Correspondence

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Psychotic experience: things to consider

Kelleher et al.’s study is very interesting and raises some important questions, but we think that it also has some confounding factors that need to be addressed before conclusions are made. In addition, there are some methodological issues which we would like to be clarified. The response rate in study 1 is 52%, which might not be enough to support the conclusion of this kind of study. Second, owing to the different inclusion criteria in studies 1 and 2, there is a strong case for non-response bias. The way in which the first interview sample (study 3) was assembled seems unclear. Also, the way in which the second interview sample (study 4) was composed raises questions as to whether it can truly be considered a sample that represents the general population as claimed in the article. As far as confounding factors go, there is no mention of psychoactive substance misuse. With the potential of drugs to produce hallucinogenic effects, and the known link between conduct disorder, depression and attention-deficit hyperactivity disorder with substance misuse comorbidity, there is a chance that this could lead to results that do not reflect the true nature of the link between psychotic symptoms and non-psychotic disorders.

Another thing that could possibly be of interest and could affect the overall conclusions of the study is whether the study made any kind of differentiation between hypnagogic, hypnopompic and daytime hallucinations. Last, there is no mention on the psychotic experience: things to consider in the context of febrile illness.

Authors’ reply: There are a number of misunderstandings put forward by Kostic et al that we should clarify. First, it is important to correct the authors with regard to their understanding of the issue of confounding: a confound is a variable of relevance in epidemiological models of causation. To be clear, we did not suggest in our report that psychotic symptoms somehow cause psychiatric disorder. Symptoms and signs of course cannot cause pathology; rather, they act as clinical risk markers for disease. Using an analogy from respiratory medicine, the authors’ suggestion that we should control for substance misuse (which is a potential cause of psychotic symptoms) makes no more sense than suggesting that respiratory researchers should control for cigarette smoking when looking at haemoptysis as a risk marker for lung pathology. That is, haemoptysis alerts the clinician to the likely presence of pathology (i.e. it is a risk marker); the cause of the pathology remains to be determined. Similarly, we showed that psychotic symptoms act as risk markers for a broader range of psychopathology than has generally been recognised (and, in particular, for multimorbid psychopathology). In the same way that there are multiple mechanistic causes for the occurrence of haemoptysis in lung pathology (e.g. cigarette smoking, infection, trauma), there are also likely multiple mechanistic causes for the occurrence of psychotic symptoms in psychopathology. In this regard, we would direct the authors to paragraph three of the Discussion, in which we put forward a number of suggestions for such causes.

Kostic and colleagues also wonder whether the response rate in study 1 or the fact that study 4 specifically overselected for psychopathology may have affected the validity of these findings. Unfortunately, we do not have space to provide a comprehensive explanation of the epidemiological impact of response rates on findings; however, it is important to clarify that, although response rates can introduce bias with regard to reported incidences or prevalences, they usually have little effect on statistical measures of association. With regard to study 4, which purposely oversampled for psychopathology, this is, in fact, the very methodological basis of a case-control study. A statistical weight must be applied to determine population prevalences from such an approach but, as evidenced by the many thousands of case-control studies in the medical literature, this does not create problems for identifying associations that can be generalised to the population. Quite aside from this, we would remind the authors that the best way to address the possibility that sampling and other biases are responsible for a set of results is independent replication; our findings were replicated across multiple independent studies, led by multiple independent teams in multiple independent centres. With regard to symptom inclusion, in accordance with the guidelines of the interview instrument (the Schedule for Affective Disorders and Schizophrenia for School-Aged Children), hypnopompic, hypnagogic and drug-induced hallucinations were excluded, as were symptoms experienced only in the context of febrile illness.

Last, Kostic and colleagues state that there was no mention of the potential role of ‘school and family problems’ in our findings, although we specifically suggested this as an important issue in our discussion. In fact, we have already published results from study 4 (in this journal, in fact) on the relationship between


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psychotic symptoms and a number of measures of school and family problems, including bullying, interparental domestic violence and physical and sexual abuse.\textsuperscript{3} We cited this in the paper. Furthermore, Kostic \textit{et al} will be glad to know that a report on the relationship between childhood trauma and psychotic symptoms in another of the samples (study 2) is currently under review (details available from the authors on request). However, it is important to recognise that, again, the authors are raising an issue of causality in the relationship between psychotic symptoms and psychopathology: the point of the current paper, on the other hand, was to highlight new developments in our understanding of the importance of psychotic symptoms as clinical risk markers for psychopathology.

We appreciate that Kostic and colleagues are certainly not the only individuals who may have had conceptual misunderstandings about the above epidemiological points and we thank them for the opportunity to clarify some of these issues for the benefit of other readers with similar questions. We are also pleased to find that the \textit{Journal's} readers are actively discussing the importance of assessing psychotic symptoms in the context of non-psychotic psychopathology. As well as recognising that psychotic symptoms are risk markers for a range of non-psychotic Axis I disorders in general, and for multimorbidity in particular,\textsuperscript{3} we would also especially encourage discussion about findings on the importance of these symptoms as risk markers for suicidal behaviour in young people with psychopathology.\textsuperscript{3} Considering the serious implications of these findings, an improved awareness of the significance of these symptoms among clinicians is urgently needed.

M. \textit{et al} have also raised the issue of recovery for individuals who may have had conceptual misunderstandings of the importance of psychotic symptoms as clinical risk markers for psychopathology.

To help in another of the samples (study 2) is currently under review (details available from the authors on request). However, it is important to recognise that, again, the authors are raising an issue of causality in the relationship between psychotic symptoms and psychopathology: the point of the current paper, on the other hand, was to highlight new developments in our understanding of the importance of psychotic symptoms as clinical risk markers for psychopathology.


\textbf{Author’s reply:} I agree with Dr Shepherd that there is a need to better define outcomes in clinical trials. It is correct that we defined recovery as a sustained remission of psychiatric symptoms. Indeed, we followed the definition recommended by the International Society for Bipolar Disorders (ISBD).\textsuperscript{3} The term recovery in the ISBD consensus guidelines is based on sustained absence of or low-severity symptomatology without considering functional outcomes.

Observational studies in bipolar disorder, however, have in fact shown that symptomatic remission is not always accompanied by functional recovery,\textsuperscript{2,3} which supports Dr Shepherd’s point that symptom resolution is not always followed by improved functional outcomes such as adaptation to the experience.

I agree with Dr Shepherd that functional outcomes allow clinicians to make better treatment decisions that are more patient-centred. Furthermore, in the consideration of regulatory approval around the globe, symptom improvement is the main criterion for a new treatment to get approved. Including functional outcomes in the regulatory approval of pharmacological treatments would be beneficial to patients.


\textbf{The need for inclusion of concepts of recovery in clinical trials}

The study by Tohen and colleagues addresses a field of clinical practice that has traditionally posed a great deal of therapeutic challenge.\textsuperscript{1} Evidence of potential therapeutic response in initial trials are therefore welcome and the authors are right to call for further research to assess the efficacy of olanzapine, while cautioning in relation to the high non-adherence rates observed with this medication.

The authors also attempt to explore the degree of recovery experienced by individuals within their trial. It is correct that this concept is addressed, even in early trials such as this. By considering concepts such as recovery, clinical trials can provide information that allows clinicians and service users to make truly informed decisions in relation to treatment options. Calls for the inclusion of recovery-oriented outcomes in clinical trials into various disorders have been made.\textsuperscript{2,3}

However, in this study the authors appear to make the mistake of conflating the concepts of recovery and symptom remission. The concept of recovery is generally recognised as being more than simple remission of symptoms, instead involving a deeper acceptance of disorder and personal adaptation to experience. In this journal, a narrative review by Leamy \textit{et al} described five main themes of recovery that are representative of this concept; they are the sense of connectedness, hope, identity, meaning and empowerment.\textsuperscript{4}

Measures such as the Montgomery–Åsberg Depression Rating Scale (MADRS) are valuable in their sensitive detection of change in the symptoms of depressive disorders but they do not address the core concepts of recovery.\textsuperscript{5} Simple definition of recovery as a sustained period of symptom remission (MADRS $\geq$ 12 for $\leq$ 4 weeks) as in this paper is therefore inadequate.

The development of suitable recovery-oriented outcome measures for inclusion in clinical trials is urgently required to allow us to develop an evidence base that considers all aspects of treatment and allows us to provide service users with the information they require to make informed treatment decisions.


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Is this a non-inferiority trial?

Crawford et al have set out to investigate whether screening for suicidal ideation among people who attend primary care services and have signs of depression increases the short-term incidence of feeling that life is not worth living. It seems to me that this is a non-inferiority trial, i.e. the authors want to show that screening is no worse than not screening. This raises a number of design issues.

First, the trial is powered to detect an increase in the proportion who felt their life was not worth living from 30% to 45%. This seems a clinically large increase and suggests that anything short of a 50% increase in relative risk is acceptable. Second, having calculated the sample size based on relative risk, they analyse the main results using odds ratios rather than relative risk, so that it is difficult to see what sort of increase in relative risk was found and impossible to see the confidence interval around the relative risk. Third, if this is seen as a non-inferiority trial, arguably screening would be regarded as non-inferior provided that the possibility of the suicidal ideation rate being 50% worse than non-screening could be ruled out (in the sense that the 95% confidence interval for the difference in ideation rates would not include 50% inferiority relative to the non-screened group).

We only have the confidence interval around the odds ratio to go on, but given how wide that is, it is highly likely that the confidence interval would include the 50% increase in relative risk. For these reasons I think the results should be treated with caution.


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Delay in starting clozapine and treatment guidelines

There is a reasonable level of information to suggest that clozapine is effective in patients who have treatment-resistant schizophrenia. Hence, clozapine should be started at the right time so that patients can draw maximum benefit from it. In this vein, the article by Howes et al provides important insights into the clinical practice with regard to the use of clozapine. The authors showed that clozapine is delayed by about 4 years and many patients are treated with polypharmacy and receive higher than recommended doses, which is contrary to the recommendations made by several practice guidelines. However, it is important to note that the conclusions drawn about the delay in starting clozapine might not be a true reflection of actual delay, because often patients who are offered clozapine refuse to take it. Hence, some of the delay may be due to lack of agreement of the patient and this in general does not reflect the delay in the clinician offering the medication. It would have been better had the authors extracted the data pertaining to initial offering of clozapine and the number of patients who refused clozapine at the first instance as part of this study. This would have actually given the true clinical picture.

Another issue is the definition of duration of illness used. The authors have defined duration of illness as ‘the time from the first recording of the diagnosis of a psychotic illness by a clinician to the present’, which may not be a true reflection of duration of

Authors’ reply: Peter O’Halloran raises a good point about this study: it was underpowered. Even slightly higher levels of suicidal thinking among people who are screened for suicide risk would be clinically important and our study was only powered to detect a fairly large difference.

However, at the start of the study we faced a dilemma; a sizeable minority of local general practitioners told us that they were uncomfortable asking people with depression about suicidal thoughts because they were concerned that this could ‘make them feel suicidal’. Subsequent discussions with medical students and trainee psychiatrists (and indeed members of the ethics committee that reviewed the study protocol) revealed that these concerns were shared by others. A sample size calculation based on a non-inferiority hypothesis and using a smaller but still clinically important difference in levels of suicidal thinking would have required a sample size several times larger than the one we recruited. As Norman and colleagues have recently pointed out, sample size calculations are usually a compromise between statistical considerations, economics and logistical constraints. When we embarked on the study we knew that we did not have the resources to recruit a sample large enough to detect a small difference in levels of suicidal thinking among those who were and were not screened. However, we hoped that we could rule out the possibility of a large difference and this is therefore what we set out to do. The 95% confidence intervals around the odds ratio for the likelihood of suicidal thoughts among those that were screened were broad (0.66–1.18) and are compatible with either higher or lower levels of suicidal thinking in those who are screened compared with those who are not. Despite this limitation, these are the first data that test the veracity of a belief that was held by many and may have been an obstacle to screening for risk of self-harm in this high-risk group.

As we pointed out in the Discussion of our paper, it was not possible to collect data needed to calculate relative risks associated with screening because this would have meant collecting baseline levels of suicidal ideation from all those in the study. This would have exposed those in the control arm of the study to the very factor that the study was designed to examine.
illness, because there may be varying periods of duration of untreated psychosis and this can have its own treatment implications. Despite these shortcomings, findings of the study suggest that even with a national healthcare system in place and the wider dissemination of treatment guidelines, there is still only a modest impact of these on real clinical practice. The possible effect of treatment guidelines is reflected by the fact that today patients receive fewer trials of other antipsychotics (2.8 vs. 4 trials) before being started on clozapine compared with earlier studies.\(^1\)


Authors’ reply: The first point raised is that the delay to clozapine initiation may not be a true reflection of the actual delay because patients may have been offered clozapine but refused it. This, of course, depends on what delay you are interested in. In our study we used the delay from the point at which treatment guidelines recommend a patient should start clozapine. In our view this is the key, clinically relevant, delay. However, Sharma & Grover are right in suggesting that this delay does not necessarily mean that clinicians have delayed offering clozapine, although if this were the case it implies that it has taken on average 4 years for patients to agree to start clozapine. In practice it seems likely that there are a number of patient, clinician and service factors that may underlie the delay we observed in our study. Understanding these will be important if delays are to be reduced in the future. The availability of biomarkers for treatment resistance, as indicated by a recent study,\(^2\) could also contribute in the future. Understanding these will be important if delays are to be reduced.

Declaration of interest

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Attention-deficit hyperactivity disorder across the lifespan

Michielsen et al conclude that the personality traits they call attention-deficit hyperactivity disorder (ADHD) ‘do not fade or disappear in adulthood.’\(^1\) Yet such a gradual extinction throughout life is precisely what their study proves.

The authors quote prevalences from previous studies as high as 7% in children and 4.4% in working-age adults. Their own study shows a prevalence in old age of 2.8%, with higher rates in the 60- to 70-year age group (4.0%) than in those over 70 (1.1%). In other words, there is a steady decline in the prevalence of ADHD caseness throughout life, way over and above that which could plausibly be caused by higher mortality among impulsive individuals.

These data show conclusively that, in common with many problematic personality styles, poor attention, impulsivity and hyperactivity tend to gradually lessen in intensity with age. Thus the study is further evidence that ADHD merely represents a cluster of personality traits which, given their high prevalence, cannot even be considered abnormal, rather than a disease entity.

Declarative interest

The views expressed are those of the author and are not necessarily shared by his employer.


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Michielsen et al,\(^1\) while describing the background and aim of this study, mention that ADHD could lead to significant impairment in older age without providing evidence of such impairment. Certainly from clinical experience and previous studies we know that there are other mental disorders such as depressive illness, anxiety disorder and dementia which are relatively common in older age and likely to cause either similar or more severe impairment. The authors discuss this in some detail in their description of the limitations of this study but fail to consider this when drawing a conclusion about prevalence.

It is essential, according to DSM-IV criteria, for a diagnosis of ADHD to rule out any possibility of the symptoms being better accounted for by another mental disorder.\(^2\) Unfortunately, the authors do not rule this out while studying the prevalence despite using a diagnostic instrument strongly based on the DSM-IV criteria.

Before we start diagnosing ADHD in older age groups it is important to exclude more prevalent and widely recognised mental health problems such as mild cognitive impairment and dementia. Looking at the diagnostic instrument DIVA 2.0, we can easily identify many symptoms which can be more readily explained by other more prevalent functional and organic illnesses.\(^3\) This explains why the DIVA 2.0 (as the authors in this study rightly mention) has no evidence for its use in old age. Is retrospective data collected from an older person’s recall of being inattentive or hyperactive as a child in different situations valid? More so when DSM-IV clearly advises caution for diagnosing this in adults without any corroborating information, which was missing in this study.

We would thus suggest extreme caution before we start even suggesting the concept of ADHD in older adults and taking this
any further. There are greater and more relevant issues in older age that need to be tackled before we start inventing any new diagnoses.


Authors’ reply: Braithwaite wonders why we state that ‘the personality trait’ ADHD does not disappear in adulthood, while in our study it seems that ADHD does gradually lessen with age. A first comment is that ADHD is not a personality trait, but a neuropsychiatric disorder. It has an early onset and symptoms do persist into adulthood. Our study aimed to assess whether this also extends into later life and we found that this was indeed the case in 2.8–4.2% of those examined. We agree that the prevalence rates found over the lifespan decrease a little and in our study we found lower prevalence rates among the oldest old. However, the prevalence rates we found are substantial and, if replicated, this would mean that ADHD is by no means limited to children or to younger adults.

Routh & Jackson rightly point out some limitations of the paper. The first point is that we did not rule out any other DSM-IV diagnosis, and the second pertains to the limited validity of recollecting childhood memories in old age. We agree that both points are important and have discussed them in the Discussion of the paper. A third point is that according to Routh & Jackson we have found no evidence of impairment of ADHD in old age, which might be taken as evidence of limited validity of our measurement of ADHD. Only few studies have been conducted in older adults with ADHD and those studies did find impairments.1–3 In our study, those diagnosed with ADHD did report lifelong impairment in four of the five areas of functioning assessed, which is substantially more than DSM-IV requires for the diagnosis.4

We agree that other psychiatric disorders may explain impairment and that the study would have been stronger if psychiatric comorbidity had been assessed. However, as the diagnosis of ADHD requires not only a current but a lifelong history of the typical symptoms, we think we have been able to discriminate from disorders with a later onset. Mild cognitive decline or dementia is indeed very impairing and an important health problem in older age. Although we did not diagnose these disorders, we did exclude respondents with lower IQ and persistent cognitive decline on the Mini Mental State Examination. Except for three excluded persons, all respondents were able to answer the questions of the interview. Therefore it is very unlikely that respondents with dementia were included in our study.

The conclusion that ‘there are greater and more relevant issues in older age that need to be tackled before we start inventing any new diagnoses’ seems ill founded. We agree that it is wise to be conservative in proposing new psychiatric diagnoses which may add to the ever increasing numbers of patients eligible for mental health treatments. However, ADHD is not a new diagnosis and it is extremely unlikely that it ceases to be active at any particular age.


Corrections

Dementia in the acute hospital: prospective cohort study of prevalence and mortality. BJP, 195, 61–66. Table 3 (p. 64), last row, variable should read: Death within 14 days of index admission (n=75), %.

Karl Jaspers – reflection (extra). BJP, 202, 4. The doi is: 10.1192/ bjp.bp.112.112334. The online version has been corrected in deviation from print and in accordance with this correction.

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