Is DISC1 really a gene predisposing to psychosis?

In their editorial on chromosomal abnormalities and psychosis Muir et al (2006) concluded that DISC1 ‘is an important modulator of risk for schizophrenia and severe affective disorder in people without cytogenetic abnormalities and may also influence cognition and brain structure in the general population’. They base their conclusions on work that originated in the finding of a rearrangement between chromosomes 1 and 11 in a single large family with polymorphic psychiatric syndromes (Millar et al, 2001). The two genes (DISC1 and DISC2) that they are concerned with were identified at the breakpoint and by linkage analysis were postulated to be relevant to psychiatric disease within that family.

Muir et al argue that these findings are relevant to schizophrenia in general. However, the evidence is less compelling than they suggest. Figure 1 presents the findings of the three largest linkage studies to date in relation to the location of DISC1 on chromosome 1 (the location of another ‘candidate gene’ RG34 is also shown). Each study included over 300 sibling pairs with schizophrenia or schizoaffective disorder and each included markers spaced at 10 cM intervals across the genome. The Lod (log of the odds) score is a measure of linkage – transmission of a disease state with particular genetic markers within families – and values above 3 are generally taken as significant evidence for linkage. In these three studies there is no evidence of linkage at the DISC1 locus or elsewhere on chromosome 1. The two claims of linkage made in Table 1 of Muir et al’s editorial relate to post hoc subdivision of one of these populations by diagnosis and to a finding in a separate smaller Finnish study. Given the ubiquity of psychosis across populations, and the relative uniformity of incidence of the core syndrome, and in the face of lack of evidence of linkage in populations of over 1000 sibling pairs (Crow, 2007), it is difficult to see that DISC1 can have an ‘important role in the development of psychosis’ as Muir et al argue. The evidence has been overinterpreted.

**Correspondence**

**EDITED BY KIRI AKOS XENITIS AND COLIN CAMPBELL**

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**Authors’ reply:** Professor Crow takes issue with our view that DISC1 is important to schizophrenia in general and is not restricted to the initial family in which disruption of this gene was reported. His argument is based on a selected set of sibpair studies whose results do not support linkage anywhere on chromosome 1. This finding was unsurprising in view of the lack of power of such studies in the presence of genetic heterogeneity in schizophrenia susceptibility, which was not mentioned by Professor Crow. We and a large number of other workers in the field consider that such locus heterogeneity is highly likely and have shown that the sib-pair strategy has limited power to detect a locus that contributes less than 20% of the variance (Macgregor et al, 2002). Where heterogeneity is expected then linkage analysis, especially of extended multiplex pedigrees, and gene candidacy identified through the investigation of psychosis-associated karyotype anomalies are appropriate research strategies. Where there is a priori evidence from cytogenetic and linkage studies (such as the Finnish studies mentioned in the editorial) then the case–control association approach provides a useful resource to delineate potential population haplotype distortions that may indicate underlying functional mutations.

We would therefore disagree strongly with Crow in his statement that we have ‘overinterpreted’ the importance of DISC1 and commend an excellent review of schizophrenia neurobiology which emphasises heterogeneity (Ross et al, 2006). Although our theoretical framework differs from that of Bleuler (1950), we feel that the recent genetics and neurological discoveries are in agreement with his position that there is indeed a ‘group of schizophrenias’.

**Prof. Edward Bleuler**

**Dementia Praecox or the Group of Schizophrenias**


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**Fig. 1** Linkage studies of DISC1 in sibling pairs with schizophrenia or schizoaffective disorder. — DeLisi et al, 2002 (382 sibling pairs); --- Williams et al, 2003 (353 sibling pairs); — Suarez et al, 2006 (409 sibling pairs).
Hippocampal and amygdala volume reductions in first-episode schizophrenia

Steen et al (2006) performed a systematic review and meta-analysis of cross-sectional and longitudinal magnetic resonance imaging (MRI) studies of brain volumes in patients with first-episode psychosis and healthy controls. Despite some methodological differences, the findings were in line with a recent meta-analysis performed by our group (Vita et al, 2006).

A significant decrease in hippocampal but not amygdala volumes was found in patients at illness onset in both reviews. Another relevant paper reporting amygdala and hippocampal volumes in a large sample of patients with first-episode schizophrenia was published after these two meta-analyses (Velakouls et al, 2006). Thus we considered it worthwhile to conduct a new set of meta-analyses including these MRI data.

The results of the new meta-analyses for hippocampus (7 studies, 290 patients, 355 controls) and amygdala (5 studies, 218 patients, 175 controls) confirmed our previous findings. Even with the inclusion of the study of Velakouls et al (2006), the composite effect sizes for the hippocampus remained significant ($d = 0.357$, 95% CI 0.208–0.541 for the right hippocampus and 0.574, 95% CI 0.405–0.742 for the left hippocampus) whereas those for the amygdala were not ($d = -0.046$, 95% CI $-0.247$ to 0.154 for the right amygdala and 0.025, 95% CI $-0.175$ to 0.226 for the left amygdala).

These results, in line with those of Steen et al (2006), support the hypothesis of different patterns of involvement of temporo-limbic structures over the course of schizophrenia, with the hippocampus affected earlier than the amygdala. In our opinion, these findings have important implications for future neurobiological studies of schizophrenia and emphasise the importance of longitudinal studies to address the issue of different times of occurrence and progression of brain abnormalities in people with first-episode schizophrenia.


Effectiveness of cognitive–behavioural intervention by mental health nurses in schizophrenia

Turkington et al (2006) report on outcomes of an effectiveness trial of brief cognitive–behavioural therapy (CBT) by mental health nurses in schizophrenia. Unfortunately there are flaws in the methodology, which casts major doubts on the validity of the study (Quitkin et al, 2000). First, although the authors claim to have a control group, it seems that patients in the control group did not have a placebo-like intervention; for example, the nurses could have spent the same amount of time with the patients without providing the CBT intervention. What is more surprising is that the study was powered to give a 90% chance of detecting only a 25% level difference in overall symptoms at the 0.01 level of significance. A 25% difference between a treatment and non-intervention group can easily be accounted for by a placebo effect. It is well known that the placebo response rate is usually around 30% in psychiatric trials. For over 50 years the inclusion of a placebo control group has been the standard for determining the efficacy of an intervention. Without an adequate comparison group and without adequate comparison conditions, it is impossible to differentiate any specific effects from other ‘non-specific’ factors, including chance variation, regression to the mean, healthcare provider attention, treatment credibility and rationale, persuasion, patient expectation effects, researcher allegiance effects, effort justification, spontaneous remission, demand characteristics, etc. (Lohr et al, 1999).

Given the lack of a true control group this study would be called nothing but an open-label trial. Open-label trials require at least a 50% level difference in overall symptoms between baseline and post-intervention response; moreover they do not require huge numbers of patients to show a tendency towards improvement.


Authors’ reply: We believe that Dr Alam has misunderstood the difference between efficacy and effectiveness research. The national guidelines on the clinical management of schizophrenia (National Institute for Clinical Excellence, 2002) confirmed CBT to be an evidence-based treatment for persistent symptoms of schizophrenia. However, that decision was based almost entirely on efficacy trials where CBT was given by expert therapists to highly selected samples of people with schizophrenia without comorbidities and using an active comparator such as befriending or supportive counselling (e.g. Sensky et al, 2000). Expert therapists and uncomplicated patients are
has for some years used reinforcement principles to target illicit opiate and crack cocaine use. Urine samples are regularly tested and the results used alongside clinical judgement to determine the proportion of a client’s total daily opiate dose which may be administered intravenously as opposed to orally. In this way, access to injectable rather than oral opiate preparations is the ‘reward’ for positive behaviour. Staff increase or decrease the injectable proportion of the client’s prescription depending on the client’s stability.

As a first step towards developing an intervention study (Medical Research Council, 2000) we completed qualitative interviews with staff and clients to assess attitudes towards the further development of reinforcement methods. Staff and clients both cautiously supported reinforcement principles, and staff perceived clients to be more stable and less likely to use illicit substances under the present reinforcement scheme. Nevertheless, challenges were also highlighted. Most staff had reservations about developing voucher-based contingency management, citing possible increased workloads and a potential for damage to staff–client relationships. Despite a strong commitment to harm minimisation strategies at the clinic, some staff also had ethical objections to the development of voucher-based contingency management.

Our study was small and more research is required to explore the feasibility of voucher- or prize-based contingency management. However, as Petry emphasises, contingency management strategies have a good evidence base in a complex and challenging client group where positive outcomes are elusive. It is surely time to evaluate whether contingency management has a place in UK drug treatment services. Our work suggests that debate about the theoretical basis of contingency management and its ethical implications is needed to win support for experimentation among hard-pressed drug treatment workers in the UK.

**National Institute for Clinical Excellence (2002)**
Care Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care. NICE.


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**Contingency management for substance misuse**

Petry (2006) provides a welcome review of contingency management in substance misuse settings and expresses surprise that it has not been employed more widely in Europe, particularly given the greater acceptance of ‘harm minimisation’ here than in the USA, where contingency management has been championed. This is broadly true but some UK drug services are experimenting with interventions informed by reinforcement principles.

The injectable opiate clinic at the Chelsea and Westminster Hospital in London Centre, Chelsea and Westminster Hospital, London, UK

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**Author’s reply:** McQuaid et al report that clinicians working in their injectable opiate clinic were cautiously supportive of the use of injectable opiates for reinforcement but more hesitant about the use of voucher- and prize-based contingency management procedures.

These perceptions mimic those of clinicians in the USA. Upon initial exposure to contingency management interventions, many clinicians express concerns ranging from hesitation to outright opposition. However, after observing the beneficial effects in practice great shifts in attitude occur. Some who were initially the greatest critics become the strongest supporters of contingency management once they see its benefits with particularly difficult clients.

As in the London programme, critics often evoke ‘ethics’ to dismiss contingency management. This denunciation is paradoxical, as reinforcement principles upon which contingency management interventions are based are operative in every facet of life. Furthermore, one must wonder about the ethics of withholding an efficacious intervention. It was not long ago that opiate substitution treatment, now considered one of the most effective prevention interventions for HIV transmission, was itself labelled unethical.

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**Depression and anxiety after myocardial infarction**

Dickens et al (2006) stress the importance of detection and treatment of anxiety and depression for quality of life after myocardial infarction and point to the mediating role of energy and fatigue.
We agree that depression following myocardial infarction predicts long-term quality of life and we recently showed that this effect persists after controlling for cardiac condition and quality of life at 3 months post-myocardial infarction (de Jonge et al., 2006). However, it is unclear whether and how detection and treatment of depression can counter these effects. In the SADHART study Glassman et al. (2002) found that the effects of sertraline were modest and appeared to be restricted to depression with an onset before the infarction, but Dickens et al. found that depression and anxiety which were present before myocardial infarction did not predict quality of life. In the ENRICH/D trial (Berkman et al., 2003), cognitive–behavioural therapy had modest effects on depressive symptoms at 6 months post-infarction in patients with depression and social isolation, but these effects diminished over time. In the EXIT trial (Appels et al., 2005), where the focus of treatment was explicitly on vital exhaustion, only some intervention effects were observed and these were modified by the presence of a previous cardiac history.

We agree with Dickens et al. that there is a need for improved detection and treatment of depression and anxiety following myocardial infarction but several questions need to be addressed. These include: ‘can the effects of depression and anxiety be linked to specific subgroups of emotional disorders based on symptoms and/or on set?; ‘can interventions that were developed in general psychiatry be applied to depression post-myocardial infarction or should they be adapted?; and ‘how can psychiatric interventions be integrated into regular cardiac Aftercare?’

**Authors’ reply:** We agree that although observational studies have shown that depression is associated with subsequent impairment in health-related quality of life in coronary heart disease, intervention studies have failed to provide convincing proof that treating depression improves this outcome. Previous intervention studies have not addressed this question satisfactorily because the SADHART study (Glassman et al., 2002) was not sufficiently powered to demonstrate the efficacy of antidepressants in coronary heart disease and the ENRICH/D study (Berkman et al., 2003) did not anticipate very high rates of spontaneous remission of depression or unplanned prescription of antidepressants in the control group. The results of these trials, however, together with our own results are valuable for planning future treatment trials.

We also agree that there are many unanswered questions relating to the nature of the association between depression and negative outcomes in coronary disease. As mentioned by de Jonge & Ormel, the timing of the onset of depression (Dickens et al., 2004a), the specific aspects of depression or anxiety that are associated with poor outcome and the possibility of vulnerable sub-populations of patients (such as those without social support) (Dickens et al., 2004b) require further investigation. Furthermore, whether the association between depression and negative outcomes in coronary disease is the result of residual confounding by severity of heart disease (Dickens et al., 2005) remains unsolved. Further research is required to address these questions, although it is likely that most will only be convincingly resolved through intervention studies.

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**High female suicide rates: ecological fallacy or sad reality?**

Yip & Liu (2006) present a demographic perspective of female suicide in China, the only country in which the suicide rate is higher among women than men. However, this reversed gender representation also exists in certain communities in other countries. In the Indian subcontinent suicide rates are higher in men than in women but the difference is lower than in most countries: the male:female suicide ratio in India is 1.3:1 (Cheng & Lee, 2000). Suicide among immigrants from the Indian subcontinent to Britain was higher among young married women than men (Soni Raleigh et al., 1990). Tadros & Salih (2006) also reported that significantly more Asian women than Asian men killed themselves in Birmingham and Solihull, a clearly reversed gender ratio compared with suicide in the White population and in other ethnic groups in Birmingham and the UK as a whole.

Suicide terrorism is not an egotistic suicide but none the less is a form of fatal self-harm in the legal and human sense and has a distinct underlying political, individual and social logic. The support of and acceptance by the attackers’ own communities ensure an endless supply of volunteers who seek ‘voluntary violent death’ in a bizarre act of so-called martyrdom, in order to promote what they firmly believe to be a just cause. Women carried out 15% (64) of such attacks over the past 25 years (Pope, 2005). Chechen women carried out 60% of all suicide bombings in Russia.
and 70% of such attacks were executed by Kurdish women in Turkey (Pope, 2005). There is also a high proportion of women suicide bombers in the Tamil Tigers (30%), al Qa‘ida, which associates itself with Islamic fundamentalism, never used female suicide attackers from its formation in 1993 until the tragic attack in Jordan in 2005.

In general, women are at a lower risk of suicide than men and a protective effect of child-bearing in terms of suicide risk has been postulated (Catalan, 2000). This does not appear to apply to female suicide bombers or to some countries and cultures in which gender representation in suicide is reversed. A higher female:male suicide ratio is not unique to China. The significantly higher rate of female suicide observed outside China is not an ‘ecological fallacy’ but a sad reality.

We also believe that socio-economic deprivation and poor social support – the ‘sad reality’ – faced by young women in rural China are underlying causes of the high suicide rates. Like the young married Indian women in Britain, there is some indication that young married women in rural China might be at high risk (Pearson et al, 2002). This reminds us that the lives of married women differ greatly across regions, countries, cultures and economies, and there is a need to avoid oversimplification when describing suicide in different countries; one size does not fit all.

Over 60% of the world’s suicides occur in Asian countries where low male:female ratios for suicide are common (Yip et al, 2000). Although the official male:female ratio for suicide in India was still greater than 1 (1.2:1 in 2002), the ratio was 0.8 among those aged 14 or below (World Health Organization, 2006). However, unlike China (Yip & Liu, 2006), the small size of this population subgroup meant that the national male:female ratio remained greater than 1. (This is the essence of our ecological fallacy argument.) In addition to specific social factors, the similarity in the methods of suicide used by males and females, together with the poor access to medical facilities, might explain the low male:female ratio in India and China. Restricting access to pesticides will prevent many suicides in Asia. In the long term improving economic and educational opportunities, especially for rural women in deprived areas, raising awareness of depression and better treatment will be pivotal for preventing suicides.

Authors’ reply Salib & Tadros highlight the important issue of high female suicide rates among Indian migrants and the use of female suicide bombers. Like the high suicide rates among young females in rural China (Yip & Liu, 2006), these deviations from the general pattern should not be discounted as mere exceptions but should be considered as representative of the distressing situations faced by some women in Asia.

**Self-poisoning with pesticides in India**

Bertolote et al (2006) report the global response to deaths from pesticide poisoning. Suicide rates in southern India have been reported to be high (Joseph et al, 2003; Aaron et al, 2004; Abraham et al, 2005; Prasad et al, 2006), with 1741 suicides documented in a population of about 100,000 from 1986 to 2005. Hanging (804 of 1741, 46.2%) and poisoning (746 of 1741, 42.8%) were the methods most commonly employed. Although people under 40 years tended to use poisons, older people tended to choose hanging ($\chi^2=36.71, \text{d.f.}=4, P<0.001$). Significantly more males (465 of 984, 47.3%) than females (281 of 757, 37.1%) ($\chi^2=17.6, \text{d.f.}=1, P<0.001$) chose death by poisoning. There was no significant change in the overall rate of suicide or the method employed during the period. Detailed analysis of the data from 2001 to 2005 revealed that only 68% of the fatal episodes of self-poisoning were a result of ingestion of pesticides.

Self-poisoning with pesticides is a significant public health problem in low- and middle-income countries. The majority of such poisoning occurs in rural agrarian households. Some suggestions to reduce such deaths are currently difficult to implement. Enforcing the hazardous chemicals and wastes conventions to restrict and control the sale and use of pesticides in such regions is no small task and requires major political, administrative, financial and social commitment. Given the many competing demands on limited governmental resources in low- and middle-income countries, such protocols are difficult to implement. In addition, the improved recognition and treatment of mental illness may not have a significant impact on the overall suicide rate as many people in the low- and middle-income countries who die by suicide do not have severe mental illness. Rather, the majority of such attempts are impulsive and follow stressful life events. Although reducing accessibility to pesticides will decrease such impulsive attempts and consequent deaths, social, economic and cultural factors must also be addressed to make a real difference. Thus, although the World Health Organization’s intersectoral global initiative is a step in the right direction, it is imperative that practical issues related to its implementation are discussed. It is necessary to consider
strategies to encourage governments to set up suicide prevention programmes to reduce suicide rates in populations as a whole rather than method- and site-specific rates.

Suicide in low- and middle-income countries is not only a medical and public health problem but is also related to economics and culture. A coordinated and a comprehensive response is needed to make any impact.

One hundred years ago

The increase of temperance

The Inland Revenue returns show a steadily progressive decrease in the consumption of beer and spirits in the United Kingdom since 1899; that is in encouraging contrast with the equally steady but more rapid increase up to that date.

The beer consumption in 1899–1900 was 32.2 gallons per head of the population, making a total of 36.5 million barrels, but in 1905–1906 this had fallen to 27.9 gallons per head and to 33.5 million barrels.

The spirit consumption has also fallen each year from 1.17 gallons per head and a total of 48 million gallons for 1889–1900 to .90 gallons per head and 39.1 million gallons in 1905–1906.

The reduction in the consumption of spirits is very striking, and in addition to the reduction in the total quantity of beer consumed there is to be added the large increase in the proportion of the lighter beers of home and foreign manufacture.

Pauperism, crime, and insanity are so largely attributable to the abuse of alcoholic drinks that the statistics of each should be carefully watched during the next few years for any indication of an improvement. It is, of course, possible that this reduction may be due only to the greater moderation from necessity or improved habits of the middle and upper classes only, although it would appear to be too large to be thus explained.

Abuse of alcohol, in the statistics of the causes of insanity, has fluctuated very little for many years past, so that any distinct diminution would be very significant, and should encourage a still more vigorous crusade in favour of true temperance – the use without abuse of the cup that cheers and may inebriate.

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