist has been shown to reverse memory loss associated with being drunk. In theory, Professor Nutt explained, that suggests it might be possible to develop inverse agonists that would remove the ataxic effects, the aggressive effects and the liking associated with alcohol and thus reduce the harms associated with the drug.

However, Professor Nutt argued, more intriguing is the idea that ‘given we know alcohol is so toxic and we know how it works, why not make a safe version. It’s dead easy – we just make subtype-selective GABA drugs, which have the real advantage that we have antidotes. So people could go out, have their cocktails, have fun, take an antidote and drive home safely.’

‘Modern neuroscience gives us a safe alcohol; modern regulations don’t allow us to use it. So we are trapped in this bottle of using alcohol as our primary intoxicant because regulations don’t allow us to produce a safer one. It’s absurd, it’s antiscientific and it’s got to change.’

References