Excellence in psychiatry: hopes and hubris

Over-confident leaders taking excessive risks, the benefits of early treatment of bipolar disorder, serendipity in the quest for an Alzheimer’s disease treatment along with strategies to minimise harm from drug therapy all played a part in the annual meeting for psychiatrists that is the Latest Advances in Psychiatry Symposium. Steve Titmarsh went along to the Royal College of Physicians in London, in March to find out more.

Hubris syndrome

The keynote lecture was given by Lord David Owen. He reviewed what he had been writing about hubris syndrome focussing on diminished empathy and unbridled intuition and relationships between the two. Neither is mentioned directly in the 14 signs and symptoms of hubris syndrome (Table 1) which Lord Owen developed with Jonathan Davidson in 2009.1 He considered how his work might develop in future in the hope that he would encourage greater research into hubris syndrome.

Lord Owen said hubris is an occupational hazard for political, military and business leaders. Company CEOs may be prone to taking excessive risk and rely more on intuition than rational thought. And even though hubristic behaviour may well have played a part in the downfall of huge international companies with significant impact on national economies, there has been little research into the causes of the behaviour, neurobiological or other, let alone potential treatment.

Although risk taking can be destructive, stifling it completely and taking a safe approach to business will affect a capitalist economy; so there is a fine balance to be struck. Indeed, risk exists in life and probably has an important role to play, but it is how risk is handled that is important, Lord Owen said.

Lord Owen set up the Daedalus Trust (www.daedalustrust.com) to support research into and raise awareness of personality change associated with the exercise of power and the effect on decision making. However, although he acknowledged the importance of medicine and medical treatment, Lord Owen felt he had to resist the medical model as a sole answer to dealing with hubris syndrome as he feels strongly that a more holistic approach is needed, involving all facets of human nature, if an answer to containing and constraining those who develop hubris syndrome is to be discovered.

Early intervention in bipolar disorder improves outcomes

It is somewhat surprising that, compared with schizophrenia, there are few data on early intervention in bipolar disorder, indeed, Professor Lars Vedel Kessing, Professor of Psychiatry at the Psychiatric Centre Copenhagen and University of Copenhagen, knew of only one study. Early intervention has been shown to result in better outcomes in schizophrenia and Professor Kessing said there are seven indications from observational studies that early intervention in bipolar disorder may improve the course and outcome of the illness:

1. The risk of recurrence increases with every new episode^2^.
2. Delay to first treatment is associated with more time depressed, greater severity of depression, greater number of episodes and more days of ultrarapid cycling^3^.
3. Response to lithium monotherapy decreases with the occurrence of multiple prior episodes^4^.
4. The rate of response to lithium in monotherapy is increased when started at first psychiatric contact rather than at later contacts. The same is true for starting lithium at the first ever manic episode^4^.
5. Mood stabilisers prescribed for bipolar disorder may have neuroprotective properties^5,6^ so early intervention may prevent progression.
6. The prevalence of cognitive dysfunction may increase with affective episodes and the risk of dementia seems increased by two to three times over ten to 20 years for patients with bipolar disorder compared with the general population^7^.
7. Patients may profit from psychoeducation before potential cognitive disturbances may occur during the long term course of illness^8^.

Professor Kessing and colleagues have tested whether treatment in a specialised outpatient mood disorder clinic, combining optimised pharmacological treatment with group psychoeducation among
patients discharged after their first, second or third hospitalisation for bipolar disorder, is better than standard psychiatric outpatient treatment in the early course of bipolar disorder.9 Patients were followed for up to six years. Time to readmission was significantly longer among patients who received specialised care (n=72) compared with patients who received standard care (n=86) (HR 0.60, 95% CI 0.37–0.98; p=0.043). Professor Kessing said that represented a substantial effect of specialised care. In the early days after discharge when the risk of suicide, for example, is 240 times greater than among the general population, the number of patients who had specialised care relapsing was less than among those treated with standard care. After two years patients who received specialised care reverted to standard care. However, Professor Kessing pointed out the relapse rate remained lower than among patients who received standard care from the beginning of the study. That is in contrast to what is seen in early intervention in schizophrenia.10

Further analysis of Professor Kessing’s study revealed that total time spent in hospital was significantly less for patients who received specialist care compared with those who received standard care (median 33 days vs 49 days; p=0.01). Patients who had received specialist care showed greater adherence to mood stabiliser (59% vs 32.4%; p=0.001) and antipsychotic medication (59.5% vs 34.9%; p=0.01) as reported by patients at two years.

In economic terms the specialist service makes sense too. Analysis of two-year treatment costs show that the total direct net cost (including saved hospital beds) was 3,194 Euros less per patient in the specialist service compared with standard care, or 11% of the cost of standard care.

Lastly, Professor Kessing said there is a general belief that young patients (under 25 years of age) with bipolar disorder are difficult to treat. However, Professor Kessing’s study shows that outcomes were best for patients aged 18-25 years treated in the mood disorder clinic (n=29; HR 0.33, 95% CI 0.10-1.07; p=0.064).11

Will we ever have effective dementia treatments?
One in three people will die with dementia and virtually everyone will be touched by it some way, Professor Robert Howard, Professor of Old Age Psychiatry and Psychopathology at King’s College, London, told the meeting.

In mild, moderate and severe Alzheimer’s disease cholinesterase inhibitors offer modest improvements in cognitive function and activities of daily living (ADL). But
the drugs have no effect on overall decline. And when the drugs are stopped there is quite a profound withdrawal effect involving worsening cognition and function and earlier nursing home placement.

The evidence for treatment of behavioural symptoms and psychosis in AD is not as good as that for cognition and ADL. Only risperidone has an evidence base to show that it is convincingly superior to placebo in treatment of agitation, aggression and psychosis in AD. Indeed, risperidone is the only drug that has a licence for treatment of aggression in AD in Europe. And once an antipsychotic is stopped psychosis returns.

Disappointingly the cholinesterase inhibitors and memantine are ineffective in treating behavioural symptoms and psychosis in AD.

Sadly, despite knowing the pathology and neuroscience of dementia and a US$60 billion investment in research by the pharmaceutical industry there is as yet no sign of disease modifying treatments for AD. Of the 101 drugs that have come to trial in the last ten years none have progressed beyond phase III.

But there may still be hope: ‘Almost all psychiatric treatments were not discovered through translational development but through serendipity,’ Professor Howard said. Repurposing – taking a drug that has one indication and testing it for a new indication that it shows some promise for – could prove fruitful. One example is a trial with nilvadipine, a calcium-channel blocker developed for treating hypertension which seems to promote excretion of amyloid in the urine. Another involves minocycline for which there is evidence of neuroprotection.

A second glimmer of light is hippocampal neurogenesis. There is evidence to show that people produce 700 new neurones a day in each hippocampus right into their seventies. If that process could be stimulated there may be a benefit in people with AD.

What do the latest guidelines say about bipolar disorder?

In terms of treatment, there has been a big shift in the most recent version of NICE clinical guideline on bipolar disorder compared with previous versions. While previous guideline focussed around medications to reduce symptoms, stabilise mood and prevent relapse, the new guidance gives much greater prominence to psychological interventions, Dr Matthew Taylor, Senior Lecturer at King’s College, London, told delegates.

The latest NICE guideline includes a separate section on primary care recognition and management. The guideline does not recommend using questionnaires in primary care to identify bipolar disorder in adults (in contrast to recommendations in the previous edition of the guideline on secondary care assessment advice). Psychological interventions for bipolar depression can be initiated. But primary care initiation of lithium or valproate is not recommended.

Triggers for referral or re-referral to secondary care are similar to the previous guideline:

– poor or partial response to treatment
– functioning declines significantly
– treatment adherence is poor

![Figure 1. Comparative efficacy and acceptability of antimanic drugs in acute mania](Reproduced from: Cipriani, A et al: Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis Lancet 2011; 378:1306-15 (copyright Elsevier))
– comorbid alcohol or drug misuse is suspected
– the person is considering stopping any medication after a period of relatively stable mood.

And two new triggers for referral or re-referral:
– the person develops intolerable or medically important side effects from medication
– a woman with bipolar disorder is pregnant or planning a pregnancy.

In secondary care, questionnaires are no longer recommended for assessment, which Dr Taylor felt was interesting as he has always found them quite useful as a starting point.

For mania or hypomania in people not taking an antipsychotic or mood stabiliser NICE recommends first-line haloperidol, olanzapine, quetiapine or risperidone. If the person is already taking lithium then clinicians should consider adding haloperidol, olanzapine, quetiapine or risperidone, after checking the patient’s plasma lithium levels to optimise treatment. A new recommendation is that lamotrigine should not be used to treat mania (Figure 1).

For people taking antidepressant monotherapy who develop mania or hypomania, stopping the antidepressant should considered and an antipsychotic offered whether or not they stop the antidepressant.

The CANMAT guidelines style is very different with quite complicated algorithms, but Professor Howard felt they complement the NICE guidelines. BAP guidelines are similar to NICE, starting with antipsychotics or valproate and recommending lithium for milder manic symptoms.

Bipolar depression is more challenging. Recently, with new treatments and well run trials there is more hope in this area. NICE recommends starting with psychological interventions such as those specifically developed for bipolar disorder that have a published evidence based manual on how they should be delivered, or a high intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with the NICE clinical guideline on depression.

Dr Taylor commented that the recommendation to use psychological therapies is perhaps driven less by evidence, which is mostly of low or very low quality, and more by service user demand. One disadvantage of this approach is that it might impede the development of more effective treatments, he added.

SSRIs are no longer recommended by NICE for bipolar depression. An olanzapine / fluoxetine combination or quetiapine are recommended first-line with lamotrigine or olanzapine second-line. Some trials seemed have been missed in the evidence gathered by NICE. That has been addressed in an online analysis by Taylor and colleagues from the Maudsley.22

Relapse prevention is a big part of bipolar treatment. A new recommendation in the NICE guideline for people who have some persisting symptoms between episodes of mania or bipolar depression is to offer a structured psychological intervention (individual, group or family).

Dr Taylor commented that group therapy seems to be more effective than one-to-one sessions.23 That’s good news in these cash-strapped times because group therapy is a little less expensive to deliver than the individual format, he commented.

When planning long-term drug treatment to prevent relapse the NICE guideline says clinicians should discuss with people whether they want to stay with their current treatment or switch to lithium. It should be explained that lithium is the most effective long-term treatment for bipolar disorder. Dr Taylor commented: ‘I am a great fan of lithium. I think it’s probably underused but I am not entirely sure whether you can say it’s the most effective long-term treatment for bipolar disorder.’24

Indeed, in Dr Taylor’s opinion, the options for long-term treatment recommended by NICE are fairly limited: lithium first line with the addition of valproate if it is ineffective. Valproate or olanzapine are recommended for those patients who do not tolerate lithium or do not agree to routine blood monitoring, or a new recommendation, to offer quetiapine for those who responded during an episode of mania or bipolar depression.

Dr Taylor concluded by saying it is clear now that treatments for bipolar disorder are not like-for-like equivalents. They differ in clinically important ways and in terms of efficacy. And the drugs that work for the acute phase seem to work in a proportionate way in the long term.25

Risk management of medicines
Professor Saad Shakir, Director of the Drug Safety Research Unit in Southampton, discussed some of the strategies employed to monitor medicines and to try to reduce some of associated risks when they move from the somewhat artificial realms of clinical trials into the real world where they may be taken by patient groups who may not have been represented in trials.

Pharmacovigilance and risk management are important because:
• 5% of all hospital admissions are for ADRs
• 5% of all hospital inpatients suffer an ADR
• ADRs are the 5th most common cause of hospital death
• Estimated 197,000 deaths in the EU from ADRs
• EU societal cost of ADRs is 79 billion Euros per year

Clinical trials are limited in their ability to pick up adverse reactions to drugs, not least because they often include too few patients, inclusion criteria are too restrictive, they run for too short a time and do not reflect real world practice.

Thus when a drug is used in the wider world it is important risk management is instituted which involves a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

Secondary care event monitoring studies are one means by which pharmacovigilance data can be captured. Many of these are required as part of the licensing of some drugs.

References