Serotonin and the mode of action of electroconvulsive therapy

The French philosopher Pierre Charron wrote that the true science and study of man is man. Professor Yatham and colleagues deserve commendation for their application of modern brain imaging techniques to study the mode of action of electroconvulsive therapy (ECT) in living patients with depression. The final assertion that their findings may put to rest the controversy about the role of brain serotonin in mediating the antidepressant effects of ECT may, however, be premature.

The authors suggested a common mode of action among ECT and antidepressant drugs, that is, the down-regulation of brain 5-HT$_2$ receptors. There is, however, evidence to question the overlap between the mode of action of ECT and antidepressant drugs that target serotonin. Selective serotonin reuptake inhibitors (SSRIs) inhibit the serotonin transporter. The gene that encodes the serotonin transporter has a promoter region that contains a polymorphism, and the allelic status of this polymorphism is associated with the probability of both improvement and recovery with an SSRI. The allelic status of this polymorphism is not associated with the outcome of ECT. A proportion of patients with depression treated successfully with an SSRI will experience transient relapse during acute tryptophan depletion, which in turn depletes serotonin. This is not observed in patients with depression treated successfully with ECT.

There is also evidence to suggest more of an overlap between the mode of action of ECT and antidepressant drugs that target catecholamines. A history of failure to recover with an SSRI during the index episode has no bearing on the probability of remission from unipolar non-psychotic major depression with subsequent ECT; in contradistinction, such a failure with buproprion, which does not target serotonin at all, or a heterocyclic antidepressant is associated with a reduced probability of remission with subsequent ECT. The only known allelic status that is associated with the outcome of ECT in patients with depression concern polymorphisms believed to affect the concentration of dopamine in the forebrain. Modern brain imaging techniques have also been applied to study the effects of ECT on brain dopamine: binding to the D$_2$ receptor in the rostral anterior cingulate, an area of the brain implicated in the pathophysiology of depressive illness, fell by 25% over a course of bilateral ECT, a finding compatible with an increase in the availability of dopamine.

None of these observations on its own disproves the hypothesis suggested by the authors. Nevertheless, these observations too concern living patients with depression treated by ECT, and together cast doubt on the central role of brain serotonin in the mode of action of ECT in major depression.

A care pathway for schizophrenia

Swaran Singh has recently argued for a care pathway for psychosis or schizophrenia.1 We have recently argued for a staging approach to schizophrenia.2 Such an approach argues that there are different stages in the development of schizophrenia, and that therefore different stages of the illness will require different interventions to optimise treatment, be it pharmaceutical, social or psychological. Furthermore, logically, the different stages will require different goals of treatment and different expected outcome measures. Thus, for example, the aim of treatment in the first or ‘at risk mental state’ stage of psychosis is to prevent psychosis developing, while the aim of the second stage, or the first-episode stage, is to end the psychotic episode and return the patient to work and education.

Staging in schizophrenia also extends to the phase of chronic illness, and here the goal will be, depending on the severity of the illness, to limit the positive and negative symptoms of the illness, to prevent relapse, and to optimise social inclusion, promoting a return to work if possible. Such a staging approach to schizophrenia is underpinned by the neuroimaging evidence, since the loss of grey matter linked with schizophrenia does start in the prodromal ‘at risk’ phase, becomes more prominent in the first episode, and then becomes incrementally more severe in the later stages of the disease.3–5 Furthermore, different stages of the illness appear to be mirrored in different patterns of change in such structures as the hippocampus and the amygdala,6 as well as changes in pituitary volume.7,8 Thus, a ‘staging approach’ to schizophrenia does provide a logical framework for the development of a care pathway for schizophrenia, with different stages or phases requiring the development of specialised teams with different expected outcomes, but who will always, in each phase of the illness, strive to optimise treatment in order to achieve the best results. Hence, such a pathway may include an ‘at risk mental health’ team, which will attempt to reduce the rate of transition to full psychosis in patients who are developing ‘prodromal’ symptoms. This would be followed in the pathway by a first-episode service which will work assertively with patients so as to deal with the first episode and return patients to work and education, and at the other end of the spectrum, assertive outreach teams will work with patients who are difficult to treat who have demonstrated the most serious deterioration in functioning.

What, however, is missing in this care pathway is the treatment of those patients who are returned to community mental health teams (CMHTs) after 3 years in an early intervention service and who are not deemed ill enough to require referral to the assertive outreach teams. These constitute the majority of patients with long-term schizophrenia. Unfortunately, since CMHTs have other priorities, and indeed are oriented to dealing with patients with relatively less severe forms of mental illness, many of these patients may receive suboptimal care, sometimes consisting of the simple delivery of medication within a depot or clozapine clinic, and without the systematic delivery of psychosocial interventions. As a result, in many cases, social inclusion is not optimised as a direct result of the loss of the assertive approach to care. It is therefore small wonder that both the Lambeth Early Onset (LEO)9 and the OPUS10 services report a loss of improvement in outcomes within 5 years of first treatment, after patients have been transferred from early intervention teams to the care of CMHTs.

It is of interest that a study in Russia,11 where patients were followed up assertively for 5 years, has shown no such loss of improvement in outcomes. It is urgent that the development of ongoing assertive, specialised teams for psychosis, as suggested by Singh, should proceed in order to complete the schizophrenia care pathway. The CMHT cannot provide such an assertive service, since it is focused on other things. Seen in this perspective, recent suggestions that early intervention and assertive outreach teams should be amalgamated into CMHTs and provide elements of specialised care within the CMHTs must further confuse the focus of the CMHTs and constitute a serious misreading of the evidence.

References


Author’s reply: I am grateful for Dr Agius’ comments and entirely agree that a staging approach allows the development of a comprehensive care pathway for psychotic disorders. With such an approach, the most efficacious and potentially less harmful interventions can be appropriately targeted at an earlier clinical stage of an emerging illness. Such a staging model is widely used in medicine and has recently been described as a heuristic framework for intervening early in all youth mental health problems.12

Half of all adult mental disorders begin in late adolescence, usually with an initial presentation of non-diagnostic symptoms. Mental health services, especially community mental health teams (CMHTs), offer interventions only when an illness is severe.

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enough to reach a diagnostic threshold. This is partly due to the reactive nature of CMHT care and partly because of concerns about treating ‘false positives’, benign and transient states that will not make a transition into a major mental disorder. An unfortunate consequence of this well-meaning caution is that young people are denied earlier and safer interventions, which are not only clinically appropriate at an early stage, but have the potential for altering the prognosis and preventing the emergence of more serious illness.

A staging approach also offers exciting possibilities for developing specific clinical and biological markers of mental illnesses and understanding the relationship between clinical states and neuropathological and neurophysiological changes that accompany illness progression.1

I also share Dr Agius’ concern about the short-term financial pressures that may encourage managers to amalgamate early intervention services into CMHTs. This will simply dilute the well-established effectiveness of early intervention services in caring for vulnerable young people, while offering no improvement in CMHT functioning.


Dilemma over antipsychotic use in dementia

The editorial by Treloar et al1 has raised a controversial but justified issue regarding antipsychotic prescription in patients with dementia. We agree with the editorial supporting the cautious use of these drugs based on the ethical premise of reducing patient distress and palliation. However, we felt that there was a relatively quick and unchallenged submission to another important premise of the observed harm, which is intricately related to the topic in question. Our strong concern is that such unequivocal acceptance of the observed risks is likely only to enhance the ethical dilemma in a reader’s mind. The decision to use these drugs, even for palliative purposes, is likely to be strongly governed by our safety and risk assessments. Are we not in a dilemma over the available safety evidence as well?

Is the observed harm specific to antipsychotic drugs, old age, dementia or behavioural and psychological symptoms of dementia (BPSD)? Is the observed association necessarily causation or are there certain limitations to a definite conclusion? For example, many a time the indication for which a drug is prescribed in dementia may be the cause of increased mortality rather than the drug per se. To quote the detailed Department of Health report,2 people with dementia and BPSD may be more likely to die (and to be prescribed antipsychotic drugs) than people with dementia and no BPSD. Safety concerns regarding the use of antipsychotic drugs in elderly populations are a valid consideration, but are the risks also specifically higher for elderly people with dementia? The landmark meta-analysis of randomised controlled trials (RCTs),3 which concluded with a small increased risk for death with antipsychotics compared with placebo, also mentions that these results should be considered as hypothesis-generating. None of the individual drugs included in the 17 RCTs was sufficient to conclude for an increased risk, but a combined statistical effect was found. Does this call for a verification or should it be taken as conclusive?

Regarding efficacy studies, antipsychotic drugs have mostly been tested for treating BPSD. Behavioural and psychological symptoms of dementia is quite a heterogeneous term, used for an array of challenging behaviours such as restlessness, agitation, wandering, vocalisations, resisting help with dressing and personal hygiene, and verbal and physical aggression. Although the use of the term BPSD is quite appropriate in social dementia research (e.g. caregiver burden), is such a heterogeneous amalgamation of behaviours, which may or may not be of psychotic origin, a justified end-point to study clinical efficacy of drugs, or do we need more specific symptom clusters as indications of antipsychotic use in dementia? Further, is the number needed to treat (5–11) for antipsychotics for behavioural improvement in dementia any different from numbers needed to treat for antipsychotics in schizophrenia?2

Undoubtedly, from a clinical perspective, extreme care and caution should be exercised in prescribing antipsychotics in old age, especially for those with an underlying organic illness (e.g. dementia). Regarding the dilemma whether they should ‘ever or never’ be prescribed for patients with dementia, our point of contention is: (a) we cannot focus the debate only on the ethical angle to resolve this dilemma, there are several unanswered medical questions; (b) we cannot close our eyes to the caveats in existing safety and efficacy studies; and (c) we need to resolve the ambiguity surrounding the available evidence to empower us for an ethical as well as informed decision. More than ever, the dilemma is to arrive at certain indications for which we can use antipsychotics with relative safety.


I agree with the views expressed by Treloar et al regarding antipsychotic use in dementia. This is not only an ethical dilemma, but an issue of medical prescribing practice that has entered public and political domains. The present widespread use of antipsychotics seems to be unjustified but the emphasis should be on more rational use of these medications rather than an either/or debate. Our focus should be to develop policies and protocols which can lead to justified use of antipsychotics, with continuing reviews of the need for these medications. Their editorial is a step in the right direction.

It seems that antipsychotic use in dementia is being demonised in the media.2–4 Policy makers are also pushing for a decrease in their use. I have two issues with the direction this debate is taking us. First, I hope the pendulum does not swing
so far in the other direction, that psychiatrists find it hard to prescribe the medication even to those who will benefit from its use. 

Second, although the main push seems to be towards reduction of antipsychotic use, less is said on how to develop the resources that can provide good non-pharmacological approaches. Audits and targets should not solely focus on the quantity of antipsychotic use in dementia but also on the quality of non-pharmacological approaches available to this population. Long strides are required in this direction to improve behavioural and psychological symptoms of dementia care in the community, hospitals and care homes.


2 Hope J. More than 100,000 dementia patients are given anti-psychotic drugs that 'may kill'. Mail Online 2008; 28 April.


Interventions for self-harm: are we measuring outcomes in the most appropriate way?

Kapur and colleagues provide a brief review of contact-based interventions for self-harm and note their continuing appeal, despite largely unconvincing trial results. The question the authors should have posed is not ‘How might these interventions work?’ but ‘Why, when participants report that the interventions are of benefit, are trial results so unconvincing?’

The importance of self-harm lies in its strong association with suicide. The ultimate aim of interventions in this area is to prevent suicide, but the rarity of suicide makes it difficult to use as an outcome measure. Of those studies reviewed by Kapur et al, only two used death as an outcome. The remainder used repetition of self-harm, which is the best available proxy measure.

Measuring repetition of self-harm is problematic. Hospital-treated episodes represent the standard measure but fail to capture the true pattern of self-harming behaviour, most of which occurs in secret and does not result in hospital presentation. Those who repeatedly self-harm avoid accident and emergency (A&E) departments at all costs and, when forced by the severity of their injuries to present, are adept at concealing the self-inflicted nature of those injuries, resulting in possible misconceiving of visits. There is a need for a reliable, user-designed self-report instrument and a better understanding of the relationship between acts of self-harm and hospital visits.

Hospital-treated episodes do not provide a measure of reduction in self-harm; only a measure of reduction in clinical encounters for self-harm. It is debatable whether reducing clinical encounters is a beneficial outcome for this highly vulnerable and hard-to-reach population (repeat self-harmers). Reducing the number of hospital presentations may cut service costs in the short term; it may not save lives.

In a recent pilot study of a text-messaging intervention for self-harm, we had an interesting case. One of the participants reported during the trial that the intervention (a text message) had saved their life by interrupting a suicide attempt and prompting them to call for help instead of taking an overdose. They were conveyed to A&E and treated for very severe lacerations. Partly as a result, their visits to A&E increased during the 6-month pilot trial compared with 6 months prior to entry: a negative result using hospital-treated episodes as a measure. Two further participants told us that a suicide attempt had been interrupted by the timely arrival of a text message and begged to be allowed to continue to use the intervention at the end of the trial, yet standard reporting of the results of the study would not provide convincing evidence of effectiveness.

So why are trial results unconvincing, despite qualitative evidence to the contrary? The low status of qualitative data is one possible reason. Another is that we are measuring outcomes in inappropriate ways. We do not yet understand what outcomes are important to those who engage in repeated self-harm, nor how best to measure them.


Authors’ reply: We agree with much of what Dr Owens says, but take issue with three points.

First, we disagree that we asked the wrong question. The possibility that a brief message of concern from toxicologists that the individuals may never have met might halve the number of repeat episodes of self-harm is intriguing. Of course we need to ask what the possible mechanisms might be.

Second, self-harm greatly increases the risk of suicide but it is much more than a proxy measure in trials. As clinicians working in accident and emergency departments and mental health settings will testify, self-harm is important in its own right – there may over 200 000 hospital presentations for self-harm in England every year.

Third, although we are all fans of qualitative research and the additional insights it provides, the main reason for negative trial results is not the low status of qualitative data. Negative findings are more likely to reflect the fact that trials to date have been too small to detect clinically important effects (or alternatively that the interventions simply do not work).

Outcomes for trials are definitely an issue and Dr Owens summarises a number of the key considerations. Many studies to date have used repeat episodes of self-harm presenting to hospital as the principal outcome measure. We did argue (perhaps somewhat clumsily) in an earlier version of our article that such repeat presentations might actually be an indication of positive engagement with services. We deleted the offending passage following editorial and reviewers’ comments. The case study that Owens briefly presents is very interesting and of course would not be picked up by standard reporting of trial results. Using qualitative data to comprehensively measure outcomes on all participants in large trials is impractical. A challenge for self-report measures may be the painfully low response rates. However, we would support Dr Owens’ call for a variety of outcome measures – hospital-based and self-report, quantitative and qualitative.

Declaration of interest
N.K. is Chair of the Guideline Development Group for the forthcoming National Institute for Health and Clinical Excellence (NICE) guideline on the longer-term management of self-harm. The views expressed in this letter are those of the authors and not those of the Guideline Development Group, NICE or the National Collaborating Centre for Mental Health.


Correspondence

Correction

Failure to communicate effectively or failure of feedback? (letter). BJP, 197, 332–333. The first author’s name is Raman D. Pattanayak. The online version of this letter has been corrected in deviation from print and in accordance with this correction.

doi: 10.1192/bjp.197.6.503a
Dilemma over antipsychotic use in dementia
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Access the most recent version at DOI: 10.1192/bjp.197.6.501

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