Correspondence

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Clozapine treatment following blood dyscrasia

Dunk et al (2006) investigated 53 patients who were rechallenged with clozapine following leucopenia or neutropenia during previous therapy and found that 33 did not experience a second episode of blood dyscrasia and were able to continue drug treatment. This result is of considerable clinical relevance because it suggests that some patients with leucopenia or neutropenia may unnecessarily be denied effective clozapine treatment.

We agree that there may be two types of clozapine-associated neutropenia: an early sign of incipient agranulocytosis and a more common transient and harmless phenomenon, not necessitating the discontinuation of drug treatment. Transient neutropenia (defined as a return of the neutrophil count to normal values without changing the clozapine dosage) was found in 22% of 68 patients treated with clozapine for the first time (Hummer et al, 1994). Neutropenia of short duration (2–5 days) and weekly benign variations of the neutrophil count have been reported. Marked circadian variations in the number of circulating neutrophils (morning pseudoneutropenia) have also been described in several clozapine-treated patients (Ahokas & Elonen, 1999; Esposito et al, 2004).

The actual issue might therefore not be which patients could be rechallenged with clozapine following drug-associated neutropenia but which could be maintained on clozapine despite this side-effect. Laboratory screening tests, including the use of a hydrocortisone test, are being devised to determine whether clozapine-associated neutropenia is transient or malignant (Murry & Laurent, 2001). Until these tests become available for routine use, it is necessary to increase the frequency with which white blood cell counts are determined. As first suggested by Ahokas & Elonen (1999), when the absolute neutrophil count is below the normal range in the morning, the test should be repeated in the afternoon of the same day before a decision to stop clozapine treatment is made. This might be the basis for further clarification of the significance of transient neutropenia.

Although Hummer et al (1994) reported transient neutropenia in 22% of 68 patients they defined leucopenia as a white cell count <3.5×10⁹/l and neutropenia as a neutrophil count <2.0×10⁹/l. The mean neutrophil count at the time of the transient neutropenia was 1.78×10⁹/l. In the UK and generally, the cut-off points for leucopenia and neutropenia used in clozapine monitoring are lower (3.0×10⁹/l and 1.5×10⁹/l respectively) and patients with counts higher than this are not required to stop clozapine but are monitored more frequently. The relevance of the findings of the study to all clozapine-treated patients must therefore be considered with this point in mind.

The use of a hydrocortisone test to distinguish between benign and malignant neutropenia is of great interest but findings must be interpreted with caution as the study involved only three patients (Murry & Laurent, 2001). Furthermore, the risk of further stressing a compromised bone marrow must be borne in mind with such interventions. Whether it is possible to distinguish between transient neutropenia and the prelude to agranulocytosis in clozapine-treated patients remains to be determined.

Declaration of interest

L.D. has undertaken consultancy for Novartis UK and Novartis Australia and received a fee from Novartis Australia for the preparation of the paper; she was formerly employed by Novartis UK. L.A. and C.A. are employed by Novartis UK.


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doi: 10.1192/bjp.189.2.186

Authors’ reply: We agree that attempts should be made to continue patients on clozapine if at all possible in order to give them an adequate trial of the drug. The Clozaril Patient Monitoring Service (CPMS) routinely advises that samples should not be taken first thing in the morning for patients with borderline white cell/neutrophil counts to avoid the problem of morning pseudoneutropenia. Taking samples after a brisk walk has also been suggested in such patients.

Personality disorder and outcome in depression

Newton-Hoves et al (2006) attempted to definitively answer the question of whether comorbid personality disorder affects outcome in people with major depression. Their search strategy, study selection, data summary and analysis are clearly described.
However, the heterogeneous nature of their data does not allow such definitive answers as they claim. As has been noted previously (Charney et al., 1981; Black et al., 1988; Mulder, 2002) people with depression and comorbid personality disorders are less likely to receive drugs or electroconvulsive therapy (ECT), precisely the treatments (as this meta-analysis reports) that they are more likely to respond to. Therefore, the only fair assessment of the effect of personality disorders on outcome is the randomised controlled trial (RCT). When the meta-analysis was confined to such trials the effect size was smaller but was still significant. A recent meta-analysis that restricted itself to RCTs of drug treatment reported no effect of recent comorbid personality disorder on outcome in people with depression (Kool et al., 2005). This suggests that better studies with more effective treatments will report less effect of comorbid personality disorder on outcome.

What does this mean clinically? Less than the authors claim, I would suggest. The sample size required to detect the difference between the outcome of patients with depression and personality disorders and similar patients but without personality disorder exceeds 1000 (and this by using all trials rather than just RCTs), suggesting minimal effect in normal clinical practice. Although it seems like a good idea, there is no evidence that targeting comorbid personality pathology is necessary and will result in better outcomes for those with depression. The numbers needed to show an effect of personality disorder on outcome suggest that a treatment trial specifically designed to look for a treatment effect would require such large numbers that it will never be performed.

What the meta-analysis suggests, along with many recent studies, is that good treatment of depression, particularly using drugs and ECT if indicated, will result for the most part in a similar outcome for people with and without personality disorders. Such treatments may in fact be effective for the comorbid personality disorder. Clinicians should be encouraged that aggressive treatment of mood disorder is likely to lead to a positive outcome in those with depression and comorbid personality disorder.


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Authors' reply: We did not set out to provide a definitive answer to a specific question; our objective was to provide a comprehensive synthesis of all available studies and, by using a systematic approach to data collection with limited exclusion criteria and a robust statistical analysis, we have produced the best summary available to date. Although data from RCTs are valuable, they are not the sole arbiters of association and so our information covers much more than the necessarily short-term span of an RCT. Even if we confine our analysis to the 14 RCTs in our review, we obtain an odds ratio of 1.60 (95% CI 1.25–2.06), indicating better resolution of a depressive episode without comorbid personality disorder. Both cohort studies and case series support this finding, with all groups identifying a poorer outcome in those with a personality disorder.

The overview by Kool et al. (2005) included just six RCTs, all of which involved drug treatment with antidepressants and none of which extended beyond 24 weeks. The judgement that these were the only trials of ‘high quality’ may be suspect, as it is difficult to assess quality from published papers (Soares et al., 2004). In addition, despite their claim that studies were excluded when ‘they presented reanalyses of a study population that was already included’, we believe that their two largest studies (Hirschfeld et al., 1998; Russell et al., 2003) both stem from the same trial (albeit with different outcomes) first reported by Rush et al. (1998). Excluding Russell et al. (2003), from their meta-analysis slightly widens the 95% CI for the reported (inverted) odds ratio of 1.14 from 0.93–1.39 to 0.88–1.45, neither of which is inconsistent with our own estimate above.

Our review also suggested that there may be a better response to the treatment of comorbid depression and personality disorder with antidepressant drugs than with other treatments, which is consistent with Kool et al. (2005). We remain optimistic about treating personality pathology successfully in this group, and think that newer treatments which focus on personality should be compared with aggressive pharmacotherapy for those who are regarded as having ‘resistant’ depression.

Declaration of interest

P.T. and T.J. belong to a UK Medical Research Council Cooperative Group (Mencog) evaluating mental health interventions. P.T. is Editor of the British Journal of Psychiatry but had no part in the evaluation of this letter.


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doi: 10.1192/bjp.189.2.187

Stillbirth – psychological impact on fathers

Although there is a lot of information on the psychological impact of stillbirth on mothers, data on the effect on fathers is very rare. We often fail to acknowledge that fathers can have a difficult time after a stillbirth in separating their own grief from that of the mother. Their role in supporting the mother through this ordeal cannot be overemphasised and the recent article by Turton et al (2006) is important because it describes the psychological stress and needs of fathers during subsequent pregnancy and the puerperium. However, I would like to raise a few points which need further discussion.

Social support from family or partner following such a life event can have a substantial impact on subsequent mental and physical well-being, which may also determine the subsequent level of coping. Turton et al measured support from partner and family as a dichotomous (yes/no) variable, which does not seem entirely appropriate. Social support is a multidimensional construct and should have been analysed in terms of quantity and quality. Various questionnaires such as the Norbeck Social Support Questionnaire, http://nurseweb.ucsf.edu/www/NSSQ-Instrument.pdf are available to evaluate social support in a holistic and objective manner. Second, Turton et al, relaxed the inclusion criteria by including four couples after the safe arrival of their babies. This might have skewed the final result.

Interestingly, the fact that fathers often refused to take part in the interview could have led to underestimation of the psychological impact of stillbirth and the underlying psychiatric morbidity. It would have been informative if the authors had identified the reasons for their refusal. This is particularly important since it is well accepted that fathers generally tend to minimise their problems, put on a ‘brave face’ and refuse to speak out. There is no mention of the reliability or validity of the scale used for the assessment of marital satisfaction. Moreover, exclusion of Black participants and those from minority ethnic groups limits the application of the results to a wider general population.

However, I think this is a relevant and significant study which may prove to be beneficial for a wider understanding of this poorly recognised problem. It highlights the importance of actively encouraging fathers to be more forthcoming about their problems and also helps health professionals to focus on high-risk couples.


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Authors’ reply: We would like to expand on the points raised relating to sampling and assessment tools. We accept the criticism that relaxing the inclusion criteria might have skewed the final results, but have already explained our rationale for this decision. Unfortunately it is not possible to make any inference about the psychological morbidity of non-participants. Non-responding fathers fell into two groups: those who were persistently unavailable and those who declined to take part. Only one father gave a reason for his refusal: rejection of what he perceived as a false assumption that it was possible for a parent to ‘recover’ from a stillbirth. Although we were active in seeking fathers’ participation, ethical considerations did not permit us to persist in questioning fathers who declined to take part. Black couples and those from minority ethnic groups were not excluded from the study; rather they were underrepresented as a result of higher non-participation rates.

Two factors contributed to our use of a single dichotomous variable for the presence or absence of appropriate social support. First, social support at the time of loss was not a primary focus of the study and we felt it appropriate to limit the number of questionnaires that participants had to complete. Second, research in this field has relied on a range of assessment tools (e.g. Zeannah et al, 1995; Lin & Lasker, 1996). The use of multiple complex tools limits the comparison of data across studies. However, we accept the view that elaborating on the quality of support would deepen the findings. The Golombok Rust Inventory of Marital State, which was used to assess marital satisfaction, is a short and easy-to-administer assessment which has high face and content validity and good reliability (Rust et al, 1988).

We hope that continuing research in this field will lead to greater awareness of the needs of parents experiencing stillbirth.


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doi: 10.1192/bjp.189.2.188a

Promotion of psychiatric drugs

Dr Moncrieff (2006) attacks the pharmaceutical industry for promoting the idea that depression is ‘caused by imbalances in brain chemicals’ and berates it for the fact that people are taking more prescription drugs than ever before. She implies that because the biochemical basis of depression is not known, the promotion of antidepressants is a plot to encourage profit-seeking.

The history of medicine teaches us that many crucial and life-saving drugs were and still are used despite a lack of knowledge of their scientific action (e.g. the use of steroids in asthma). In fact, there are very few instances where the scientific basis of action of crucial medicines is fully understood. The history of psychiatry teaches us that before antidepressant medication there was no treatment for depression except waiting for natural recovery: frequently a long and painful process during which the patient often starved to death or ended life by suicide.

One can easily take, like Moncrieff, an extreme view of the pharmaceutical industry, emphasising how it controls research and uses advertising to influence clinicians, and I note that the current issue of the Journal has no fewer than 12 full-page colour advertisements promoting psychotropic medication. The alternative view, however, would be that the industry has helped us to move out of the dark ages when all we could offer was asylum and...
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.


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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, 2003). 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.


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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.


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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.


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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 diagnosis, 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.
Corrigendum

Generalisability of the individual placement and support model of supported employment: results of a Canadian randomised controlled trial. *BJP*, 189, 65–73. The percentage for ‘Any competitive job over 12 months’ in the ‘Usual service’ group in Table 2b (p. 71) should be 17.6. The doi for this paper is 10.1192/bjp.bp.105.012641; the doi included with the online version has been corrected in deviation from print and in accordance with this corrigendum.
Obsessive-compulsive disorder and central nervous system autoimmunity
D. K. Sokol, L. M. McGuire, N. S. Johnson, D. R. Wagenknecht and J. A. McIntyre
BJP 2006, 189:190-191.
Access the most recent version at DOI: 10.1192/bjp.189.2.190