Is depression one thing or many?

Until 1980, manic depressive illness (MDI) was defined as follows: the presence of recurrent severe depressive or manic episodes alternating with periods of normal mood or markedly decreased mood symptoms.1 In that year, the DSM-III rejected this definition of MDI and replaced it with two different conditions: bipolar disorder and major depressive disorder (MDD). Bipolar disorder meant the presence of manic and depressive episodes, not manic or depressive episodes – a huge difference between bipolar disorder and MDI. Recurrent episodic severe depression, previously called MDI, was redefined as MDD, which also included other varieties of depressive symptoms (such as neurotic depression). In the last few decades, the broad heterogeneous definition of MDD has been accepted by many clinicians as if it was a single entity, completely different from bipolar disorder, without awareness that both conditions were seen as one illness in the past: MDI.

We present the case of a patient with severe recurrent depression who achieved clinical remission after treatment with lithium monotherapy despite non-efficacy of standard antidepressants.

The patient was a 36 year-old White, married woman with a positive family history for bipolar disorder. She had no history of manic episodes.

At 32 years of age, 2 weeks after delivering her first child, she presented feelings of inadequacy and guilt, anhedonia and decreased appetite. She had difficulty falling asleep because of ruminative pessimistic thoughts about the future. These symptoms met DSM criteria for a major depressive episode and improved in the next few weeks without medications.

Six months later, anhedonia increased prominently and she presented depressed mood, feelings of worthlessness and occasional suicidal thoughts. She was admitted to the in-patient service and was treated with sertraline 250 mg/day.

In the following 2 years she had three depressive episodes per year lasting about 2 months each without full interepisode recovery. Her treatment was modified to clomipramine 225 mg/day. Depressive episodes recurred more frequently and lasted about 1 month each.

At age 35, she was admitted to the in-patient service after impulsive ingestion of high doses of benzodiazepine and antidepressants as a suicide attempt. Clomipramine was gradually discontinued and treatment was modified to lithium 600 mg/day (serum level 0.5–0.7 mEq/l). Lithium was maintained in monotherapy; depressive symptoms were well controlled and there were no mood recurrences for the following 12 months.

In this case, four features support the hypothesis of underlying MDI: presence of recurring depressive episodes, positive family history for bipolar disorder, postpartum onset of first depressive episode, and improvement of affective symptoms with a mood stabiliser. Randomised studies indicate that standard therapeutic levels of lithium are effective in recurrent depressive episodes, whether bipolar or unipolar, in both acute and maintenance treatment phases.2,3

DSM-III made a radical change in dividing the broad MDI concept into the narrow bipolar and broad MDD concepts. Given decades of research suggesting that MDD is a heterogeneous concept, and the perspective that course (recurrence of mood episodes) may be highly important in diagnosis, rather than symptoms (depression v. mania),4 case examples such as this one raise the question whether therapeutic response also supports a return to the MDI concept that emphasised diagnosis based on recurrence of episodes, irrespective of depressive or manic polarity.

This nosological approach would have important clinical implications if MDI is the disease that produces both depressive and manic symptoms. William Osler’s view that the medical profession should primarily treat diseases, not symptoms,5 would imply that mood stabilisers such as lithium should be the main long-term treatment of choice in patients with recurrent depression. Addition of low doses of antidepressants could be considered for short-term symptom improvement, rather than long-term prevention of mood episodes, while monitoring emerging manic or mixed episodes.

Declaration of interest

S.N.G. has provided research consulting to Sunovion and Pfizer, and has obtained a research grant from Takeda Pharmaceuticals.


CBT for psychosis: not a ‘quasi-neuroleptic’

As members of the recent National Institute for Health and Care Excellence (NICE) clinical guideline update for schizophrenia1 (M.B. and D.S.), we read with interest the excellent meta-analysis of CBT for symptoms of schizophrenia by Jauhar et al.2 The results are broadly in line with the NICE review and particularly that of Wykes et al.,3 which showed that studies with high methodological rigour, including masking, have a small effect size for positive and total symptoms. Clearly cognitive–behavioural therapy (CBT) is no panacea; but neither is it ineffective. Meta-analyses bring together all trials, with patients drawn from heterogeneous populations, including different phases of illness. The tests for...
heterogeneity not accounted for by chance ($I^2$) in this meta-analysis were all high. The question therefore arises, 'For whom is CBT in psychosis most effective and for what outcome?' Likely groups are individuals at ultra-high risk for psychosis, those in the early phase of psychosis and perhaps those with chronic stable symptoms, appearing to benefit the most; the Prevention of Relapse in Psychosis trial suggests that those beginning treatment early in the course of recovery from acute symptoms do not benefit. These trials focus on individuals in receipt of medication, with enduring symptoms. They therefore ask the question, 'Does CBT offer added value compared with medication alone?' We might also ask the converse, 'Does antipsychotic medication offer added value to CBT alone?' It is known that up to 50% of individuals will not adhere to medication; a recent pilot trial of CBT in those not taking medication showed an effect of CBT equivalent to that of drugs. Given the low acceptability of antipsychotic medications and their serious impact on health, this is an important question for further research. We note that our trial of CBT for commanding hallucinations is included in the analysis for hallucinations; however, this trial did not predict a reduction in hallucinations, but reported a 'high' effect size for harmful compliance (not reported), which has been the subject of a large multicentre trial, soon to report. We argued some time ago that CBT for psychosis should not be conceived and evaluated as a 'quasi-neuroleptic': the dimensions of delusions (power, distress) and general affective dysfunction are, we believe, among the most appropriate targets for CBT, with strong theoretical justification. Given the evidence from systematic reviews of antipsychotics that the improvements claimed for antipsychotics are of questionable clinical utility, with effect sizes smaller than for adverse side-effects, there is clearly much work to be done to improve care, as the Schizophrenia Commission outlined in their 2012 review of current treatment and services (www.schizophreniacommission.org.uk).


Jauhar and colleagues' review and meta-analysis of cognitive–behavioural therapy (CBT) for the reduction of particular symptoms associated with schizophrenia is interesting but incomplete. For example, the review does not examine the clinical significance of dose or duration of CBT treatment. This limitation is considerable, as an analysis of effective elements of CBT for psychosis found that 'consistent delivery of full therapy, including specific cognitive and behavioural techniques, was associated with clinically and statistically significant increases in months in remission, and decreases in psychotic and affective symptoms', while 'delivery of partial therapy involving engagement and assessment was not effective'.

Jauhar et al have also excluded measurement of long-term outcomes from their analysis, measuring only end-of-study data. This is another considerable limitation, as symptom reductions maintained at 9- or 18-month follow-up represent a substantial benefit of effective CBT. Further, although reduction of psychotic symptoms is an important treatment outcome to measure, CBT is particularly focused on reducing distress associated with such symptoms and improving an individual's ability to cope with them. As psychotic symptoms can continue even with administration of powerful antipsychotic medication, improvements in these areas may be clinically significant for many CBT recipients. Indeed, a comprehensive synthesis of qualitative research into patients' experiences of CBT for psychosis found that the most commonly identified 'key ingredients' of CBT included increased understanding of psychosis and of coping strategies, reappraisal of distressing beliefs, and normalisation: 'Participants did not necessarily experience an actual reduction in the frequency or distressing content of psychotic experiences, but instead gained an increased ability to cope and an increased perception of personal power'. It is also important to consider that not all individuals want their 'symptoms' eradicated, and such appraisals are common in the wider literature on recovery from psychosis or schizophrenia: 'Learning to cope to accept that you hear voices or whatever your symptoms are. Recovery is ... to be able to live with it'. So, although analyses of CBT that focus only on psychotic symptom reduction are important, they are also incomplete; 'secondary' outcomes such as reduced distress or self-defined recovery may be valued more highly than symptom reduction alone by many patients, and such outcomes are increasingly well measured in CBT trials. Future meta-analyses of CBT will contribute more meaningfully to our understanding of its effectiveness by examining these wider outcome domains and acknowledging their value as long-term benefits.

Declaration of interest

R.E.B. was a member of the National Institute for Health and Care Excellence guideline development group 'Psychosis and schizophrenia in children and young people', and is involved in National health Service-funded CBT for psychosis research.

**Correspondence**

Authors’ reply: Birchwood et al make two points that require clarification. First, their statement that our findings from studies with high methodological rigour, particularly masking, imply that cognitive–behavioural therapy (CBT) has small but by no means negligible effects on positive and total symptoms broadly in line with the National Institute for Health and Care Excellence (NICE) review and particularly that of Wykes et al, seems to us questionable. Wykes et al\(^4\) reported an effect size of 0.37 for positive symptoms, which reduced slightly to 0.31 in masked studies. This latter value was four times larger than the value of 0.08 we found for masked studies of positive symptoms. Ratings of bias were made for the studies included in the 2009 NICE guideline\(^2,3\) however, no analyses excluding low-quality studies or otherwise examining methodological rigour were actually carried out.

Second, Birchwood et al’s argument that a finding of significant heterogeneity among studies implies that CBT is effective in certain subgroups of patients is not formally correct. It could simply mean that there are systematic differences in effect size between studies at high and low risk of bias. Tending to support this latter interpretation, in our meta-analysis of positive size between studies at high and low risk of bias, Tending to effective in certain subgroups of patients is not formally correct.

Stimulant treatment for ADHD

We read with great interest the article by Groenman et al,\(^1\) which highlights an important facet concerning substance use in attention-deficit hyperactivity disorder (ADHD).

The authors suggested, through the generalised estimating equation model, that the risk of developing substance use disorder reverses after 18 years of age, indicating that it may be mediated by modulation in parental support. However, we wish to raise concern for this conclusion as a possible biased finding since the researchers have included patients exposed to stimulants intermittently or for short durations along with those exposed continuously (n = 358), which may have falsely led to the results. Possibly, analysis of the combined no-stimulant treatment group (stimulant-naïve and those with short or inconsistent stimulant use) against the stimulant treatment group for age variable (as had been done in the correlation analysis) may have validated the statement.

In what appears to be a printing mistake, Table 1 incorrectly shows the percentage of males in the no-stimulant group as being 9.0%, which must be higher given the n in this group (36/61).

Meta-analysis also concludes that treating ADHD during childhood reduces the incidence of substance use disorder by half, whereas failure to treat doubles the risk for substance use disorder.\(^2\) We concur with the authors that stimulant treatment impact on nicotine dependence should be interpreted with caution, warranting future larger-sample, longer-term prospective studies inspecting the role of non-stimulant medications in modulating substance use disorder in ADHD.


Authors’ reply: In their letter, Verma and colleagues make the interesting point that possibly the age at first stimulant use × current age interaction effect found in our paper\(^1\) might be influenced by our selection of patients. Including individuals with stimulant treatment duration longer than 12 months in our analyses, we found a protective effect of earlier age at first stimulant use on the development of substance use disorder (odds

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ratio (OR) = 0.95, Wald $\chi^2 = 13.78$, $P < 0.001$). Verma et al are concerned that we excluded patients with shorter treatment durations. However, when we include all individuals who ever used stimulants, we find the same effect (OR = 0.95, Wald $\chi^2 = 11.89$, $P = 0.001$). Purely for illustrative purposes, we plotted the predicted probability of substance use disorder for the control group in Fig. 1. The figure shows that delay in the first age at stimulant use leads to marked increases in the probability of developing substance use disorder. In our article, we examined whether the effect of stimulant treatment depended on other factors (i.e. current use of stimulants, age at stimulant treatment initiation, age-adjusted duration of stimulant use and age-adjusted cumulative dosage), but found no other significant predictors than age at first stimulant use.

Verma and colleagues refer to a meta-analysis, but provide the wrong citation. Recently, a meta-analysis on this topic was published.2 Here no difference was found between treated and untreated patients in risk of developing substance use disorder (including alcohol, marijuana, cocaine and non-specific drugs) and nicotine use. Unfortunately, in this meta-analysis specific moderator variables such as age at first stimulant use were not taken into account, probably because of the relatively low numbers of studies to date that include such variables.

We thank the authors for discovering the mistake in the table, 9% should have read 59%.


The threat of ‘small’ subspecialties being assimilated by the generalist type of liaison services is a reality. However, the question remains – is this the best way forward? Mental health trusts have already benefited from a number of diversifications of services.6 The rapidly changing demographics in the UK population – with the older population doubling by 2050 from 10 to 19 millions and the expected 80% increase in people with moderate or severe dementia in the following 15 years8 – argues for urgent diversification of the health services to meet older people’s health requirements, including their mental health. In this respect, it would be counterproductive to rely on liaison services catering for a single commodity. The steady growth of LSOA demand provides further support that this is the area for diversification of not only the psychology medicine portfolio, but also mental health services in general.

We have read with interest the editorial by Sharpe.1 Recognition of liaison psychiatry as valuable to patients, general hospitals and commissioners has been a long time coming.

We agree that the crisis of identity in psychiatry may have indeed resulted from the many decades of isolation from the rest of medicine. As such, there may be a temptation to redefine psychiatry based on the path of least resistance which is one left by the ‘compassion’ vacuum highlighted by the Francis inquiries.2 Psychiatry does indeed ‘retain strengths in humane social and psychological care’, although it has much to learn from the involvement of patients in the design of care3,4 and often struggles with the interface between physical and mental healthcare itself.

There is indeed a need to ‘enhance the patient’s experience of medical care’ and for medicine to move away from purely ‘disease-focused medical care’.1 However, we differ on the opinion that liaison psychiatry or psychological medicine ‘aims to put these skills back into medical care’.2 We may be at risk of medicalising the distress that is prevalent in healthcare settings.3 Healthcare professionals have a duty to improve the experience of people they care for and to respond to their distress in a humane and compassionate manner.5,7 From our experience of delivering training and support in general hospital settings, there are many barriers to liaison psychiatry being able to achieve this kind of change, not least the sheer scale of the task. This may actually be a strength of the current trend of psychiatric superspecialisation occurring in general hospital settings – more psychiatrists advocating and modelling change.

In the article, an excellent point is made that the current approaches to commissioning liaison psychiatry may be less than ideal.1 It is unlikely that teaching from another specialty, let alone another organisation, will address these issues to a satisfactory extent or in a timely manner. We could avoid the temptation of calling for more training. Instead, perhaps each specialty and organisation could take seriously the responsibility of creating the right culture and putting patients first.

Indeed, it may be that lessons can be learned from psychiatry, but we have many lessons to learn ourselves. The key to medicine rediscovering its humanity may be more likely to lie in re-engaging with its patients and carers than looking to another medical specialty.


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10.1192/bjp.204.6.492

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Given my interest in liaison psychiatry, I could feel the passion in Sharpe’s1 piece, which he has extended to include the proposed future of psychiatry as a discipline. However, even though he has mentioned patient safety in passing, I would like to urge a wider debate on the fact repeatedly highlighted by several publications of the National Confidential Enquiry into Suicide and Homicide by People with Mental Illness. In its last publication, it again highlighted that 72% of those who die by suicide (between 2001 and 2011), had no contact with mental health services in the year before their death. Given the massive variation in funding of mental health services across the country and some viewing it as a Cinderella service, I feel mental health providers and advocates have failed to grasp the nettle in terms of attempting to reach out to that group of individuals who ‘successfully’ take their own life. We are aware that a majority of those individuals could be diagnosed within F43.0 (Reaction to severe stress, and adjustment disorders) of the ICD-10.8 Yet we fail to invest in services and concentrate efforts on a narrow remit to severe mental illness. With the 2007 amended Mental Health Act 1983 in England and Wales, we have successfully replaced the erstwhile four categories with a single category of mental disorder. Along with it, we have replaced ‘treatability’ and ‘care’ tests with appropriate treatment tests. Yet we do not seem to adequately invest and respond to the above-mentioned category, costing
potentially a lot more to the community than accepted under the mental illness umbrella.

I raise this issue again with the hope of extending our roles not only to the ‘Holy Grail’ of reducing costs and improving outcomes, as the editorial focuses, but also to the wider losses our community and society suffer but are unable to react to. On another note, the editorial mentions the RAID model (Rapid Assessment Interface and Discharge). This along with the latest iteration of the National Institute for Health and Care Excellence guidance on schizophrenia, which refocuses attention on combined physical and mental healthcare and the mandate around parity with physical and mental healthcare just debated in the English Parliament, gives us hope for the future. Psychiatrists are unique in addressing the boundary disputes between specialties and offer value for money even in this economy.


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Assessing and staging bipolar disorder

We congratulate Duffy et al on their paper.1 We have long argued that bipolar disorder is often underdiagnosed by community mental health teams, and that the reason for this is often failure to assess the longitudinal trajectory of patients with recurrent depression.2,3 We have attempted to remedy this by developing 29 questions to be used in the history-taking of all patients with depression and recurrent depression to demonstrate the developmental trajectory of the illness.4 These questions are presently being field tested in Bedford, UK, and at the University of Perugia, Italy. We have also demonstrated that when the systematic assessment of the trajectory of bipolar disorder is carried out in a community mental health team, the number of patients with bipolar disorder among the patients assessed by the team increases, but there remain a number of patients who do have unipolar depression;5 in other words, the assessment of the trajectory of patients with mood disorder enables the discrimination between bipolar and unipolar depression.

We would comment that Duffy et al raise an important point in suggesting that a history of use of lithium by relatives of the patients changes the trajectory of bipolar disorder; however, in our experience it is very difficult to collect this information from patients, who often do not know details of their relatives’ illnesses. Furthermore, Duffy et al are right in proposing that it is possible to suggest a staging of bipolar disorder similar to McGorry’s staging of schizophrenia, but the schizophrenia staging is underpinned by Pantelis’ neuroimaging of the different stages of schizophrenia. To propose a staging model of bipolar disorder, we require similar neuroimaging results describing the differences between the individual stages.


Author’s reply: It is encouraging that the ideas expressed in my editorial on psychological medicine have stimulated such interest and associated correspondence. The three letters published above support the thrust of the editorial that a re-engagement of psychiatry with other areas of medicine in the form of psychological medicine services (also called liaison psychiatry) would benefit both medicine and psychiatry. Each letter also raises specific additional points.

Rowett & Udo doubt whether psychiatry is up to the ‘sheer scale of the task’ in helping other areas of medicine to address the ‘compassion vacuum’ highlighted by the Francis Inquiry. They conclude that medicine should put its own house in order by re-engaging with its patients and carers rather than seek solutions from another specialty. They are clearly correct in noting that the task is great and that the change required cannot be delivered by psychiatry alone. But I think they are too pessimistic, both about the appetite for change within medicine and about how much can be achieved by psychological medicine; it cannot transform medicine on its own, but it can be an important facilitator of change.

Mukaetova-Ladinska & Scully emphasise the importance of old age psychiatry in light of the rising age of general medical patients. They argue for the specific development of liaison psychiatry of old age. Although fully agreeing with them that expertise in the psychiatry of old age is an essential ingredient of a modern psychological medicine service, I am less convinced of the merit of subspecialised services. Integration with medical services requires that we map onto the way in which they are provided and the very demographic trend they have highlighted is breaking down the division between adult medicine and geriatrics. Hence although the skills of old age psychiatry are increasingly important for psychological medicine services, setting up service barriers defined by age is unlikely to achieve effective integration with medicine.

Finally, Kripalani makes the important point that we need to consider the role of psychiatry in ensuring patient safety. The point is made that services which concentrate on ‘severe mental illness’ may miss the risk of suicide posed by the individual suffering from stress and adjustment disorders. I am sure that most practitioners working in psychological medicine services would endorse this point. Psychological medicine can play an important role in helping medical services to reduce risk, as well as in improving patient outcomes and experience and making medical care more efficient.

I wish to thank these correspondents, and others who have emailed me personally, for their interest in the points raised in the editorial. The opportunities for psychiatry to re-engage with clinical medicine are enormous. I would strongly urge all those with an interest in developing integrated patient-centred psychological medicine services to help psychiatry to rise to this challenge. Our patients and our specialty need us to succeed.

response to long-term lithium in the affected parent. Second, the staging model proposed by McGorry and colleagues was originally based on clinical observations in help-seeking youth (clinically high risk) and only later validated by conversion rates to psychosis and more recently neurobiological findings. Our cohort is a genetically high-risk cohort and we are intensively investigating markers of illness predisposition and progression through the clinical staging model. In regard specifically to neuroanatomical markers, in collaboration we have reported that enlarged right inferior frontal gyrus volumes may be a marker of bipolar disorder predisposition in high-risk offspring.

Author’s reply: In the article we presented data describing the clinical stages in developing bipolar disorder based on longitudinal repeated assessment of the offspring of well-characterised parents with bipolar disorder. The findings emphasise the importance of including family history and clinical course in the diagnostic formulation to improve early identification, given that early risk syndromes are non-specific and include anxiety and depressive syndromes. We also showed that offspring of lithium-responsive parents develop classic episodic mood disorders, whereas offspring of parents with a lithium non-responsive illness follow a trajectory that overlaps with psychotic disorders – both in early and end-stage disorders. We did not suggest that ‘a history of lithium use in relatives changes the trajectory’, rather we used an operationalised published protocol to identify a more homogeneous subtype of bipolar disorder based on the excellent epidemiological change in the caseload of a community mental health team when bipolar disorder is accurately assessed and diagnosed. Psychiatry Danub 2013; 25 (suppl 2): 129–34.

Correction

Stimulant treatment for attention-deficit hyperactivity disorder and risk of developing substance use disorder. BJPsych, 203, 112–119. In Table 1 (p. 115): of those with ADHD in the no-stimulant treatment group, the percentage of males is 59%.

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Assessing and staging bipolar disorder
Mark Agius, Jonathan Rogers, Eva Bongárds, Stuart O’Connor, Norma Verdolini and Sandro Elisei
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