restraint. The reality is probably somewhere between these extremes.

As a general psychiatrist with a special interest in psychological treatments (especially cognitive–behavioural therapy) I am not proposing that medication has all the answers or is even the preferred choice in all cases. However, I have to persuade many patients on a regular basis to take antidepressant medication before improvement can occur. The 'chemical imbalance theory' is a useful working hypothesis for one cause for depression. There is a current climate of opinion among those who regularly surf the internet that medication is all bad, dangerous and addictive. Clinical psychiatrists like me have an uphill battle to persuade patients to take life-saving medication which articles such as those by Moncrieff, and the websites she directs us to, make even harder.

Moncrieff, J. (2006) Psychiatric drug promotion and the politics of neoliberalism. *British Journal of Psychiatry*, **188**, 301–302.

R. Stern The Priory Hospital, Priory Lane, London SW15 5JJ, UK. Email: rsstern@btinternet.com
doi: 10.1192/bjp.189.2.188b

Author's reply: By mentioning the use of steroids in asthma, Dr Stern highlights an important contrast between our understanding of how drugs work in general medicine and how drugs work in psychiatric conditions. In general medicine the effects of drugs can usually be understood by their actions on some level of the pathological process that generates the symptoms. Thus, steroids reduce the inflammatory response that gives rise to some of the symptoms of asthma. In contrast there is no evidence that drugs used in psychiatric conditions act on specific neuropathological processes. No specific physical pathology has been established for any major psychiatric condition and other evidence that drugs might be specific is lacking. Instead I have suggested elsewhere the alternative hypothesis that psychiatric drugs do not correct pathological brain states or chemical imbalances but create them (Moncrieff & Cohen, 2005, 2006). These drug-induced states might sometimes prove useful in psychiatric conditions, but the negative aspects of such states are often likely to outweigh the benefits that can be gained. However, drug companies and the psychiatric profession have presented psychiatric drugs as disease-specific treatments that correct chemical imbalances. This view helps to downplay the disadvantages of long-term drug use and may help to create the context for the expansion of markets for psychiatric drugs.

As far as antidepressants are concerned, there is little evidence that they have specific antidepressant effects (Moncrieff & Cohen, 2006) or that they are 'life-saving' in terms of reducing suicide (Moncrieff & Kirsch, 2005). There is no evidence that there is a chemical imbalance in people with depression, and I do not understand how we can be justified in persuading patients to see their problems in this way. Doing so runs the risk of undermining patients' own coping mechanisms and thereby increasing chronicity, dependence on services and use of prescribed drugs.

Declaration of interest

I am co-chairperson of the Critical Psychiatry Network.

Moncrieff, J. & Kirsch, I. (2005) Efficacy of antidepressants in adults. *BMJ*, **331**, 155–157.

Moncrieff, J. & Cohen D. (2005) Rethinking models of psychotropic drug action. *Psychotherapy and Psychosomatics*, **74**, 145–153.

Moncrieff, J. & Cohen, D. (2006) Do antidepressants cure or create abnormal brain states? *PLoS Medicine*, **3**, e150.

J. Moncrieff Department of Mental Health Sciences, University College London, 48 Riding House Street, London WIN 8AA, UK. Email: j.moncrieff@ucl.ac.uk
doi: 10.1192/bjp.189.2.189

Initial rate of improvement in major depression

Dr Mitchell (2006) suggests that it may be pertinent to re-examine another commonly quoted recommendation – that an antidepressant trial must be at least 6 to 8 weeks before switching drugs. The evidence on which switch guidelines are based is weak but these guidelines are applied frequently in daily clinical practice. In previous studies symptom improvement at earlier time points in relation to *response* has been investigated (e.g. Koran *et al*, 1995) but the ultimate goal of depression treatment is complete *remission*. Remission takes longer than 4–6 weeks to achieve but substantial improvement is unlikely after 10–12 weeks (Trivedi *et al*, 2006). Quitkin *et al* (2003) investigated the relationship between initial change in symptoms and remission by week 12 and demonstrated that even when there was no improvement after 6 weeks of treatment, an antidepressant trial should be continued because the proportion of patients attaining remission by week 12 was still considerable (i.e. greater than 30%). They argued that a switch of antidepressant medication would be unlikely to have resulted in higher remission rates. Furthermore, large studies are required in which change in symptoms is frequently measured at uniform time-points and dimensions other than those measured by conventional questionnaires for depression are assessed. These might be more sensitive to early change following the initiation of antidepressant treatment (Harmer *et al*, 2004), and therefore might better predict which patients will attain remission. Calculation of the sensitivity, specificity, area under the receiver operating characteristic curve, and positive and negative predictive power to assess the likelihood of remission for various levels of symptom change at different time-points would help clinicians to decide on clinical applicability. Results from such studies will improve the evidence on which switch guidelines are based.

Harmer, C. J., Shelley, N. C., Cowen, P. J., *et al* (2004) Increased positive versus negative perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry*, **161**, 1256–1263.

Koran, L. M., Hamilton, S. H., Hertzmar, M., *et al* (1995) Predicting response to fluoxetine in geriatric patients with major depression. *Journal of Clinical Psychopharmacology*, **15**, 421–427.

Mitchell, A. J. (2006) Two-week delay in onset of action of antidepressants: new evidence. *British Journal of Psychiatry*, **188**, 105–106.

Quitkin, F. M., Petkova, E., McGrath, P. J., *et al* (2003) When should a trial of fluoxetine for major depression be declared failed? *American Journal of Psychiatry*, **160**, 734–740.

Trivedi, M. H., Rush, J., Wisniewski, S. R., *et al* (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry*, **163**, 28–40.

A. C. M. Vergouwen Department of Psychiatry, St Lucas Andreas Hospital, Jan Tooropstraat 164, NL-1006 AE, Amsterdam, The Netherlands. Email: vergouwen@slaz.nl
doi: 10.1192/bjp.189.2.189a

Author's reply: I agree that the evidence base for strategies for treatment-resistant

depression has been poor but it is (slowly) improving (DeBattista, 2006). Dr Vergouwen's suggestion that predictors of remission should be sought scientifically is most welcome. The studies mentioned are some of a number that look at the proportion of patients who respond late when early antidepressant response is disappointing (e.g. Mulsant *et al*, 2006). I am sure it will not be long before someone performs a meta-analysis yielding more-conclusive results. However, in clinical practice the alternative to continuing a drug which has generated a poor response is most commonly switching to another. However, from an evidence base standpoint this is where things get complex.

When considering analysis of benefit from a switch strategy after a certain number of weeks (say an 8-week *v*. 4-week switch with follow-up at 24 weeks), the methodology of an ideal trial is not straightforward and hence rare (to the point of invisibility!) in the literature. Three arms are required. Arm 1 includes patients who switch if non-responsive at 4 weeks; arm 2 those who switch if non-responsive at 8 weeks and, equally importantly, arm 3 patients who do not switch and stay on their original antidepressant for the duration of the trial. The third arm establishes how many would continue to enter remission even if initially non-responsive. Comparing switch with maximisation or augmentation or combination strategies would also ideally require a study of similar design. I know of no such studies, and the recruitment of the necessary number of patients with some level of treatment resistance is very difficult. A recent review of combination trials for treatment-resistant depression found only two that were randomised against a drug plus placebo arm (Dodd *et al*, 2005).

The other important issue is exactly how to separate responders from non-responders (or remitters from non-remitters) (Israel, 2006). In my view, because any definition of response is arbitrary, the threshold taken to define response (20%, 30% or 50% improvement, for example) will affect the success of the switch strategy. The main danger of switching too early is robbing a patient who was on a trajectory of good improvement from continuing successful treatment. The danger of switching too late is leaving a patient with distressing symptoms longer than necessary without effective treatment. In reality, ratings on a depression scale at 4 or 8 weeks after starting treatment will be somewhere between baseline and entirely asymptomatic – thus virtually all patients could be considered 'partial responders'. Many areas of psychopharmacology are moving towards early identification and treatment. I doubt that treatment-resistant depression will be the exception.

DeBattista, C. (2006) Augmentation and combination strategies for depression. *Journal of Psychopharmacology*, **20** (suppl.), 1–18.

Dodd, S., Horgan, D., Malhi, G. S., *et al* (2005) To combine or not to combine? A literature review of antidepressant combination therapy. *Journal of Affective Disorders*, **89**, 1–11.

Israel, J. A. (2006) Remission in depression: definition and initial treatment approaches. *Journal of Psychopharmacology*, **20** (suppl.), 5–10.

Mulsant, B. H., Houck, P. R., Gildengers, A. G., *et al* (2006) What is the optimal duration of a short-term antidepressant trial when treating geriatric depression? *Journal of Clinical Psychopharmacology*, **26**, 113–120.

A. J. Mitchell Department of Liaison Psychiatry, Brandon Unit, Leicester General Hospital, Leicester LE5 4PW, UK. Email: alex.mitchell@leicspart.nhs.uk
doi: 10.1192/bjp.189.2.189b

Obsessive–compulsive disorder and central nervous system autoimmunity

Dale *et al* (2005) found high levels of anti-basal ganglia antibodies (ABGA) in the sera of children with obsessive–compulsive disorder (OCD) compared with control groups of children with streptococcal infection without OCD, paediatric autoimmune disease and neurological disorders (stroke, movement disorders and encephalitis) and concluded that central nervous system autoimmunity may play a role in a significant subgroup of children with OCD.

Recently, we found another auto-antibody, anti-phosphatidylethanolamine (aPE), which may have been associated with the sudden onset of OCD in a 5-year-old girl. Six weeks prior to showing symptoms of OCD, the girl was diagnosed with an ear infection, for which she received a full course of antibiotics. She presented at our clinic 2 months after the onset of OCD symptoms. Past medical history was significant for recurrent ear infection. Physical and neurological examinations were normal; no tics were observed. There was no family history of OCD.

At the index visit, the patient was negative for streptolysin O antibody. Throat cultures were negative for *Streptococcus pyogenes* and *Streptococcus* group A antigen. A test for deoxyribonuclease B, a marker for prior streptococcal infection, was negative.

To investigate an autoimmune diathesis, the patient was tested for IgG, IgA and aPE, anti-phosphatidylserine, anti-phosphatidylcholine and anti-cardiolipin antibodies (Sokol *et al*, 2000). Serial anti-phospholipid antibody testing revealed the persistence of IgG aPE antibodies; aPE antibody levels were coincident with the expression of OCD symptoms. The index and day 113 sera were also positive for IgG anti-phosphatidylserine antibodies. The patient was begun on a low dose of sertraline and her OCD improved.

We believe that this patient has a 'paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection' (PANDAS-like condition) because the criteria, except for evidence of a group A streptococcal infection, were met. She had a history of repeated ear infections but her OCD symptoms occurred after the most recent infection. Without documenting the infectious agent, the elevated levels of aPE antibody suggest that she mounted an autoimmune reaction following another ear infection which led to the development of OCD.

We have found aPE antibodies in other neuropsychiatric conditions. An adolescent girl with a basal ganglia stroke had IgA aPE antibodies in her serum and IgG and IgA aPE antibodies in her cerebrospinal fluid; she experienced seizures and depression subsequent to the stroke (Sokol *et al*, 2000). Furthermore, aPE was the most frequently detected anti-phospholipid antibody in the serum of patients with psychosis (O'Brien *et al*, 2004). One-third of cerebrospinal fluid samples from this group contained IgG aPE antibody in the absence of this antibody in serum, suggesting intrathecal synthesis. We propose that aPE antibody may attack the basal ganglia, leading to its association with OCD and other disorders of the brain.

Although we report the finding of aPE antibodies with OCD in a single patient, we believe that aPE antibody should be considered as an additional autoimmune marker in post-infectious OCD.