Correspondence

EDITED BY KIRIAKOS XENITIDIS and COLIN CAMPBELL

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Depression post-myocardial infarction

Van Melle et al (2007) reported that cardiac prognosis post-myocardial infarction was not improved by antidepressant treatment (MIND-IT trial). The SADHART and ENRICHD trials reported similar findings and Carney & Freedland (2007), in their commentary in the same issue, suggest these negative findings are a result of insufficient statistical power in the trials. These results are disappointing but perhaps they might have been anticipated.

There is strong evidence that individuals with depression show increased morbidity and mortality from coronary heart disease (Rugulies, 2002) but the mechanisms involved remain unclear. Individuals with a history of recurrent depression, who are otherwise healthy, show increased inflammation, platelet activation, endothelial dysfunction, and reduced heart rate variability and baroreceptor sensitivity. However, with the exception of platelet function, which improves with selective serotonin reuptake inhibitors, these anomalies are not corrected by antidepressant treatment. Furthermore, endothelial function and baroreceptor sensitivity, which can lead respectively to progression of the atherosclerotic process and to sudden cardiac death, do not improve when depressive symptoms are in remission (Broadley et al, 2006). Thus there is no evidence that treatment of depressive symptoms post-myocardial infarction corrects these underlying pathological processes and, if it does not, cardiac outcomes disclosed by clinical trials are unlikely to show improvement irrespective of their statistical power. By analogy, although hyperglycaemia characterises diabetes, tight glucose control alone has only a modest impact on cardiovascular events. Similarly, depressive illness is characterised by acute episodes of depression, but other systemic abnormalities are present and persist between acute depressive episodes. Accordingly, it may be unreasonable to believe that treatments assessed by their influence on the affective state alone will reduce cardiovascular events.

Although it is important to alleviate the suffering associated with developing depression post-myocardial infarction and improve prognosis by addressing the secondary effects of depression (e.g. reduced adherence to treatment and poor health behaviours), treatment needs to be aimed at earlier stages of the disorder. Atherosclerosis begins in childhood and becomes manifest much later in life, with myocardial infarction as a very late presentation. Similarly, depression is a lifelong disorder with onset in early adulthood. It should be noted that currently depression is not even included in cardiovascular risk tables and that individuals with depression might benefit from introduction of statins, or other preventative measures.

We agree with Carney & Freedland (2007) that treatments for depression might alter the risk of cardiac events via pathways that are unrelated to their effects on depression. However, if the focus of research were shifted to the study of earlier stages of coronary heart disease in people with depression, this could be clarified by monitoring earlier indices of heart disease in relation to treatment of depression. It is also recognised that mechanisms for associations between depression and onset of heart disease may differ from those between depression and progression of coronary heart disease post-myocardial infarction. These pathways need to be better understood and present evidence suggests that survival times following myocardial infarction could be improved by developing treatments for depression that also target the underlying cardiovascular abnormalities and by augmenting these by preventative programmes for coronary heart disease in individuals with mood disorders.

Coronary heart disease and depression are two major public health problems and it is of concern that reports of treatments for depression failing to enhance survival post-myocardial infarction may result in less interest in studying the links between them.


A. Korszun Wolfson Institute of Preventive Medicine, Barts and the London, Queen Mary’s School of Medicine and Dentistry, London, UK. Email: a.korszun@qmul.ac.uk

S. Stansfeld, M. Frenneaux Wolfson Institute of Preventive Medicine, Barts and the London, Queen Mary’s School of Medicine and Dentistry, London, UK. doi: 10.1192/bjp.191.5.455

Van Melle et al (2007) present findings from their randomised controlled trial examining the effects of antidepressant treatment for depression following myocardial infarction. I would like to comment on the design of the study. Patients were allocated to two arms: antidepressant treatment and care as usual. Patients in the care-as-usual arm were not told about their research diagnosis of depression. The authors quote Zelen (1979), thus implying that they are following the research design he proposed. However, Zelen’s method seems best suited to trials where there is a ‘gold standard’ control treatment available and the trial is attempting to evaluate a new experimental treatment (Zelen, 1979). In this design, the ethical concerns are mainly about randomising before consent is sought. It must be pointed out that after randomisation, consent is sought from patients in the experimental arm. If they decline, they are moved to the ‘gold standard’ arm (Torgerson, 2001). I am not sure whether the trial of van Melle et al fits into this category.

Furthermore, there are ethical issues about not informing patients about their diagnosis of depression. I am disappointed that the paper did not discuss these in further detail. Their information pack stated
that all patients were free to seek help for their mood problems. Patients may feel tired and low in mood but may not recognise this as depression, for which there are effective interventions available. Is it ethical to withhold information regarding the diagnosis from such patients? Will patients seek help if they are not told they have depression?

Performing research can raise difficult ethical issues and I hope this letter will encourage some debate on this.


A. Shetty  Crisis Team West, Queen’s Medical Centre, Derby Road, Nottinghamshire NG7 2UH, UK. Email: dradarshshetty@yahoo.co.in doi: 10.1192/bjp.191.5.455a

Van Melle et al (2007) found no difference in efficacy and cardiac prognosis between treatment with antidepressive medication and care as usual in patients with depression after myocardial infarction. Carney & Freedland (2007) commented that the lack of difference in efficacy prohibits the demonstration that effective treatment of depression improves survival. They emphasised the need for developing highly efficacious treatments for depression following myocardial infarction. Such a treatment, however, already exists, as electroconvulsive therapy (ECT), and has been shown to have superior efficacy compared with antidepressive medication (ECT UK Review Group, 2003).

A trial using ECT as an intervention will more likely find a superior efficacy compared with treatment as usual and may demonstrate that effective depression treatment improves survival. Because of concerns about the cardiac risks some textbooks do not recommend the use of ECT within 3 months of myocardial infarction. Zielinski et al (1993) found a higher rate of cardiac complications during ECT in patients with a pre-existing cardiac abnormality compared with patients with no pre-existing abnormality. Most complications, however, were transitory and did not prevent the completion of the ECT course. Rice et al (1994) found that ECT increased the risk of minor but not severe complications. They pointed to the advances in ECT techniques which have resulted in improved safety in cardiac patients. The risk of ECT has to be weighed against the risk of an inadequate treatment of depression, which is known to increase mortality (van Melle et al, 2007). Considering the high risk of cardiac events of 13% in the 18 months following myocardial infarction (van Melle et al, 2007), which may partly be attributable to the inadequate treatment of depression, treatment with ECT could be safer because of its superior efficacy as an antidepressant.


K. H. Kho  GGZ Delfland. St Jorisweg 2, 2612 GA, Delft, The Netherlands. Email: kkhko@xs4all.nl doi: 10.1192/bjp.191.5.456

Authors’ reply: To explain why antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs) does not improve cardiac prognosis, Korszun et al suggest that SSRIs may not alter the mechanisms through which depression leads to increased cardiovascular morbidity and mortality. However, two other explanations may be more plausible. First, the effects of antidepressant treatment on depression itself are not strong enough. In the ENRICHD and SADHART trials, the response rates of patients in the active treatment arm hardly exceeded those of patients receiving usual care or placebo. Second, the cardiotoxic effects of depression are limited to patients for whom antidepressant treatment is not effective (Grace et al, 2005; de Jonge et al, 2006b). We have shown that the cardiotoxic effects of depression are concentrated in incident post-myocardial infarction depression, whereas results from the SADHART study have indicated that sertraline is only effective in non-incident depression (of interest, Korszun et al mention mechanisms related to recurrent depression, which appears not to be cardiotoxic). If antidepressant treatment is only effective in non-cardiotoxic depression, no effects on cardiovascular prognosis can be expected.

Shetty raises ethical concerns about our study, because we used Zelen’s method of randomisation. Controls were not told about their diagnosis of depression and, as argued by Shetty, therefore may have ‘missed’ an offer of adequate treatment. However, we feel that in 1999, when the study started, Zelen’s method was both scientifically useful and ethical because no controlled comparative studies had yet investigated the clinical efficacy and safety of antidepressant drugs in depression post-myocardial infarction. At that time, the proportion of myocardial infarction patients with depression who were treated for their post-myocardial infarction depression was negligible. In addition, serious concerns existed about the safety of antidepressant drugs in cardiac patients. Moreover, in our study patients with a significant risk of suicide or severe depression were excluded from randomisation and referred for psychiatric treatment outside the study. Finally, all patients received usual care, i.e. had cost-free access to all usual treatment facilities such as normal cardiac rehabilitation programmes and healthcare from family physicians. We therefore feel it was ethical to use Zelen’s method in our study and scientifically useful as our control patients were truly representative of patients receiving usual care.

We agree with Dr Kho that we need to develop new treatments for depression post-myocardial infarction, but believe it is premature to consider electroconvulsive therapy (ECT) as an effective alternative. In our experience those types of depression that are least similar to those seen in general psychiatry (i.e. incident depression occurring for the first time after myocardial infarction; de Jonge et al, 2006b) and those that are dominated by feelings of exhaustion rather than negative self-esteem or suicidality (de Jonge et al, 2006a) are the most cardiotoxic. To our knowledge the mechanism(s) explaining this remain unclear. Similarly, it is not known whether ECT is effective in these subtypes (although it appears that antidepressive medication is not). In fact, the studies mentioned by Dr Kho suggest increased rather than decreased cardiovascular events.

New, effective treatments for depression post-myocardial infarction will improve quality of life but perhaps also survival, as rightfully argued by Dr Kho. Carney et al (2004) showed that responders to antidepressive medication had a better cardiovascular prognosis than non-responders,
using data from the ENRICHD trial. In the MIND-IT study we recently confirmed that non-response to mirtazapine and citalopram was associated with more cardiovascular events compared with responders and even untreated controls, a finding that remained after controlling for several confounders, including early cardiovascular events (de Jonge et al., 2007). However, as it is unclear what factors are related to response to antidepressive medication (these may well include the presence of somatic symptoms of depression; Tylee & Gandhi, 2005), it also remains uncertain whether it might be an improved state of the heart disease that influences depression or reversely that treatment of depression results in an improved cardiovascular prognosis. However, although causality remains unproven it suggests that more effective treatments may have cardiovascular effects as well. We are not yet convinced that this will be the case.

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**De Jonge, P., van den Brink, R. H. S., Spijkerman, T. A., et al. (2006a) Only incident depressive episodes following myocardial infarction are associated with new cardiovascular events. Journal of the American College of Cardiology, 48, 2204–2208.**


**R. de Jonge** Department of Internal Medicine and Department of Psychiatry, University Medical Center Groningen, The Netherlands. Email: p.d.jonge@med.umcg.nl

**J. P. van Melle** Department of Cardiology, Thoraxcenter, University Medical Center Groningen, The Netherlands

**J. Oremel** Department of Social Psychiatry and Psychiatric Epidemiology, University Medical Center Groningen, The Netherlands
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**Authors’ reply** Dr Berg raises the possibility that respondents in our surveys who reported persistence of ADHD in adulthood might actually have had symptoms caused by some other disorders, such as alcoholism, that are more stigmatising and less likely to be treated than ADHD. Such respondents might consciously have provided incorrect information in an effort to avoid stigma and to increase their chances of receiving treatment. Dr Berg states that such machinations occur in his country. This is an important point in view of the stigma associated with mental disorders and the fact that some healthcare systems discriminate against certain diagnoses. Mental health professionals need to increase their efforts to raise awareness and address these problems.

**That said, it strikes us as implausible that our findings are importantly affected by the sort of bias proposed by Dr Berg. First, the World Mental Health surveys are community epidemiological surveys in which no treatment is provided. Second, in a number of the participating countries ADHD is not commonly recognised as an illness, making it unlikely that community respondents would have the sophistication to seek out this diagnosis. Third, we carried out in-depth clinical reappraisal interviews with a probability sub-sample of respondents who reported adult persistence of ADHD. We excluded respondents if concerns existed that another diagnosis might be primary. Although it is possible that some respondents were so familiar with ADHD that they tricked our experienced clinical interviewers, we consider it unlikely that this was widespread. Fourth, treatment-seeking was low in most World Mental Health surveys. When it occurred, the reason for seeking treatment was not ADHD but a comorbid disorder.**

**Irrespective of whether the type of bias Dr Berg suggested exists in epidemiological surveys, our results imply that clinicians should look more seriously for ADHD in their adult patients than they have before. As more physicians screen for ADHD among adults presenting for treatment of other psychiatric disorders, the extent to which untreated adult ADHD exists among help-seekers will become apparent.**

**R. C. Kessler** Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115, USA. Email: kessler@hcp.med.harvard.edu
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**Heroin-assisted treatment: no difference in treatment retention**

Haesen et al (2007) report highly significant findings from their trial of heroin plus methadone maintenance. A small problem is that the heroin plus methadone group were, to a large extent, self-selected, with only 2.3% failing to initiate treatment in this group v. 28.8% in the methadone only arms. They state that this ‘limiting effect . . . is minimised’ by randomisation and intention-to-treat analysis. Intention-to-treat analysis makes their already significant findings even more impressive, but randomisation is limited by the unavoidable self-selection in a trial which is necessarily not masked. The paper goes on to say that ‘retention was higher in the heroin group, with 67.2% completing the 12-month treatment compared with 40% of the methadone group’, but later this is given as 56.3% for the methadone only group when the 28.8% who did not initiate treatment were excluded. The retention rate would rise again if the drop-out (‘discontinued’) rate was calculated using the same reduced denominator, and therefore retention rates would possibly differ insignificantly. Taking this into consideration would also explain the almost equal numbers of ‘discontinued’ participants in the two main arms of the trial.

The findings of this aspect of the trial are not surprising and without doubt it would be difficult to devise a control with the reinforcing power of heroin. Injectable methadone, financial incentives or pleasurable activities might approximate a substitute and produce more accurate retention figures. With the high cost of freeze-dried heroin, as used in the UK, adding these incentives might attract funding for a suitably modified study conducted here. Given that high retention rates are today’s centrally defined most desirable outcome in the UK, this sort of study might be even more attractive here.

**Authors’ reply**

Dr A. Al-Adwani & Nahata raise an important issue when evaluating the outcome of maintenance treatment, namely how to evaluate the retention rate in an unmasked trial. The special incentive for patients randomised to methadone treatment was the option to switch to the heroin group after completing 1 year of treatment. Since retention is considered one of the main outcome measures for maintenance treatment, our trial shows that heroin-assisted treatment has two advantages: it reaches a higher number of potential patients (percentage initiating treatment) and the retention rate of those initiating treatment is significantly higher (68.3 v. 56.3%, log rank $\chi^2=14.1$, $P<0.001$). Therefore, it is incorrect to say that ‘retention rates would possibly differ insignificantly’: the difference is certainly less, but still significant.

**Factors in those who repeatedly self-harm**

We read with interest the article on young people who self-harm (Young et al, 2007) but feel the outcome of factors considered would have been more viable if a further subgroup analysis was performed in those patients who repeatedly self-harm. A significant amount of our time is taken up by people who self-harm repeatedly. This subset of clients are often entrenched in their behaviour patterns and use services disproportionately. Existing studies have not adequately analysed factors responsible for repetition of self-harm and we feel that Young et al missed an excellent opportunity to investigate this, albeit in a younger age-group.

An analysis of our data from the Integrated Care Pathway (Rajwal & Gash, 2006) showed repetition rates of 40% for 2004, 42% for 2005 and 43% for 2006 of all our referrals each year. This means that 18% of our patients in 2004, 18.9% in 2005 and 19.2% in 2006 were responsible for the above statistics year on year. These data are from adults of working age and only include repetition in the same calendar year. About 13% of our referrals are under 21, and 18% of those are for repetitions of self-harm. Hence a small proportion of our clients are responsible for a large proportion of our work.

Our data support Young et al on the lack of a gender bias in the prevalence of self-harm. Females comprised 50.2% of our referrals in 2006 but only 49.0% of those repeating self-harm. The old myth of a higher proportion of females self-harming was not borne out by our statistics, although we considered the entire adult age-group.

We would be interested to know whether the results of Young et al would be different in the subgroup with repeated self-harm.

**Authors’ reply**

Kripalani et al raise an important issue by suggesting that those who repeatedly self-harm may constitute a distinctive clinical subgroup. We initially avoided including this group in our study because there remains considerable uncertainty about an appropriate definition. However, following discussion with Dr
Attachment disorders: an evolutionary perspective

In a large twin study Minnis et al (2007) have demonstrated that attachment disorder behaviours can be differentiated from other common childhood emotional and behavioural disorders and appear to be strongly genetically influenced, particularly in boys. The authors also point out that, even in a population of children that was probably healthier than the general population, behaviours suggestive of attachment disorder were identified. Conventional aetiological factors are addressed but the paper would have benefited from the inclusion of an evolutionary perspective. Evolutionary or Darwinian psychiatry examines, among other things, the potential for adaptive benefits to pre-programmed psychobiological mechanisms (e.g. depressive symptoms or attachment disorders) that are sometimes incorrectly viewed as being simply abnormal or pathological (Abed, 2000).

It was surprising that Minnis et al made no reference to Bowlby’s seminal work (Bowlby, 1958) in the area of attachment. Bowlby’s perspective on attachment was an evolutionary one, in that he viewed the associated behaviours as representing evolved and adaptive psychobiological mechanisms, protecting the child from predators and the many other dangers prevalent in our ancestral environment. This ‘adaptationist’ perspective could have been explored by Minnis et al when considering why attachment disorder behaviours occurred at all in this healthy non-clinical sample.

Chisholm (1996) and Belsky (1997) proposed in more recent years an integration of life history theory (Levins, 1968) and attachment theory. Chisholm (1996) argued that, in life history theory, life cycles constitute evolved adaptive strategies. Furthermore, individuals must prioritise the allocation of their time and resources to different components of reproductive fitness (e.g. growth, mating or parenting). Therefore, the sexual strategy employed by parents (e.g. low investment in large numbers of offspring or vice versa) is an integral component of the child’s early environment. Belsky (1997) argued that secure attachment in children functioned to promote a strategy of high-investment parenting, and avoidant attachment (child showing indifference to parent) as representing an adaptation to parental unwillingness to invest (e.g. when the parent invests instead in a short-term mating strategy with relatively little investment in individual offspring).

The anxious/ambivalent style of attachment evolved in response to parental inability (e.g. through illness) to invest, and fostered a ‘helpers at the nest style’ in the children, whereby children would cooperate in rearing siblings. For example, Turke (1988) demonstrated (independent of attachment disorders) that women from the Micronesian atoll of Ifaluk were likely to have significantly larger families when their first-born was female: an anxious/ambivalent attachment style may further accentuate such behaviour in female children, perhaps explaining in part the gender differences in attachment disorders raised by Minnis et al.

These are merely a few examples of the insights that evolutionary psychiatry can provide. In the total absence of such an evolutionary perspective, one is reminded of Abed’s (2000) cautionary comments: ‘In recent years psychiatry has attempted to circumvent such problems by engaging in an atheoretical research enterprise involving gathering masses of data and calculating sophisticated statistical associations. However, such an endeavour of itself cannot generate a scientific discipline, for science is a method of discovering the world and not simply a body of facts’.


H. P. O’Connell Clare Mental Health Services, Lisdoonvarna, County Clare, Ireland. Email: hpoconnell@yahoo.ie

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We were interested to read Dr O’Connell’s response to our paper. Unfortunately we did not have space to do justice to a discussion of reactive attachment disorder from an evolutionary point of view, although we agree that this is an important theoretical perspective. Dr Minnis first became interested in reactive attachment disorder when working as an orphanage doctor in Guatemala. Most of the children there displayed symptoms of the disinhibited form of the disorder and it seemed clear that these behaviours were adaptive in a setting where primary attachment figures were lacking. We have touched on the maintenance of these behaviours from an evolutionary perspective in a previous paper (Minnis et al., 2006).

Dr O’Connell also points out that we did not engage in a discussion of attachment theory, or the work of John Bowlby (Bowlby, 1973). We do not wish to underestimate the crucial role of Bowlby’s work in advancing our understanding of childhood development, however, we were unable to do justice to the complex interplay between attachment patterns and reactive attachment disorder within the space allowed. This important topic is the focus of our previous publication (Minnis et al., 2006). In short, children can be securely attached while suffering from reactive attachment disorder and children suffering from the disorder have difficulties in various domains of early development, not simply the domain of attachment (Richters & Volkmar, 1994; Green & Goldwyn, 2002). Research into reactive attachment disorder is in its infancy and is a field ripe for exploration on a number of fronts.


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One hundred years ago

**Stereotypy in Dementia Praecox**

[Étude clinique sur la stéréotypie des démences précoces]. (Arch. de Neurol., March, 1905.) Dromard, G.

Stereotyped movements are not limited to dementia præcox, but occur in secondary dementias, and also in some systematised delusional states. Many followers of Kraepelin, however, would bring these last largely under the head of dementia præcox.

1. **Classification:**

   (A) __Akinetik stereotypy._ – Attitudes, either of the whole body or of an individual member. Refusal of food, and mutism – though usually referred to negativism – are sometimes examples of akinetic stereotypy – e.g., a patient who refuses to eat, but who offers no resistance when fed with the nasal tube.

   (B) __Kinetic stereotypy._ – Movements, which may be further subdivided into stereotypes of (1) __speech__ – e.g., neologisms, constantly recurring words and phrases, modes of intonation; (2) __writing__; (3) __expression__ – e.g., grimaces; (4) __walking__; 

   (5) __complex stereotypies__ – e.g., special modes of sitting, eating, or dressing. Masturbation is sometimes referred to in this group.

2. **Evolution.** – The stereotypies of the acute stages of the disease must be distinguished from those of the terminal period.

   (A) __Primitive stereotypies._ – The prolonged attitudes and repeated movements of katatonia. The failure of physiological plasticity, the impeded psychical process of the katatonic, are probably of toxic origin. The movements are angular, jerky, awkward, like those of a mechanical toy. This type of movement tends to disappear in later stages.

   (B) __Secondary stereotypies._ – Those of the terminal period. These are not to be correlated with a functional failure in the cells, but with an organic defect, the result of the previous toxin. These movements therefore arise from imperfect intercellular connections – that is to say, a state of disaggregation. Secondary stereotypies are the residue of acts which, though once adapted, conscious, and voluntary, are now purely automatic. The original idea is often to be found in the hallucinations and delusions, accompanied by profound emotional colouring, which occur in the early period of the disease. “Professional” acts also frequently form the basis of subsequent stereotypies, but some automatic movements must be regarded as of fortuitous origin.

   Although the secondary forms imply a more advanced stage of disease than the primary, they nevertheless may occur comparatively early, often contemporaneously with the latter. This is analogous to the co-existence in a tissue of inflammation and sclerosis.

   Secondary stereotypies tend to become reduced in number as time goes on, those remaining being usually those first formed.

3. **Clinical value.**

   To preserve the value of stereotypy as a clinical sign, the meaning of the word must be strictly limited. A repeated action is not stereotypy if it is still joined to an idea. Acts committed under the influence of obsessions, the conjurations of paranoia, etc., must therefore be excluded.