Organic brain dysfunction in late-onset depression

Medical comorbidity is common in late-onset depression. Some studies suggest the presence of mild cognitive impairment in up to 60% of patients with late-onset depression; this constitutes a major diagnostic problem in geriatric psychiatry. In response to the study of neurological findings in late-onset depression by Baldwin et al (2005) we performed an abstract review of Medline publications using the search term LATE ONSET DEPRESSION to identify the possible aetiological factors behind the increased occurrence of neurological signs in late-onset depression. We identified 93 citations published between 1975 and 2005, of which 75 titles were relevant. After reading all citations we found 63 abstracts discussing different aspects of late-onset depression which we have included in the review. The main findings are outlined here briefly.

Although early-onset and late-onset depression are similar phenotypically, there is a possible difference in aetiology. Vascular comorbidity, including an increased prevalence of hypertension, is common in late-onset depression. There is much clinical and biological overlap between late-onset depression and dementia, sometimes the former being the prodrome of the latter. There are at least a dozen studies showing some structural, functional and electrophysiological links between late-onset depression and Alzheimer’s disease. There were observations that late-onset depression is not a prodrome for any particular type of dementia but the majority of patients who develop dementia will acquire Alzheimer’s disease or vascular dementia, as they are the most common forms. From several studies an association with genetic factors or apolipoprotein E could not be established for late-onset depression.

There are a number of structural or vascular factors identified mainly through imaging studies. Region-specific decreases in grey matter (decreased volume of frontal and temporal lobes), ventricular enlargement, sulcal widening and decreased volume of hippocampus and caudate nucleus were reported in more than one study. Deep white matter lesions and increased evidence of vascular events were also found in late-onset depression. Functional imaging studies showed an association of impairment of regional cerebral blood flow in the left anterior temporal and left anterior frontal regions associated with late-onset depression. There is evidence of more frequent electroencephalographic changes in late-onset depression compared with early-onset depression. Moreover, a few studies examining psychological factors concluded that there is a less association between life events and late-onset depression than early-onset depression.

These findings stress the importance of thorough physical examination in late-onset depression, as recommended by Baldwin et al (2005). In the absence of clear guidelines for neuroimaging in psychiatry, a detailed physical examination is necessary for the identification of the patient group in which more expensive and invasive investigations are indicated.


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Recurrence of post-partum and non-post-partum psychosis

The report by Robertson et al (2005) on the rates of recurrence of post-partum and non-post-partum psychosis in women who have experienced a previous episode of post-partum psychosis teaches us something new about the prognosis for these women. The risk of developing a subsequent non-puerperal episode is increased in women who have a family history of mental illness and is non-significantly increased for women with a personal history of illness prior to the puerperal episode. Robertson et al (2005) report rates of relapse following subsequent deliveries of 57%. They did not report the effects, if any, of treatment in preventing further puerperal episodes. Prophylactic treatment was only alluded to in the discussion, where, following a listing of the side-effects associated with lithium and other mood stabilisers, it was stated that treatment should only be instituted following a ‘very careful weighing up of risks and benefits’. This apparently negative emphasis may be unintentional but is unfortunate for two reasons. First, although there are few studies in this area, the rates of recurrence of post-partum psychosis vary widely and have been as high as 90% (Kendell et al, 1987). It is very probable that these recurrence rates vary according to whether women are actively managed with prophylactic medication. Second, clinical observations of the benefits of lithium prophylaxis in post-partum psychosis are supported by some published reports which suggest that lithium prevents recurrence in up to 90% of cases (Stewart et al, 1991; Cohen et al, 1995).

The relatively low rates of recurrence of puerperal psychosis reported by Robertson et al (2005) may partly result from the now common practice of treating women prophylactically with mood-stabilising medication. For perinatal psychiatrists, the risk-benefit weighting of treatment with mood stabiliser v. no treatment in the puerperium for women who have had a prior episode of post-partum psychosis falls down very convincingly on the side of active treatment.


Finally, it is our experience that women have strong views on the acceptability of taking medication during pregnancy and while breast-feeding. This may account for the fact that out of the 54 women in our study who went on to have a further pregnancy, only six took prophylactic medication in the puerperium (lithium or haloperidol). Although only two went on to have a recurrence of puerperal psychosis, the numbers are clearly too small to draw conclusions regarding the efficacy of prophylaxis.

This is an area, therefore, in which management decisions are not straightforward but the frequency and severity of post-partum episodes in women with bipolar disorder must weigh heavily in the risk–benefit analysis. What is needed, we can all agree, is further research to provide empirical data on which clinicians, women, and their families can base these difficult decisions.

| Authors’ reply: We agree with Dr O’Keane regarding the severity and potentially devastating consequences of post-partum psychosis in women with a history of bipolar disorder and assure her that any negative emphasis she detected in our brief comments regarding prophylactic treatment were indeed unintended. The brief report format did not allow us to discuss this aspect of management at length but we have taken up this issue more fully in our recent editorial (Jones & Craddock, 2005).

We would also argue that the evidence base for the use of prophylaxis in women with bipolar illness in the post-partum period is not as robust as would be ideal. As Dr O’Keane has outlined, the literature does support the use of lithium in this context, although the retrospective (and partially overlapping) studies differed in when lithium was commenced – important as there may be practical problems in achieving therapeutic levels quickly following delivery and the onset of puerperal psychosis is typically in the few days following delivery. In our series of 101 women with post-partum psychosis more than half had an onset on days 1–3 with over a fifth on the first post-partum day (further details available from the authors on request).

With regard to other mood stabilisers, there are few data in the literature. A recently published study demonstrated no efficacy for sodium valproate (Wisner et al, 2004) and, despite anecdotal reports of the benefit of typical or atypical antipsychotic medication as prophylaxis, there are no data regarding their use in this context.

Value of measuring suicide intent

The paper by Harriss et al (2005) addresses the very relevant issue of measuring suicide intent in the evaluation of future suicide risk. Measuring suicide intent is more useful than measuring the lethality of the attempts (i.e. the degree of danger to life resulting from self-injurious behaviour; Beck et al, 1975). Assessing the intent can be particularly useful in situations where there is no correlation between the expected and actual outcome of the method used as may happen in those with a low level of literacy. Accuracy of expectations about the likeliness of dying moderates the relationship between suicide intent and medical lethality (Brown et al, 2004). Identifying a cut-off to differentiate between high-intent and low-intent attempts is very difficult. Median scores on the Suicide Intent Scale (SIS) were used by Harriss et al (2005) to categorise high-intent and low-intent attempts. Their results showed that women with high intent repeat suicide attempts whereas men with low intent tend to do so. Since there was a gender difference in the median values, the cut-off score used for males (10) was higher than that used for females (8). By virtue of using separate cut-off scores, men were classified as having low intent even if they had similar scores on the SIS to women in the high-intent group, possibly affecting the repetition rates. Quantifying and classifying suicide intent have been approached in different ways by various researchers. Baca-Garcia et al (2004) studied the characteristics which influence emergency psychiatrists in decisions to hospitalise after a suicide attempt, and found that a cut-off of 11 on the SIS correctly classified 72% of participants. However the authors clearly acknowledge the advantages of using an extensive clinical checklist over an instrument such as the SIS. Although the SIS was not originally designed to predict repetition of self-harm, it may be possible to identify similar cut-off points to predict the likelihood of repetition of suicide attempts when used with other known risk factors. For any risk assessment to be clinically meaningful it should be based on a composite index which takes into account various factors, including the level of suicide intent, the severity of depression, the degree of hopelessness, the impact of life events and the lethality of the attempt.

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Free will and volition

Although I agree with Professor Henderson (2005) that we should acknowledge that
many psychiatric patients have a greater degree of volition, or free will, and hence of moral responsibility, than they are often considered to have, I think that he has made things far too easy for himself. Professor Henderson has simply assumed that we have free will, at the same time maintaining that ‘as brain function comes to be increasingly understood, it is possible that abnormal behaviour will be attributed less to the person’s power of choice in regard to action, and more to abnormalities of brain function or genotype’. Both these assumptions are not uncontroversial and would deserve at least some arguments to lend them plausibility. One of many questions which arise here is ‘why should only abnormal behaviours be attributed less to the person’s power of choice in regard to action and more to abnormal brain function?’ Could not normal behaviour equally be attributed less to the free will of the agent and more to normal brain function as we come to understand brain function better? Henderson has given us no reason to think that this could not be the case with normal behaviour as well.

Interestingly Henderson cites Libet et al (1999) but curiously omits to mention Libet’s famous discovery of a readiness potential arising in the brain some 350 ms before a conscious decision to act is experienced. This finding is usually interpreted as evidence of unconscious initiation of the volitional process, and hence as evidence against freedom of the will. Henderson also quotes Alper (1998): ‘Even if human beings are genetically deterministic systems, their behaviour may still be unpredictable and they may still possess free will’. But if our behaviour is unpredictable or random, then we do not have free will, because free will implies that we are autonomous agents who can bring about our actions intentionally.

Alper, J. S. (1998) Genes, free will and criminal responsibility. Social Science and Medicine, 46, 1599–1661.

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Authors’ reply: Dr Crichton’s points are most useful. He can be assured that I tried to make the topic as easy as possible for the reader, not for myself. He is correct that I have not considered whether free will really exists, simply choosing to make volition the central topic of the editorial. Yes, what I have said applies just as much to minds free of mental illness. There, biological contributions to behaviour are equally likely to be present. What I wrote deliberately did not consider the unconscious, whether or not its presence might be revealed by readiness potentials preceding an action. We are all aware that psychoanalytic theory has made extensive proposals about unconscious origins for normal behaviour. But psychoanalysis and free will are matters to be considered elsewhere, preferably by philosophers rather than clinicians. For myself, I simply retain an interest in the place of personal responsibility in the presence of mental illness. It has been encouraging that the editorial has already caught the attention of some senior judges and lawyers.

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 Violence and offending in people with learning disabilities

I found Reed et al’s (2004) study fascinating, as it demonstrates the apparently random nature of a forensic label in our patients. It is clearly not to do with risk. I am confused by some of the results. The whole gist of the argument is that the offender group is less violent than their non-offender counterparts. However, it is stated in the non-offender group that the challenging behaviour diminishes from 0.79 incidents per week to 0.36 and that for the non-offender group from 0.23 to 0.11. This is challenging behaviour generally but this suggests that those in the offender group exhibit greater challenging behaviour throughout their stay than those in the non-offender group. Table 2 states the opposite. I would be interested to see how this inconsistency can be explained.


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Escitalopram for social anxiety disorder

We noted the findings of Kasper et al (2005) and their conclusion that ‘escitalopram was efficacious in treatment of social anxiety disorder’ with interest. They reported a difference of 7.3 (P=0.005) on the Liebowitz Social Anxiety Scale (LSAS) from baseline to week 12, favouring escitalopram over placebo. They suggested that this difference was comparable to three previous studies that reported the efficacy of paroxetine in the treatment of social anxiety disorder (Stein et al, 1998; Allgulander, 1999; Baldwin et al, 1999).

Unfortunately, without the confidence interval (CI), reliable interpretation of the above difference is not possible. Hence we calculated the standardised effect size, which was 0.22 (95% CI 0.01–0.43). Although the lower limit of the CI is not reassuring, by convention, the point estimate of 0.22 can be interpreted as ‘small’.

We appreciate that small effect sizes can be clinically relevant, especially if the condition treated is common and the putative treatment is easily available, cheap and without adverse effects. In addition, the given treatment must perform better than
other options. We compared the above effect size with the effect sizes for the three studies quoted above. These were 0.83 (95% CI 0.53–1.13), 1.36 (95% CI 0.90–1.80) and 0.38 (95% CI 0.14–0.61), respectively.

We then looked at the number needed to treat (NNT) based on the responders as per the Clinical Global Impression – Improvement (CGI-I) scores. The NNT for the study by Kasper et al. (2005) is 7 (95% CI 4–20) and for the comparative studies, 2 (95% CI 2–3) and 3 (95% CI 3–4), respectively. van der Linden et al. (2000) reported a meta-analysis of the effectiveness of serotonin reuptake inhibitors (SSRIs) in the treatment of social anxiety disorder. They found a collective NNT of 4 (responders on CGI-I) and a mean effect size for all SSRIs of 1.0 (the SSRI/placebo difference at end-point on the LSAS). None of the ten SSRI studies in the meta-analysis included escitalopram.

It is tempting to suggest that the placebo response in the study of Kasper et al. (2005) was high and distorts results. However, if randomisation is presumed to have been successful, an equivalent placebo effect would have occurred in the escitalopram group. The impressive P values reported by Kasper et al. (2005) are likely to be because their study was overpowered and they used analysis of covariance (ANCOVA) which is known to have greater statistical power.

Based on our analysis, among the different SSRIs medications escitalopram is less likely to be effective in the treatment of social anxiety disorder. We suggest that P values can mislead and should not be interpreted as measures of magnitude of effect.


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Authors’ reply: We thank Drs Lele and Joglekar for drawing our attention to the absence of the 95% CIs for the primary efficacy end-point (treatment effect measured as the difference in the Liebowitz Social Anxiety Scale (LSAS) scores from baseline) in our article on the treatment of social anxiety disorder with escitalopram (Kasper et al., 2005). The treatment difference between escitalopram and placebo was 7.3 (95% CI 2.2–12.4) with a standardised effect size of 0.30 (95% CI 0.09–0.51).

When comparing the results of this trial with the literature we looked at the size of the effect of the active treatment, that is, the adjusted change from baseline in LSAS scores, not the standardised effect size. These values are 33.0 (Allgulander, 1999), 29.4 (Baldwin et al., 1999) and 30.5 (Stein et al., 1998), which are comparable to the 34.5 change in our study with escitalopram (Kasper et al., 2005). The main difference between these studies is the placebo response, which was largest in our study.

In interpreting differences in placebo response rate (and hence standardised effect sizes) it is important to recognise differences in study design. One of the paroxetine studies (Allgulander, 1999) was a small (n=92) single-centre trial with a 40% placebo withdrawal rate (compared with 18% for paroxetine) and patients were also required to have been treated for at least 2 weeks. These factors may be responsible for the small placebo effect with the last observation carried forward (LOCF) analysis. In the studies of Allgulander (1999) and Stein et al. (1998) patients were not excluded if they had comorbid depression, which was the case in our study.

Finally, in our escitalopram study the mean baseline LSAS scores in the placebo and treatment groups (95.5 and 96.3) were higher than in the paroxetine studies (70.4 and 78.5 in Allgulander, 1999; 78.0 and 83.5 in Stein et al., 1998; and 86.1 and 87.6 in Baldwin et al., 1999).

We would like to emphasise the appropriate powering of our study. ANCOVA is overpowered if the distribution is skewed but our data are fairly normally distributed. Allgulander (1999) state that their data were skewed and non-parametric tests were used.

In line with the results of our study additional recent data (Lader et al., 2004) confirm the efficacy of escitalopram in social anxiety disorder. In a 24-week study the placebo response was 43.4 compared with 60.8 with 20mg escitalopram and 53.1 with 20mg paroxetine (mean change from baseline). The treatment difference (observed cases) between escitalopram and placebo was 17.4 (95% CI 11.5–23.2) with a standardised effect size of 0.77 (95% CI 0.51–1.03). The treatment difference for escitalopram and paroxetine (observed cases) was 7.71 (95% CI 2.0–13.4) in favour of escitalopram with a standardised effect size of 0.34 (95% CI 0.09–0.59).

After 12 weeks the number needed to treat (NNT) based on the responders as per Clinical Global Impression – Improvement (CGI-I ≤2, LOCF) scores for Kasper et al. (2005) was 6.4 (95% CI 4–19) and 4.8 (95% CI 3–10) for Lader et al. (2004).

To judge a single medication based on the NNT it is necessary to consider all available studies and, based on the evidence published in the literature, we therefore do not agree with the statement of Drs Lele and Joglekar that paroxetine is superior to escitalopram for the treatment of social anxiety disorder.

Declaration of interest

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Choosing psychiatry as a career

As a graduate of 2000 and a participant in Goldacre et al’s survey, I was keen to reflect on which influences led me towards psychiatry and how these compared with those of others. Interestingly, the paper reports that only a small percentage of those entering the specialty had intentions to do so before medical school (18%). Thus major influences on career choice are the curriculum, clinical experience and inspiring teachers. My own experience would be consistent with this, along with an interest held by my peer group at medical school. As an Edinburgh graduate I was interested to find that Edinburgh had the highest percentage of doctors choosing psychiatry, after 3 years, of all UK medical schools. Edinburgh has a notable academic department through which the curriculum is conducted but other medical schools with large academic units do not appear to attract as many candidates into the discipline. If recruitment into psychiatry became a problem, at what point should the curriculum at medical schools be reassessed at a national level or by the Royal College of Psychiatrists? Surely the future of psychiatry is dependent on the engaging of prospective students with the corpus of academic and clinical excellence.


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One hundred years ago

Family care of the insane

In drawing attention last March to the conclusions favourable to the family care of the insane which could fairly be arrived at from the reports of our Special Commissioner on the Care of the Insane Poor, we promised to return to the subject when our Commissioner should have had an opportunity of supplementing his report on the progress achieved on the Continent and in Scotland, and should have given an account of the boarding out of the insane as it is practically carried out in England.

We accordingly invite the careful perusal of the report appearing in this number of the British Medical Journal by our Commissioner on the Family Care of the Insane Poor in England and Wales. From beginning to end this document furnishes a very remarkable contrast to the earlier reports. In every country where family care has been carried out with an intelligent desire to improve the condition of the insane, the method has found warm advocates, and even where there has not been unanimity of approval in detail, family care is proudly pointed to as the most advanced and most beneficent mode of dealing with a great number of the most afflicted class of the population. But in England so little is known of the matter, and so little public interest has been excited in the topic, that many persons were probably unaware of the existence of an English form of family care. It would most likely be hardly justifiable to say that the procedure is carried out in a surreptitious manner, but certainly it is seldom spoken of. Nobody appears to be proud of it, and those who read our Commissioner’s reports will not wonder at this. The system of dealing with these 5,000 and more unfortunate persons of unsound mind is not altogether creditable to a country which, in the early days of non-restraint, was proud to consider itself in the van of progress with regard to the treatment and care of the insane. This is the more remarkable seeing how much attention has been paid to the perfection of the family-care system in almost every other country in Europe.

The condition of the victims of this system is much the same practically as that of all the insane before there were any lunacy laws whatever. These patients are, as our Commissioner justly observes, detached from the general lunacy administration of the country. They are regarded merely as paupers, and are only supervised in so far as they are dependent upon the rates. The public appears to forget that these poor people are sufferers from a condition which renders them particularly dependent. It is notorious that custodians of the insane are particularly liable to the temptations of cupidity and of cruelty, leading, unless there be careful supervision, to the probability of ill-usage and almost the certainty of neglect. The elaborate precautions which the law has gradually made more stringent for the protection of the insane in asylums are well known. Here in great institutions, running like clockwork, where hundreds of eyes are upon everybody, the law provides the most elaborate machinery to prevent abuses. In ludicrous contrast to this is the official neglect of the wretched pauper imbecile, who, being unable from his poverty, friendlessness, and dementia, to make efficient representations for himself, should be the special object of care. At the bottom of all this absurdity and inconsistency is the perverse view of insanity which the English law has made familiar. The law is unwilling to recognize anything as insanity which does not involve danger to the person or the pockets of the lieges. Even where there is personal danger, however, that great nightmare “the liberty of the subject” is always ready to gallop across the scene. Society scarcely recognizes that it owes any duty to the insane who are not dangerous and are not in asylums. The duty of curing the victims of a pitiable disease or of securing kindly and sufficient care for those whose infirmity has obviously made them subjects for public protection, would seem to be insufficiently understood.
It is very unsatisfactory that any of the insane who are under public cognizance, even so far as being paid for out of the rates to the amount of 2s. 6d. to 4s. a week, should be allowed to remain in the disgusting condition described by our Commissioner as not infrequent. If the small payments made by the public, and the very insufficient inspection provided, do not suffice to prevent filthy and insanitary surroundings, overcrowding – ruinous to decency and even morality – and utter neglect of occupation, then it is obvious that other methods must be put in operation.

The facts contained in the earlier reports of family care in other countries has fully demonstrated that the faulty conditions in England and Wales are not inherent in that system. Indeed, the history of the Scotch system tells an instructive story. The insane were long boarded out in Scotland under circumstances even more unfavourable than those now existing in England, often under conditions that were appalling. After the exertions of Sir Arthur Mitchell, and when his exposure of the state of affairs had roused public attention, the present system was organized in that country under the control of the General Board of Lunacy. How this now works our readers know. The early introduction of similar reforms in England should be earnestly striven for.

The general recommendation made by our Commissioner deserve, we venture to think, most careful consideration. If in all cases pauper lunatics were under the jurisdiction and subject to the inspection of the Commissioners in Lunacy it might be expected that more careful selection of guardians and of patients would be made and stringent regulations enforced as to the removal of patients from guardians should unsuitability be found on either side. Boards of Guardians have neither the leisure nor the knowledge to work a system of boarding out properly, and it is no fault of the Scotch system that it is too much decentralized, as every one who has had to work it is aware. The efforts of English reformers ought to be directed not only to placing the patients in family care under the Commissioners, but to strengthening the hands of the latter and reducing the intervention of the Boards of Guardians to a minimum.

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Corrigendum

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You-Seung Kim fullfils the Journal's authorship criteria with respect to the final version of this paper accepted for publication. The authors of this paper should read: Carol S. North, Betty Pfefferbaum, Pushpa Narayanan, Samuel Thielman, Gretchen McCoy, Cedric Dumont, Aya Kawasaki, Natsuko Ryosho, You-Seung Kim and Edward L. Spitznagel.
Choosing psychiatry as a career

B. J. Baig

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