Optimising therapy for schizophrenia and depression: old and new solutions

Schizophrenia and depression were in the spotlight at the Latest Advances in Psychiatry Symposium XI held in London in March 2012. Greater understanding of the mechanisms underlying these diseases are helping clinicians develop strategies that offer hope, particularly to patients who are treatment-resistant. Steve Titmarsh provides a summary of three of the main lectures at the meeting.

Schizophrenia

Dr Peter Talbot, Associate Director of Wolfson Molecular Imaging Centre and Senior Lecturer at the University of Manchester, discussed some of the mechanisms implicated in the pathogenesis of schizophrenia and how research may help shed some light on optimising therapy for individual patients. Understanding the biological processes that lead to symptoms of schizophrenia may also help in the quest to develop newer medicines for this devastating disease.

In patients with schizophrenia, abnormally elevated dopamine (DA) function has been found in the striatum, particularly in associative regions, whose function is linked with learning, habituation, memory attention, motivation, emotion and volition. Excessive dopamine release is positively correlated with positive symptoms and with good treatment response to antipsychotic drugs. In fact, patients with first episode schizophrenia show elevated striatal DA function up to three years before diagnosis, at a time when they have only prodromal symptoms, while DA function is normal at baseline in those people with similar symptoms but who do not subsequently convert to schizophrenia during the same time frame. 4 In addition, inadequate DA in the frontal cortex is associated with deficits in cognitive function, eg working memory.

Henn commented in the American Journal of Psychiatry in 2011: ‘These data strongly support the hypothesis that dopamine overactivity, specifically in the striatum, is strongly associated with the emergence of psychotic symptoms and that overactive dopamine release in the striatum is the proximal cause of psychotic symptoms. This provides the strongest evidence to date that dopamine overactivity is essential for psychosis.’

He added: ‘The Howes et al study, 4 perhaps combined with anatomical regression data or EEG spectral power studies, may present us with a reliable test battery for predicting conversion to active schizophrenia.’

That kind of ‘biomarker’ could help clinicians decide which patients are most likely to benefit from in the prodromal phase because they could target those most likely to convert to the full syndrome, Dr Talbot commented.

However, the dopamine overactivity is no longer thought to be the primary abnormality. Glutamate – the most abundant excitatory transmitter in the CNS – may be the key to the dopamine dysregulation that is seen in schizophrenia. Currently, NMDA receptor hypofunction is a favoured model for positive, negative and cognitive symptoms of schizophrenia. NMDA receptor dysfunction appears to explain more of the symptoms than DA dysfunction does.

Various strategies to correct glutamate dysfunctions have been tried: for example, inhibition of the reuptake of glycine into the glial cells by blocking the glycine transporter can increase synaptic levels of glycine and activity at the glycine receptors and improve NMDA receptor function. Glycine transporter-I inhibitors (glial GLYT-1), eg bitopertin, are currently in clinical trials for positive and negative symptoms.

Dr Talbot conjectured that if these trials are successful, clinicians in the future could be using glutamate system drugs to treat positive and negative symptoms of schizophrenia as well as cognitive symptoms and that the current antipsychotics that directly target the DA system may be used only as top-up treatments to manage stubborn positive symptoms.

References
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4. Howes OD, Bose SK, Turkheimer F, et al. Dopamine synthesis capacity before onset of psychosis: a prospective (18F)-DOPA PET imag-

ECT for depression

Ian Reid, Professor of Mental Health and Clinical Lead for Psychiatry at the University of Aberdeen, challenged the idea that the use of ECT was declining – at least in Scotland, where just over 500 episodes were recorded in 2010 compared with just under 500 in 2006. He argued that ECT is one of the most effective treatments for depression in modern medicine; for example, Scottish data show a response rate of about 75-85 per cent – better than that of antibiotics for urinary tract infection, appendectomy for acute right fossa pain, etc.

In Scotland, bilateral, bitemporal ECT is the standard treatment modality, although there has been some discussion that unilateral ECT should have advantages in terms of effects on cognitive function. However, a recent study by Kellner et al. confirmed that there is no advantage in using unilateral ECT. Indeed, Professor Reid commented, the evidence so far points to the idea that the antidepressant and cognitive effects of ECT cannot be dissociated.

Resting state functional MRI has revealed that people with depression have increased connectivity between brain areas known to be associated with mood disorder compared with matched controls. Professor Reid likened this to a ‘pathological hot wiring of activity in the brain that is responsible for depression’. Professor Reid’s group imaged a group of nine patients before and after ECT to measure activity in all parts of the brain and found a highly restricted lateralised reduction in connectivity in the left dorsolateral prefrontal cortex. This finding came as something of a surprise. But the more interesting question is: which areas of the brain have had their communication with that area (which plays a part in perception of mood, cognitive function, etc.) reduced? Professor Reid’s group have shown that the areas involved constitute a map of the neuroanatomy of depression. So ECT appears to be working by reducing the hyperconnectivity seen in patients with depressive symptoms that is not apparent in ‘normal’ controls.

References

Treatment-resistant depression

Professor Phillip Cowen, Head of the Psychopharmacology Research Unit at the University of Oxford, discussed the problem of treatment-resistant depression and therapeutic approaches that hold out hope for patients. The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study showed that just over a quarter (28 per cent) of 2876 patients with depression (80 per cent of whom had chronic or recurrent depression) achieved remission after 14 weeks’ treatment with citalopram at an average dosage of 42mg daily. However, dual therapy with mirtazapine from the outset may achieve better results, commented Professor Cowen. In a study by Blier combination treatments produced better remission rates than monotherapy. For example, 58 per cent of patients taking venlafaxine plus mirtazapine achieved remission after 42 weeks’ treatment (n=26) compared with 25 per cent in the group taking fluoxetine (n=28). If this result can be replicated, it could have a big impact on first-line treatment.

Newer antidepressant drugs are better tolerated and safer in overdose which is important, but meta-analysis does show the value of older drugs such as amitriptyline. So there may be a case for using these older drugs in treatment-resistant cases.

In Professor Cowen’s experience, it is worth persisting with pharmacotherapy, particularly in patients who have shown good premorbid personality and who have functioned well socially and occupationally. However, it should also be borne in mind that the chance of achieving remission decreases as the number of failed treatment trials increases.

There is growing evidence that some atypical antipsychotic drugs may be helpful in treatment-resistant depression. The doses used in this indication are often slightly too low to block dopamine receptors effectively, suggesting they may be acting via 5HT2 receptor blockade. In psychotic depression, of course, it is important to give high enough doses of the antipsychotic to control psychotic symptoms also.

Deep brain stimulation (DBS), already established for treating Parkinson’s disease, is now being tested in patients with refractory depression as an alternative to psychosurgery. Success with DBS will depend on the neurocircuitry of depression being known, and progress in this area is currently
being made. Three-year data suggest that patients who initially respond to DBS continue to do so. Wound infection appears to be the most common adverse effect.

Ketamine, an NMDA antagonist licensed as an anaesthetic, has also shown some promise. The drug has been shown to provide some temporary relief in treatment-resistant unipolar and bipolar depression (for up to seven days after a single dose in one study of 18 patients).

Finally, memantine, which also works at the NMDA receptor site but with a different mode of action, is being investigated as a drug that may offer a more long-lasting antidepressant effect than ketamine.

References