Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents
- Tryptophan depletion in addictive behaviours
- Encephalitis and schizophrenia: a matter of words
- Loss of autism in DSM-5
- The Department of Health and the Equality Act 2012
- Monitoring cardiometabolic risk in schizophrenia

Tryptophan depletion in addictive behaviours

We read with interest the article by Cox et al and the insightful editorial by Nutt and applaud both the research staff and the patients involved in this important study in view of the ethical issues and challenges in their work. They provide supportive evidence that low serotonin activity can increase dopaminergic responses to cocaine in humans, suggesting a possible mechanism specific to ‘a low-serotonin state’ in causing addictive behaviours. Although illuminating, the results of the study should be interpreted with caution.

First, Cox et al use acute tryptophan depletion producing a reduction in plasma tryptophan, assumed to represent low levels of serotonin in the brain. The primary neuropharmacological effect of cocaine is to block the uptake of monoamines released into synapses, thereby increasing synaptic monoamine availability. It has been shown that cocaine can increase extracellular levels of serotonin in the nucleus accumbens of rats. Notably, in Cox et al’s study, plasma concentrations of tryptophan did not significantly differ between cocaine and placebo, which appears to be an unexpected finding. This should be left open to discussion. Second, the interplay between serotonin and cocaine may be altered after repeated cocaine administration, a common manifestation in ‘real-world’ cocaine users. In this context, a study using an acute tryptophan depletion method plus repeated cocaine administration for patients with or without cocaine dependence, although ethically challenging, may obviously be of great clinical significance. Third, using repeated measures ANOVAs, it was assumed that the effects of cocaine did not carry over across conditions. Thus, it would have been clearer if the intervals between each condition were defined.

In addition to the issues raised by Nutt, as to the differences in response to various drugs of addiction, we would like to suggest that future research in the field of addiction focuses on using the tryptophan depletion test. For example, we now know that in pathological gamblers, dopamine release in ventral striatum correlates with excitement levels during the Iowa Gambling Task. However, tryptophan depletion significantly decreased, rather than increased, the number of decisions made to chase losses and the number of consecutive decisions to chase, independent of changes in mood. These findings, indubitably, did not support the hypothesis that low serotonin transmission may predispose to increased susceptibility to impulsive behaviour. It would be of interest to investigate the extent to which tryptophan depletion regulates dopamine release in patients who gamble, or in other populations with addictive behaviours, such as internet addiction or sex addiction, under control of the relevant stimuli.

Finally, in the editorial by Nutt, it is unclear as to the statement ‘it seems that this might be the case as in Cox et al’s study lowering 5-HT function by tryptophan depletion led to a reduction in the actions of cocaine to release dopamine that was to some extent paralleled by a reduction in cocaine craving’.

The study by Cox et al showed that low serotonin activity augmented, rather than diminished, dopamine release in response to cocaine.

In summary, Cox et al’s study is a valuable contribution to the field of addiction, and we anticipate further studies examining the relationship between experimental reductions in serotonin activity and endogenous dopamine release in various addictive behaviours under control of the relevant stimuli.

5 Linnet J, Moller A, Peterson E, Gjede C, Doudet D. Dopamine release in ventral striatum during Iowa Gambling Task performance is associated with increased excitement levels in pathological gambling. Addiction 2011; 106: 383–90.

Authors’ reply: Liang & Ho raise a number of interesting points. First, participants were tested following cocaine ingestion while in a low serotonin v. control state. Investigating the effects of repeated cocaine use in these states, we agree, would be interesting. Second, cocaine ingestion did not alter plasma tryptophan levels. We consider this a strength. Although acute cocaine administration increases extracellular serotonin levels, this need not be associated with decreased tryptophan levels in the periphery. In comparison, tryptophan levels fell as expected after the acute tryptophan depletion procedure, changes that are indicative of decreased availability of the serotonin precursor in brain. Third, Liang & Ho cite recent work indicating that greater striatal dopamine release in pathological gamblers correlates with higher subjective excitement and poorer performance during the Iowa Gambling Task. Our own study raises the possibility that individuals exhibiting the largest dopamine responses might have lower serotonergic tone. Although Campbell-Meiklejohn et al’s elegant study suggests that low serotonin increases sensitivity to punishment when healthy participants perform an unfamiliar task, other work indicates that serotonin induces the opposite effect in response to highly salient rewards. Moreover, numerous impulsivity subcomponents have been proposed, and serotonin’s contribution to them seems to vary. Fourth, the minimum time between cocaine test sessions was 2 days, well beyond the drug’s plasma half-life of 40–60 min. Average time between test sessions 1 and 2 was 30 days (s.d. = 19), and 36 days (s.d. = 46).
between sessions 2 and 3. These sessions were randomised and counterbalanced, and no order effects were observed.

Finally, as Liang & Ho note, Professor Nutt commented on the two main effects of acute tryptophan depletion. That is, acute tryptophan depletion increased the dopamine response when patients took cocaine, and decreased it when the drug was absent. These opposite effects in the presence of salient drug cues are present, and decreases when these stimuli are absent.5


Encephalitis and schizophrenia: a matter of words

The two recent articles1,2,3,4 on the psychiatric manifestations of antibody-mediated encephalitis are important reminders that a well-informed differential diagnosis has far reaching implications for providing optimal patient care. It is indeed instructive to note that a marked recovery is possible with immunosuppressant therapy. Additionally, the need for close liaison with plasma exchange facilities, gynaecologists, neurologists and immunologists represents a novel departure for many practitioners, we presume. We did, however, have some concerns with the title of the Lennox et al. editorial.1 Describing the encephalitis as a treatable cause of schizophrenia jarred a little. First, we were concerned that the editorial title could give the impression that other causes of schizophrenia are not treatable. This brings to mind another excellent editorial, by Williams et al.3 They proposed that we should use the term ‘neuroleptic resistance’ as opposed to treatment resistance when discussing clozapine therapy to avoid therapeutic nihilism. Second, is what is being described schizophrenia or a schizophrenia-like illness? The ICD-105 states that ‘schizophrenia should not be diagnosed in the presence of overt brain disease.’ As neuroimaging progresses, this stipulation might no longer be tenable. Is it preferable to refer to this type of presentation as a psychosis? However, these are minor quibbles and we will certainly view initial psychotic presentations differently as a consequence of these two important contributions to the psychiatric literature.


Authors’ reply: We suggest that the evidence shows that although antipsychotics are effective in alleviating some, although often not all, of the symptoms of schizophrenia, there is no evidence that they treat the underlying disorder. The editorial was highlighting the fact that the clinical syndrome of patients with psychosis and N-methyl-D-aspartate receptor antibodies is the same as those with schizophrenia, such that most patients with this new disorder have previously received diagnoses of schizophrenia. However, as O’Loughlin et al. state, having an identifiable cause invalidates the diagnosis of schizophrenia according to ICD. We agree that a syndrome of psychoses is a better diagnostic construct. This situation is not unique to psychiatry. In epilepsies, despite the rapid advance in discovery of aetiological factors, the diagnosis remains based on the clinical presentation of the seizures.

Declaration of interest

A.J.C. has received consulting fees, lecture fees and grant support from Genzyme. A.V. and the Nuffield Department of Clinical Neurosciences/Oxford hold patents, receive royalties from Athena Diagnostics, and receive payments for antibody assays.

Loss of autism in DSM-5

I wish to comment on the phrase in the editorial by Tyrer & Craddock that in DSM-5 ‘the changes are largely cosmetic.’1 This is probably correct for most of DSM-5 but not for autism, where a new, narrow definition of autism is proposed. The broader autism phenotype is accepted by professionals in this area of study. A new study has shown that only 60% of patients meet criteria for DSM-IV autism when they are assessed using the criteria of DSM-5 autism.2 A second error in this area in relation to DSM-5 is that an aspect of autism has been split off into a new category called social communication disorder. ICD-11 has not made this error. These changes in DSM-5 in relation to autism are radical and will lead to patients losing their diagnosis and services.

Monitoring cardiometabolic risk in schizophrenia

I commend De Hert et al\textsuperscript{11} for their attempt to clarify appropriate monitoring for cardiometabolic risk in schizophrenia. I agree that cardiometabolic risk is one important consideration for these patients.

I note that their findings included generally low scores for the rigour of existing guidelines and a lack of evidence of long-term patient outcomes. It is perhaps a little surprising then that they nevertheless make recommendations on what appears to be less than robust evidence.

I have previously expressed concerns that cardiometabolic screening programmes of this type are unevaluated and that the benefits are unknown, as are the risks, which seem to have received little attention.\textsuperscript{2}

The authors quite rightly highlight that guidelines can be biased because of lack of scientific evidence, but the evidence they present to support their protocol appears to fall well short of the levels of evidence recommended for interventions.\textsuperscript{3} I can find no evidence that patients will benefit from such a protocol, and none that they will not be harmed.

I also note that their suggested protocol differs from National Institute for Health and Clinical Excellence (NICE) quality and outcomes framework standards for mental illness (www.nice.org.uk/aboutnice/qof/indicators.jsp) and NICE guidelines for lipid modification, both of which recommend primary preventive screening for patients aged over 40.\textsuperscript{4}

I wish to support the notion that interventions should be evaluated before implementation.\textsuperscript{3}

Physical care of people with severe mental illness is an important clinical issue, as the potential health benefits of cardiovascular disease prevention for the general population are astonishing. Each year, cardiovascular disease kills about 20 million people, including 10 million prematurely (before the age of 65 years) and inflicts high morbidity, disability and socioeconomic costs.\textsuperscript{1} This problem is more pronounced in schizophrenia, with standardised mortality rates (SMRs) of 2.7 for diabetes and 2.3 for cardiovascular disease.\textsuperscript{2}

Cardiovascular mortality increased in schizophrenia from 1976 to 1995, with the greatest increase in SMR in men from 1991 to 1996.\textsuperscript{3}

In the current climate of austerity in the National Health Service and internationally, it is interesting to know that in high-income countries, preventing or postponing 100 cases has been reported as saving about US$1 million (€0.6 million, £0.7 million).\textsuperscript{4}

2 Reed PF. Let’s target screening more effectively. Psychiatrist 2010; 34: 540–1.
A few important issues have been highlighted by De Hert et al. First, involvement of patients and carers in screening and monitoring of patients’ physical health is a vital part of patients’ and carers’ education and empowerment, which will be reflected positively in management and outcome. Second, their study raised the legitimate question of who should screen and monitor physical health: the psychiatrist or the general practitioner (GP). The care programme approach of 2008 indicates that metabolic health professionals should consider service users’ needs holistically and aim to improve their quality of life and their health. Assessments and care plans should identify and tackle the impact that mental illness symptoms and possible treatment programmes can have on physical health and the impact that physical symptoms can have on an individual’s mental well-being. I think the way forward is a proper collaboration through the local shared care protocol as the process should be initiated by psychiatrists and results should be communicated to GPs who would plan management through proper referral to different specialties.

De Hert et al. rightly state that all previous evidence indicates that guidelines have an impact on real-life screening and that monitoring rates are minimal to poor.

The national Prescribing Observatory for Mental Health (POMH) has included screening for metabolic syndrome in community patients receiving antipsychotics as a topic for its quality improvement programme. The POMH group conducted a retrospective case-note audit of patient’s prescribed anti-psychotic medication with a standard of yearly monitoring of blood pressure, measure of obesity, glucose and lipids. Results showed that between 0 and 41% (0 and 48% at re-audit a year later) of trusts were monitoring for all four aspects on an annual basis. Our study is consistent with these figures, with 40% conducting physical examinations and liver function tests (further details available from the author on request).

Scrutinising guidelines is a very important issue but what is more important, as De Hert et al. article indicated, are clear, comprehensive, inclusive and up-to-date local policies and procedures to implement physical health check-ups, with an initial assessment of risk factors and identification of people with metabolic problems with a view to referring them to a metabolic clinic for management, and to continue to monitor patients who are on atypical antipsychotics regularly, at least annually. It has been reported that establishing a metabolic clinic and managing patients at risk has improved physical check-ups and referral to GPs for abnormal results by 25% in the re-audit. All efforts should be directed towards patient and carer involvement, education and promotion of healthy living.


Authors’ reply: Dr Najim highlights the valuable resource of the UK Prescribing Observatory for Mental Health (POMH) which appears to show that National Health Service trusts record suboptimal levels of metabolic monitoring and, indeed, of physical examination of high-risk patients prescribed anti-psychotic medication. We would be most interested to know whether the POMH database can help highlight monitoring rates in those taking antipsychotics for indications other than schizophrenia, particularly bipolar disorder and dementia. Further, are there data on metabolic monitoring in individuals taking depot antipsychotic medication? This has been a question very much overlooked in the literature to date.

Dr Reed rightly queries whether the recommendation to screen for cardiometabolic problems is evidence based. He is no doubt aware of the controversy regarding screening for depression and for dementia when screening is not necessarily translated into measurable patient benefit. We would argue that the case for screening for cardiometabolic risk has strong face validity and at least a moderate evidence base that does justify our recommendations. We concede, however, that the detail of how much and how often is not fully resolved and is disputed in the current guidelines. The case for cardiometabolic monitoring is supported by the undeniably large prevalence of the problem. Some studies suggest that as many as 90% of patients with chronic schizophrenia maintain on antipsychotics have at least one clinically important cardiometabolic risk factor. Further, in this population, the risk is at least in part iatrogenic, thereby promoting the responsibility of the medical profession to detect and deal with it. Direct evidence comes from guideline implementation studies. Screening guidelines do seem to increase monitoring rates, although the increase is less than is often hoped. We recently examined this using a meta-analysis of screening rates before and after guideline implementation. Seven studies have directly monitored rates in the same sample before and after guideline introduction and these reported on glucose surveillance. These studies showed a significant 15.4% (95% CI 4.8–25.9) increase (\( \chi^2 = 8.1; P = 0.005 \)) in glucose testing following the introduction of guidelines. This increase is significant but nevertheless rather disappointing, although when combined with gradually increasing awareness of metabolic complications could increase further with time.

Another type of evidence is the additional yield of significant complications found after the introduction of a systematic screening or surveillance programme. Several such studies exist but, as far as we are aware, none have randomised a group to metabolic screening and no metabolic screening, for ethical reasons. In non-randomised studies the yield from systematic monitoring for cardiometabolic problems is appreciable. For example, Kusumi et al.\(^7\) began testing 337 patients who had schizophrenia but no pre-existing diabetes in June 2008 across 25 Japanese hospitals. At baseline, only 51% had a normal body mass index and 12% had glucose abnormalities of which 9.3% was for the pre-diabetic type. Equally concerning, during the next year of follow-up, 42% of those with pre-diabetes progressed to probable diabetes, such that by the end of the study 25% of patients with schizophrenia had recognised glucose abnormalities.\(^4\) Collectively this seems to constitute a strong case

Correspondence

76

Heilme Najim, Consultant Psychiatrist, University Foundation NHS Trust, Basildon, Essex. Email: heilme.najim@nhs.net

doi: 10.1192/bjp.201.1.75b
for regular cardiometabolic monitoring in high-risk patients, including anyone prescribed long-term antipsychotic medication. Periodic checks were already part of routine care but the literature suggests this practice was inadequate. Systematic monitoring is an improvement but still not adequate on its own. Systematic testing must be tied to clear treatment options and also clear lines of responsibility.

Declaration of interest

M.D.H has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck JA, Pfizer and Sanofi Aventis.


Correspondence

Effects of lowered serotonin transmission on cocaine-induced striatal dopamine response: PET [11C]raclopride study in humans. BJP, 199, 391–397. Figure 3 (p. 394): blue diamonds should be labelled ‘BAL+cocaine’. Online Table DS1, the headings of columns five and six for parts (b) to (d) should read: (b) ‘BPND values on nutritionally balanced amino acid mixture + cocaine, mean (s.d.)’ and ‘% change BPND induced by acute tryptophan depletion + cocaine, mean (s.d.)’; (c) ‘BPND values on nutritionally balanced amino acid mixture + placebo test, mean (s.d.)’ and ‘% change BPND induced by acute tryptophan depletion + cocaine, mean (s.d.)’; (d) ‘BPND values on nutritionally balanced amino acid mixture, mean (s.d.)’ and ‘% change BPND induced by acute tryptophan depletion, mean (s.d.)’.

doi: 10.1192/bjp.201.1.77
Tryptophan depletion in addictive behaviours
Chih-Sung Liang, Pei-Shen Ho, Kiriakos Xenitidis and Colin Campbell
BJP 2012, 201:73.
Access the most recent version at DOI: 10.1192/bjp.201.1.73