30 October 2016

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: 29512-Revised manuscript).

Title: Treatment-adherence in bipolar disorder: a patient-centred approach

Author: Subho Chakrabarti

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 29512

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revisions have been made according to the suggestions of the reviewers. These are detailed below.

3 References and typesetting have been corrected.

4. All supporting documents have been submitted.

I would be grateful if the revised manuscript is re-evaluated for publication.

With regards,

Subho Chakrabarti

ID (02445242)

REPLY TO REVIEWERS' COMMENTS/SUGGESTIONS
(All changes have been highlighted in bold font and underlined)

REVIEWER 03529556

Comments to authors

I agree with the context of this article, and your identification of the shift towards a more 'patient centred' approach as being of great significance. However, despite this I still felt that the manuscript as a whole read as being highly 'clinician focussed' in its outlook – particularly in its approach to psychoeducation with regard to medication, 'treatment' and 'illness'. There is a great deal of academic and clinical literature relating to the enactment of 'power sharing' between clinician and patient, and the application of this within models such as 'shared decision making'. I felt that the argument you advance could have been strengthened through reference to this literature. Additionally, in considering the role of a 'patient centred care approach' I also feel that reference to developing concepts such as 'personal recovery' which shift the emphasis of 'illness' understanding more to the narrative development undertaken by patients in making sense of their experience could have been at least considered. As a result of these omissions it felt that a great number of the advances in patient-centred-care that have taken place over the past 20 years were overlooked and that the focus remained on the role of the patient in their 'compliance' with offered treatment. Finally, the manuscript could benefit from a close re-reading with regard to the phrasing in order to ensure the argument is clearly conveyed. I have attached a 'tracked comments' manuscript which draws attention to specific examples and questions within the manuscript itself.

Comments to the Editor

Many thanks for the opportunity to review this interesting manuscript. I agree with the author that this area of clinical practice and research is of high significance to the care of patients. However, despite the stated aim of the article – to review the process of adopting a patient-centred approach to prescribing and treatment in Bipolar Disorder, I felt that as a whole the manuscript itself remained almost entirely 'clinician focussed'. While this may be apt for a clinically oriented journal I felt that the concept of being patient centred required greater acknowledgement in terms of its potential implications beyond the role of client education with regard to medication side-effects and 'illness'. Instead, I felt that the article could have drawn more deeply on the wide-ranging academic literature that already exists relating to the practice, or enactment, of patient centred approaches to care – such as 'shared decision

making'. In outlining the need for a patient centred approach I was also struck by the lack of reference to 'recovery', or similar concepts, which are gaining increasing attention in both clinical and research practice globally. The implications of the idea of 'recovery' can be seen as wide reaching and should almost certainly be seen as pertinent to the concepts outlined here. As a whole therefore I felt that, while the article was interesting, it overlooked a large volume of academic literature and developments in clinical practice that have already been addressed. I would suggest either a re-write of the article to address these important topics in greater detail, or that a commentary be commissioned addressing these factors.

REPLY

1. I would agree that the editorial is more focused on a clinical than a purely sociological approach towards treatment adherence. The reasons for this are that I wanted to emphasize the gradual move from an illness-centred to a patient-centred approach to treatment-adherence specifically with regard to the treatment of bipolar disorder. To do this I had to trace the earlier thinking about illness-centred approaches to treatment adherence e.g. the belief that demographic, illness-related and treatment-related factors would predict the occurrence of non-adherence. Therefore, about half of the editorial is devoted to this aspect. The other half dwells on the need to change to a patient-centred approach and a discussion of the principal factors comprising a patient-centred approach such as attitudes and beliefs, treatment alliance, knowledge about the illness and its treatment, the role of the family and significant others and other factors. These areas have been reviewed very briefly because I did not want the editorial to become too long. Moreover, this half was meant to serve as an introduction to a patient-centred approach for clinicians, some of whom may be unfamiliar with the concepts. It was not intended to be a comprehensive review of the area. Finally, I focused only on studies carried out among patients with bipolar disorder. While this might have restricted the discussion of these factors to an extent, it remained faithful to the principal objective of the editorial, which was to discuss treatment-adherence in bipolar disorder.

2. I completely agree with the reviewer that there is much more to the patient-centred approach such as concepts of shared decision-making, personal recovery as well as ethical, clinical and research issues that derive from this approach. However, because of constraints of length and because all these concepts have not yet been fully explored among patients with bipolar disorder, I have not focused on them in greater detail. Nevertheless, in the revised manuscript I have included a few lines about these concepts and acknowledged that these issues are pertinent though they are beyond the scope of this editorial on treatment-adherence in bipolar disorder.

3. The objective of this editorial was to highlight the move away from compliance-based approaches to those based on concordance in the treatment of bipolar disorder. This issue has been briefly but duly emphasized. Therefore, I hope that the focus is no longer on compliance-based approaches to adherence since this was not intended objective.

4. I have only mentioned the studies on psychoeducation in bipolar disorder that are related to the move from illness-centred to patient-centred approaches to treatment adherence. An extensive review of all studies was not possible.

5. Nevertheless, I have tried to address all the specific comments and suggestions made in the attached word document. The revised version of the manuscript now incorporates all these changes made. (See below).

6. Because of the limited scope of this editorial, I would certainly agree with the suggestion of a separate article or commentary focused entirely on the developments in the patient-centred approaches to treatment-adherence in general and their implications for the treatment of patients with chronic psychiatric disorders. However, this has to be obviously left to the editors to decide.

CHANGES MADE IN ACCORDANCE WITH SUGGESTIONS IN THE "TRACKED COMMENTS"

AR 1 - (Title: Treatment-**adherence** in bipolar disorder: a patient-centred approach)

Would use of the word concordance (instead of adherence) be more apt here?

Reply- The term "adherence" was chosen because it is the most commonly used term across clinical studies of bipolar disorder. Although the concept and the term "concordance" is equally appropriate it has not been as widely used in clinical studies.

AR 2 - (Abstract - About half of the **patients with** bipolar disorder (BD) become non-**adherent** during long-term treatment, a rate largely similar to other chronic illnesses and one that has remained unchanged over the years.)

Patients diagnosed with Bipolar Disorder?

Reply - Changed to "patients <u>diagnosed with</u> bipolar disorder"

AR 3 - Non-concordant?

Reply - The term "adherent" has been retained because of the reasons cited above.

Suggestion - However, because of inconsistent results and failure of these studies to address the complexities of adherence behaviour, demographic and illness-related factors **alone** were unable to explain or predict non-adherence in BD.

Reply - The word "alone" has been inserted.

Suggestion -Bipolar disorder (BD) is **a** commonly prevalent and enduring condition characterized by recurrent episodes **and** often followed by residual symptoms. The high rates of comorbidity, suicide and functional impairment in BD also ensure that it is a common cause of disability **as well as** economic and social burden [1, 2].

Reply - Changes suggested have been incorporated.

AR 4 - (Pharmacological treatments are efficacious in both acute and long-term treatment of BD, but the benefits of maintenance treatment are less impressive in day-to-day practice.)

Unclear meaning.

Reply - Re-written as - "Pharmacological treatments are efficacious in both acute and long-term treatment of BD in clinical trials of these medications. Nevertheless, the effectiveness of medication treatments, particularly long-tem treatment with medications is less impressive in day-to-day practice."

Suggestion - Finally, the poorer quality of life, stigmatization and functional impairment which accompany non-adherence lead to added burden on the family and ~~**the**~~ society as a whole [8].

Reply - The word "the" deleted.

AR 5 - (Much of this variability can be attributed to methodological differences such as how non-adherence has been defined and assessed in these studies; the setting of the studies and their designs, the nature of the patient sample included, the phase of illness and the duration for which non-adherence has been estimated [13-17].)

Punctuation / phrasing needs review

Reply - Re-written as - "Much of this variability in rates can be attributed to methodological differences across studies. Adherence has been defined and assessed differently in different studies. Studies also differ in the settings in which they have been conducted (e.g. clinics or community), in their designs (e.g. cross-sectional or longitudinal), in the patient samples included, and in the phase of illness or the duration during which non-adherence has been estimated."

Suggestion - The fact that about half of ~~**the**~~ patients with BD become non-adherent during long-term treatment puts it on par with several other chronic psychiatric and medical disorders [4, 9, 30-32].

Reply - The word "the" deleted.

Suggestion - In a seminal article about 40 years ago Jamison et al. [37] proposed four mutually interacting domains to explain non-adherence ~~**with**~~ **to prescribed** lithium among patients with BD.

Reply - Changes made.

AR 6 - (These included factors related to the patient, the illness, the effect of medications and characteristics of the clinicians.)

Can you be specific about these factors?

Reply - Re-written as - "These included factors related to the patient (e.g. demographic characteristics), the illness (e.g. severity), the effect of medications (e.g. side effects) and characteristics of the clinicians (e.g. relationship with patients)."

AR 7 - (These determinants have been subsequently adopted by others working in the field with some significant additions.)

Such as?

Reply - Re-written as - "These determinants have been subsequently adopted by others working in the field, but some significant additions have been made in each category. For example, patient-related factors have come to include...."

Suggestion -In the 1980s and 1990s research on **treatment** non-adherence **amongst those diagnosed with** psychiatric disorders, including BD, mostly limited itself to examining demographic, clinical and medication-related factors impacting adherence [2, 17, 38, 40].

Reply - Changes made.

AR 8 - (The exclusive focus on these factors was **understandably** driven by biologically and medically orientated conceptualizations of the illness.)

Why understandably? Critiques of psychiatry from before this period focussed on challenging the primacy of biological understanding?

Reply - Re-written as - "The exclusive focus on these factors appeared to be driven by biologically and medically orientated conceptualizations of the illness, although the primacy of the biological approach had been the object of criticism for long." - to remove the word "understandably "

Suggestion - Spacing of references in text

Reply - Corrected

AR 9 - (However, though a basic level of insight may be necessary for ensuring adherence it not a sufficient prerequisite for doing so [1, 16, 36, 65, 66].)

Unclear phrasing.

Reply - Re-written as - "However, though it might be difficult for a patient to be adherent without a basic level of insight, simply having insight may not be sufficient to ensure adherence."

Suggestion - A large number of studies have found that **treatment** side effects **negatively** influenced ~~**negatively**~~ adherence in BD [7, 35, 46, 59, 70], though many of these have exclusively investigated **the** side effects of lithium [34, 67, 71-74]. On the other hand, an almost **equally large** number of studies and patient surveys have revealed that side effects are not associated with non-adherence in BD [2, 4, 26, 27, 39, 75]. It appears that fears or concerns regarding side effects rather than their actual prevalence may be more important in determining non-adherence in BD [17, 26, 41, 45, 76, 77]. The influence of treatment-efficacy on adherence has been examined less often ~~**in BD**~~, though some studies suggest that medications alleviating depressive symptoms are more likely to promote adherence [7, 51, 78-80].

Reply - Changes made.

Suggestion -For example, the higher prevalence of non-adherence during manic episodes could ~~w~~ell be due to **the** a ~~lac~~k of insight **and** or the presence of cognitive impairment during such episodes [1, 4, 41].

Reply - Changes made.

AR 10 - (These limitations of attempting to predict and target non-adherence based on demographic and illness-related factors indicated the need for an alternative perspective on treatment-adherence. The newer perspective laid greater emphasis on the patient's point of view of medication-taking, while acknowledging that problems with adherence are likely to be determined by complex interactions between the patient, the illness, its treatment and the wider socio-cultural environment in which such treatment took place [11, 27, 41, 61].)

Consider use of past tense here – have we moved beyond a patient centred paradigm?

Reply - Re-written as - "These limitations of attempting to predict and target non-adherence based on demographic and illness-related factors indicates the need for an alternative perspective on treatment-adherence. The newer perspective lays greater emphasis on the patient's point of view of medication-taking, while acknowledging that problems with adherence are likely to be determined by complex interactions between the patient, the illness, its treatment and the wider socio-cultural environment in which such treatment takes place." - to change past tense

AR 11 - (As with other chronic medical conditions, research on predictors of non-adherence in BD over the last two decades has undergone a gradual shift in thinking from an illness-centred to a patient-centred approach [40, 89]. In this patient-centred paradigm, adherence is viewed as a dynamic rather than static process which is influenced by many factors within and outside the patient [2, 13, 26, 42, 43].)

Is it correct to view the shift in this progressive manner? There were dissenting voices relating to the non-patient centred nature of psychiatry prior to the 1990s. Also, in other medical disciplines the central role of patient experience in the discourse has been apparent for a long time.

Reply - While it is true that the central role of the patient experience has been the topic of discourse for long, these concepts have been widely applied to treatment-adherence in mental illnesses only since the late 1970s to 1990s.

See for example reviews by Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001; **26**: 331-342 and Sabate E. Adherence to long term therapies: evidence for action. Geneva: World Health Organization, 2003 for the progress in adherence research in chronic medical conditions and by Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: Empirical and clinical findings. Schizophr Bull 1997; **23**: 637-651 for schizophrenia. In BD though a few studies and reviews appeared in the 1980s-1990s, the bulk of the literature on patient perspectives has begun to appear from somewhere around the late 1990s to early 2000s.

Suggestion -At the core of this process **~~lies the patients' abilities~~ lie the patients' abilities** to make decisions about their own treatment [11, 27, 90].

Reply - Changes made.

AR 12 - (Patients are the "final decision-makers," who as **rational** consumers choose whether or not continue treatment based on their own beliefs, personal circumstances and their perceptions of benefits and disadvantages of treatment.)

Is it worth reviewing the concept of a 'rational consumer' briefly given the tenuousness of this concept with current economic thinking e.g. Kahneman?

Reply - Rewritten to remove the word "rational" because a debate on whether patients are actually "rational" is beyond the scope of this editorial. The revised sentence is: Patients are the "final decision-makers" **who have a right to** choose whether or not continue treatment

based on their own beliefs, personal circumstances and their perceptions of benefits and disadvantages of treatment.

AR 13 - (The cornerstone of the concordance approach rests on open discussions of mutual views about taking medications, and a shared decision-making alliance between patients and clinicians while retaining the primacy of patients' choices.)

Is it worth referring in greater detail to the large body of literature on shared decision making?

Reply - Again, because of constraints of length a detailed review of the concept of the shared decision-making alliance is not possible. Nevertheless, a mention of these concepts has been made later. (See of the last few lines of the section on " Stigma, patient satisfaction and system-related factors' of the revised manuscript).

Suggestion -Patients appear **~~to~~** particularly unhappy with the lack of information **provided** on side effects and other aspects related to medication-treatment [75, 86, 127-129].

Reply - Changes made

Suggestion -Ref. 32 - **ChakrabartiS.What's in a name?** Compliance, adherence and concordance in chronic psychiatric disorders.*World J Psychiatry* 2014;**4**:30–36 [PMID: 25019054DOI: 10.5498/wjp.v4.i2.30]

Reply - Changes made

REVIEWER 033758880

Comments to authors

The manuscript discusses the pertinent and universal issue of non-adherence in Bipolar Disorders in particular and all chronic disorders in general. The arguments for patient centered approach in management of Bipolar Disorders have been provided. Although the ethical correctness of this approach is undeniable, there is insufficient data for this approach resulting in any drastic enhancement of treatment adherence rates.

No changes suggested

REVIEWER 02445209

Comments to authors

Dear authors, I do not have any substantial negative comment on your manuscript. I really liked reading it. The reviewer

No changes suggested

REVIEWER 02445374

Comments to authors

Excellent review article.

No changes suggested

CHANGES SUGGESTED BY THE EDITORIAL TEAM

W#1 - Provide post code

Reply - Done.

W#2 - Please offer signed pdf file of conflicts of interest.

Reply - Signed pdf file submitted.

W#3 - Please offer more details of address, such as street or avenue.

Reply - Street address included.

W#4 - Please offer the audio core tip

Reply - Audio core tip submitted