Complexities and conundrums in mental health

Delegates at the 16th Latest Advances in Psychiatry Symposium held in London in March 2017, were treated to a cornucopia of data and insights from the latest research into a range of psychiatric illnesses. Psychiatry is fully intent on proving its worth with brain imaging, genetics, and many other sophisticated clinical research techniques being used to demonstrate its interventions have value. Steve Titmash sat back and took it all in and here reports on some of what intrigued him most.

Professor Declan Murphy, Director of the Sackler Institute for Translational Neurodevelopment and Head of Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, London, reviewed some of the work his team are doing to identify targets for the treatment of autism including a new approach through collaborations across Europe between scientists and clinicians who work in parallel rather than in a sequential way, which is the traditional approach. The result is that cellular assays, animal models, translational science and clinical trials can run almost simultaneously, which it is hoped will produce better results more quickly.

Autism is associated with high levels of co-morbidity, for example around 75% of individuals with autism have depression or anxiety, high rates of epilepsy and of attention-deficit hyperactivity disorder (ADHD). Autism is also associated with a significant reduction in lifespan: people with a lower IQ who have autism tend to die around 20–30 years earlier than healthy individuals, while those with autism and a normal IQ die about 15 years early. That shortened life expectancy is due to increased risk of suicide or seizure. So, it is disorder that all psychiatrists should have an interest in, he argued.

There are no effective treatments for the core symptoms of autism. There are drugs for the associated symptoms such as irritability, sleep, depression anxiety, etc. However, there does not appear to be a consistent approach as to how these drugs are prescribed for people with autism.1

Autism is known to have strong genetic links so part of the work Professor Murphy’s team is doing is to map genetic variants onto a smaller number of molecular pathways and then onto a smaller number of biological pathways and then onto brain regions and circuits to characterise the clinical phenotype and to help identify homogeneous groups of individuals who might respond to treatment.

The second approach is to carry out longitudinal studies starting in infancy through childhood and into adulthood looking at high risk individuals and attempting to identify biosignatures to bring disparate groups of people into more biologically homogeneous groups and identify targets for therapeutic intervention.2-4

Individuals with autism exhibit different brain activity on MRI compared with normal controls. When the brain serotonin in individuals with autism is reduced those differences disappear. In a proof of concept study tianeptine – a selective serotonin reuptake enhancer (SSRE) that depletes brain serotonin – has been shown to normalise brain activity in individuals with autism.5,6 The next stage will be to test the compound clinically but only in individuals who have raised blood serotonin and also have brain function differences at baseline, so as to enrich the sample, because the difference would be undetectable using regular clinical trial techniques, Professor Murphy explained.

However, prevention is better than cure. So studies are taking place in babies at risk of autism because their mothers have already given birth to a child with autism. Their chances of developing autism are around 25–30%. The infants are examined for differences in brain biology and whether those differences predict their ultimate clinical outcome. Researchers are looking for a predictor in order that the babies can be given a behavioural intervention that has been shown to be effective. So babies are exposed to an emotional sound experiment in which they lie sleeping in a scanner while listening to a non-human sound such as pouring water or something mechanical and then human sounds that are positive, neutral or negative. Babies are known to respond to human sounds while sleeping, especially emotional sounds. They respond more to human than non-human sound in terms of brain activity. However, babies at risk of autism appear to respond more to non-human than human sounds and they respond
less to human sounds than babies not at risk of autism. There are tentative indications in this early work that these responses may be predictive of babies developing autism. Similar work in babies born to mothers who are depressed seem to show the opposite response – they are hypersensitive to emotional sounds, particularly negative emotional sounds.

**Potential role of glutamate and GABA**

It appears that the balance between the excitatory glutamate and inhibitory GABA neurochemical systems in the brain is crucial for healthy functioning. A rodent genetic model of autism shows differences in specific parts of the glutamatergic system, which can be reversed when the deleted gene in the rodent model is re-expressed. There are very preliminary indications that similar effects are replicated in human brains and riluzole appears to have some effect to modulate the functional connectivity in the brain. It may be possible to detect GABA system abnormalities in the clinic with a paradoxical motion perception test.8,9

Foetal neuroimaging is allowing researchers to measure brain glutamate and GABA in foetuses at 30–34 weeks gestation. Initial work looking at glutamate in the foetus, neonate and a few months after birth show that high risk babies have significantly different levels to those seen in ‘normal’ foetuses and neonates.

A clinical trials network has been established across Europe to further examine these ideas.10 The aim will be to target interventions at much more homogeneous groups of people. And pharmacological interventions will be combined with educational, family, psychological and other non-drug interventions.11

**Latest advances in the treatment of obsessive compulsive and related disorders**

Naomi Fineberg, consultant psychiatrist at Hertfordshire Partnership University NHS Foundation Trust, reviewed some of the latest work in obsessive-compulsive disorder (OCD).

Evidence is emerging that for the best outcomes OCD needs early vigorous treatment and treatment needs to be in place for a relatively long time as the disease tends to persist. Evidence-based treatment options in OCD are limited so a greater understanding of the brain circuitry associated with OCD and new treatment strategies are needed along with, ideally, outcome predictors.

Professor Fineberg considered whether it is possible to predict outcomes for individuals being treated for obsessive compulsive disorder. For example, there is some evidence that early improvement during treatment with a selective serotonin reuptake inhibitor (SSRI) may predict treatment response. For example, one study showed that a >= 20% reduction in baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at four weeks was the best predictor of treatment response (>=35% Y-BOCS improvement) at 12 weeks (OR = 1.05, p<0.0001): 55% who showed early improvement were responders at 12 weeks. Whereas only 20% of patients who did not improve at four weeks were responders after 12 weeks.12 A study of 213 adults with DSM-IV OCD followed up over five years showed that 39% achieved either partial (22.1%) or full (16.9%) remission. (Although Professor Fineberg noted that even patients in remission from OCD still have significant symptoms – it does not represent full recovery). Harm-related obsessions were nearly twice as likely to remit (p<0.05). Other positive predictors of remission included lower OCD severity (p<0.0001) and shorter duration of illness (p<0.0001) suggesting early intervention may be important. Primary hoarding was significantly less likely to remit (2 of 21 participants; 9.5%). However, 59% of participants who remitted subsequently relapsed. Participants with obsessive-compulsive personality disorder were found to be more than twice as likely to relapse (p<0.005) and participants were more likely to relapse if they experienced partial remission than those who achieved full remission (70% versus 45%; p<0.05).13 And children seem to have better outcomes with 80% achieving partial (53%) or full (27%) remission at three years.14 Twenty-one per cent of those who remitted subsequently relapsed. That again suggests earlier intervention in the course of illness predicts improved outcome.

For patients who do not respond to SSRI treatment there are not too many options. They include switching SSRI or increasing the dose15; move to clomipramine, or augmentation with an antipsychotic16.

Conceptualising symptoms and cognitive deficits as disordered structure, connectivity and function in large-scale neural networks in the brain may provide some clues as to potential new targets for treatment of OCD.17 And a number of small-scale randomised placebo-controlled trials have shown efficacy for a range of drugs that might be repurposed for use in OCD.18

Somatic treatments such as transcranial magnetic stimulation19,20 and deep brain stimulation21 are showing some potential but remain experimental. Ablative neurosurgery is an intervention of last resort for severely ill patients who have not responded to other treatments.22

**Body dysmorphic disorder**

Professor David Veale, a consultant psychiatrist and visiting professor in
cognitive behaviour therapies at the Institute of Psychiatry, Psychology and Neuroscience, King’s College London, explained that body dysmorphic disorder (BDD) is thought to affect around 2% of adults in the community but is not seen that frequently in general psychiatry. Prevalence in private psychiatric inpatient units is estimated at around 5% rising to around 10% in cosmetic surgery / dermatology services. It tends not to be picked up in consultations without a screening question.25

Onset is usually during adolescence but it takes around 10 years before people seek treatment. High rates of comorbidity with depression, social phobia or obsessive-compulsive disorder, for example, are seen. Levels of attempted suicide are around 25%24 and data from the USA show around 0.3% die by suicide each year.25

BDD attracts a lot of stigma and trivialisation. A low level of awareness, the fact that patients tend to present to dermatologists or cosmetic surgeons, the secretiveness that tends to surround the condition along with lack of research and inappropriate treatment – with antipsychotics or counselling, for example – means that BDD can often go untreated.

People with BDD spend more than an hour each day preoccupied with perceived defects or flaws that others do not notice or view as slight. They are extremely self-consciousness with ideas or delusions of self-reference. They may be preoccupied with any part of their body but predominantly their concerns involves the face. They typically exhibit repetitive behaviours to verify, camouflage or repair perceived ‘defects’ and this is where there is some overlap with OCD. These behaviours include:

• Mirror gazing
• Checking (touch), inspect or measuring
• Comparing self with others or old photos
• Grooming, combing, straightening, plucking or cutting hair
• Skin cleaning, picking, face peel/scrubs, bleaching
• Cosmetic procedures, dermatology.

These behaviours can take their toll on everyday life prompting people with BDD to avoid public and social activities; they are often single or have discordant relationships; they may be unemployed or be at an occupational / academic disadvantage or refuse to go to school, and they can build up debt as a result of undergoing cosmetic procedures.

A simple screening question asked of patients with depression, substance abuse, social phobia or obsessive-compulsive disorder – such as ‘some people are very bothered by the way they look. Is that a problem for you?’ – may help identify potential BDD cases in the clinic. Those who answer ‘yes’ could then be asked further questions:

• What concerns do you have about your appearance? (Is there a discrepancy between their perceived defect and actual self)
• On a typical day, how many hours a day is your appearance at the forefront of your mind?
• Do you have to check your appearance a lot?
• Is it very distressing / shameful for you?
• Does it interfere with relationships, or your ability to study/ work?
• Does it interfere in your social life?

Observations that might suggest a diagnosis of BDD

• Wearing a hat, sunglasses, baggy clothes, scarf (inappropriately)
• Heavily made up
• Head shaven
• Long hair to hide the person’s face
• Sitting in a particular way (to hide the worst side)

• Person finds it difficult in make eye contact
• Scars from skin-picking.

Professor Veale said that ICD 10 is unhelpful for BDD because symptoms may be part of hypochondriacal disorder, schizotypal disorder, delusional disorder, or other persistent delusional disorder. In ICD11 BDD is likely to be classified with obsessive-compulsive disorders.26

Management

NICE guidelines recommend CBT for mild functional impairment in BDD and a course of SSRI or more intensive CBT for moderate cases, while patients with more severe functional impairment may need a combination of the two.27

Treatment with 12 weekly sessions of CBT was found to be more effective than anxiety management once a week for 12 weeks in a small (n=46) randomised controlled study.28 Follow up over one to four years of patients treated with CBT showed that just over half (11/39;56.4%) were in partial remission but only around a quarter (11 of 39;28.2%) achieved full remission.29

Professor Veale noted that this is a difficult group to treat but that optimising the length of treatment – probably to 20–24 sessions of CBT – and maintenance follow up as well as treatment of depression may lead to improvements in outcomes. Fluoxetine for 12 weeks has been shown to have a similar effect to CBT with around half of patients responding (defined as 30% or greater reduction on the main outcome measure – the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS).30

Unlike obsessive-compulsive disorder antipsychotic augmentation is not effective for BDD.31

Patients themselves often express a preference for cosmetic
surgery. And some procedures – mammoplasty, labiaplasty and pin-naplasty, for example – may be safe, possibly because people know what changes to expect. However, commonly used procedures such as dermatology and rhinoplasty seem to be associated with the worst levels of satisfaction.

Diagnosis of BDD can make satisfaction with surgery unpredictable: many procedures are unlikely to alter symptoms of BDD or focus of the preoccupation may change. At worst, cosmetic surgery may result in patients’ preoccupation and handicap becoming worse. However, if a patient is determined to have surgery, Professor Veale’s team will usually delay therapy.

Weight gain and its management in people with psychosis

Professor Stephen Cooper, Professor Emeritus Queen’s University Belfast, reviewed strategies for the management of weight gain in people with schizophrenia, based largely on the British Association for Psychopharmacology (BAP) guideline on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment.

At the age of 20 years, life expectancy is 22.5 years shorter for people with schizophrenia compared to the general population. This increased mortality is particularly due to cardiovascular disease. People with schizophrenia have an increased prevalence of important risk factors for cardiovascular disease, such as smoking, obesity, diabetes, dyslipidaemia and alcohol misuse. Driving factors for weight gain are:

- Poor lifestyle and physical inactivity
- Effects of antipsychotics, e.g. increased risk of weight gain with many; interference with insulin secretion with some
- Pharmacogenetic differences between individuals
- Monitoring risk factors in people with schizophrenia is an important part of their management but the evidence suggests that only around 30% of patients have all five of the most important risk factors monitored. BAP guidelines recommend that the following should be measured before starting an antipsychotic and then at appropriate intervals: BMI; glucose control (using fasting / random glucose in the first 12 weeks followed by HbA1c long-term); lipid profile at 12 weeks, six months and then annually; blood pressure at 12 weeks, six months and annually, and tobacco smoking and alcohol use should be enquired about at all available opportunities.

Lifestyle interventions are recommended as the first-line approach in NICE guidelines on schizophrenia and obesity. These intervention programmes include some or all of:

- Improved eating behaviour
- Improved quality of diet
- Reduced energy intake
- Increased physical activity.

They may employ group and / or individual sessions and may involve elements of counselling or cognitive approaches to help individuals understand their eating behaviours. Data from general population studies show that diet is the most important component of interventions to reduce weight.

Evidence indicates that lifestyle intervention is effective in helping people with psychotic disorders treated with antipsychotics lose around 3kg weight and reduce their BMI by about 1 kg/m². However, there is no clear evidence regarding the optimal frequency, duration or intensity of the interventions, and the effects of lifestyle interventions are not permanent for everyone, so booster sessions may be useful.

Data from a comprehensive indirect meta-analysis suggests that switching antipsychotic treatment to a drug with a lower propensity for weight gain may be a useful strategy. However, only four RCTs have directly examined switching specifically for the purpose of weight reduction. These support switch from olanzapine to aripiprazole or quetiapine. When considering a switch clinicians must balance possible benefit with risk of inducing clinical relapse, and bear in mind that the ‘new’ medication may also induce weight gain in some people.

The use of adjunctive aripiprazole seems to be effective for some patients whose weight gain has occurred when taking clozapine or olanzapine. In three randomised controlled trials where aripiprazole was added to clozapine or olanzapine patients lost around 2–2.5kg compared with placebo. However, this combination is off-label prescribing.

Metformin has shown to assist weight loss in the people at high risk of diabetes in the general population and short-term trials in people with psychosis have shown that metformin can have a modest effect to attenuate antipsychotic-induced weight gain, though this is off-label use. A meta-analysis showed a mean weight loss of around 3.5kg in studies with follow up of 12 to 24 weeks. A study by De Silva et al. in 66 South Asian patients over 24 weeks showed a mean weight loss of 2.5kg. Impaired renal function can lead to accumulation of the drug and lactic acidosis so it is contraindicated in patients with an eGFR <30mL/min and it reduces vitamin B12 absorption in some: 7% of patients taking it may develop deficiency over four years.

References

Can early improvement be an ...?