



December 8, 2013

Dear Editor,

Manuscript # The impact of living with bipolar patients: making sense of caregivers' burden, by Pompili et al

Thank you for your reviews of this submission. The reviewer's comments were thoughtful and helpful in preparing the attached revision, with the following responses to each of the comments received.

Answers to Reviewers comments

Reviewer 1.

Review: Maurizio Pompili et al. The impact of living with bipolar patients: making sense of caregivers' burden This manuscript deals with a clinically very important issue - a burden experienced by family members caring for bipolar patients. Unfortunately, this topic has been largely neglected in the literature. This text illustrates very well both points: the role this burden plays in the course of illness of the patients, as well as the dearth of solid, quantitative literature on the subject. The aim of the manuscript was to examine objective and subjective burdens in primary caregivers of bipolar patients and to list which symptoms of the patients are considered more burdensome by the caregivers. To provide a critical review of bipolar disorder and quality of life, particularly in offspring of bipolar parents, the authors performed a detailed literature and Library search. They identified important papers and book chapters published in English between 1963 and 2011. They discovered that the highest levels of distress were caused by patient's behavior and by the patient's role dysfunction. Furthermore, the caregiving role compromised other social roles occupied by the caregiver, becoming part of the heavy social cost of bipolar affective disorder. The data the authors gathered suggest that caregiver burden is high and largely neglected in BD. Yet, the familycaregivers are central to the wellbeing of patients, but at the same time researchers, policy makers,



and formal service providers often take for granted their co-operation and welfare. Clearly, there is a need to better understand caregivers' views and personal perceptions of the stresses and demands arising from caring for someone with BD in order to develop practical appropriate interventions and to improve the training of caregivers. In summary, well written paper, important clinical topic. No points were identified that would require alterations.

Reviewer 2.

GENERAL COMMENTS (1) The importance of the research and the significance of the research contents This is a timely and significant review highlighting an important area of research. (2) The novelty and innovation of the research Very few reviews of caregiver burden in bipolar disorder are available, so this paper is a fairly new one. (3) Presentation and readability of the manuscript The results could be better organized; suggestions have been made. (4) Ethics of the research. No issues.

SPECIFIC COMMENTS Caregiver burden has received far more attention in dementia and schizophrenia than other psychiatric disorders. Therefore, any attempt to review caregiver or family burden in bipolar disorders is welcome. The authors have carried out a comprehensive and detailed review of the area and presented their findings in this context. I have a few suggestions to make:

Question 1. In their search strategy the authors mention that: In order to provide a critical review of BD and quality of life, particularly in offspring of bipolar parents we performed a detailed PubMed, BioMedCentral, ISI Web of Science, PsycINFO, Elsevier Science Direct, Cochrane Library search to identify all papers and book chapters in English during the period between 1963 and November 2013. It is not clear, when the objective was to review caregiver burden in bipolar disorder, why was the search restricted to offspring of parents with bipolar disorder? The search terms used appear to be more appropriate. I would suggest modifying this sentence.

Answer to Question 1. Thank you for this suggestion, now we have revised the indicated sentence.



Question 2. It would be better if the authors used the phrase “persons/patients with bipolar disorder” than “bipolar patients.”

Answer to Question 2. In the revised version of the manuscript we use “persons/patients” instead of “patients” as suggested.

Questions 3. If the aim was to examine objective and subjective burden in primary caregivers of patients with bipolar disorder, then the results could have been grouped under these two main areas: Objective burden – which would include problem behaviour, financial burden and the effect on the family of the patient Subjective burden – Emotional and other consequences of caring for a relative with bipolar disorder.

Answer to Question 3. Thank you for this suggestion, the indicated section has now been reorganized to group the main results under the two requested areas.

Question 4. It would have been helpful if the terms used such as caregiver, caregiver/family burden, objective and subjective burden etc. were more clearly defined. The original distinction between objective and subjective burden was made by Hoenig & Hamilton (Hoenig J, Hamilton MW. The schizophrenic patient in the community and his effect on the household. Int J Soc Psychiatry 1966; 12:165-176.)

Answer to Question 4. In the revised version of the manuscript, we provided the original distinction between objective and subjective burden that has been initially provided by Hoenig & Hamilton (1966) as suggested.

In particular, the following statement has been added:

“There is no universally accepted definition of burden of care but the concept of burden is associated with the patient’s poor social performance that is usually reflected in the caregivers burden. The original distinction between objective and subjective burden has been described by Hoenig and Hamilton (1966). They identified objective burden that included anything occurring as a disrupting factor within family life owing to patient's illness, and subjective burden that referred to the feeling that a burden is being carried in subjective sense.”

Question 5. Some mention should probably be made of the stress-coping paradigm, which is the predominant paradigm for examining burden in all disorders, including bipolar disorder (Szmukler GI, Burgess P, Herrman H.



Caring for relatives with serious mental illness: the development of the Experience of Caregiving Inventory. Soc Psychiatry Psychiatr Epidemiol 1996; 31: 137 - 48.) Other elements of this model such as appraisals, coping and mediators could be examined separately from burden.

Answer to question 5. Thank you for this suggestion, in the revised version of the manuscript we described the stress-coping paradigm explaining how it may help to understand the burden associated with psychiatric conditions.

In particular, the following statements have been added:

“The stress-coping model may be considered as a fundamental paradigm for examining caregivers burden in all disorders, including bipolar disorder. Using the stress-vulnerability model as a conceptual framework, it’s possible to understand the role of stress when the effects of the illness appear and a specific vulnerability exists. The stress-coping paradigm explains the effects of stress on health according to a contextual approach about how the coping processes allow to reduce the negative implications of stress and improve adaptation in conflicting situations (Leclerc et al., 1997).

Szmukler et al. (1996) aiming to develop a valid self-report measure of the experience of caring for a relative with a serious mental illness initially conceptualized caregiving within the “stress-appraisal-coping” framework.

Analyses of responses to the 66-item version of the Experience of Caregiving Inventory (ECI) were obtained from 626 caregivers, and then tested on 63 relatives of patients with schizophrenia in acute care. The authors investigated the degree to which the ECI complied with the stress-coping model in association with coping, and predict psychological morbidity in carers. Results showed that the ECI together with coping style predicted a large proportion of the variance in the General Health Questionnaire suggesting that the ECI identified important dimensions of caregiving distinct from coping and psychological morbidity”.

References

Leclerc C, Lesage A, Ricard N. [Relevance of the stress-coping paradigm in the elaboration of a stress management model for schizophrenics]. Sante Ment Que. 1997;22(2):233-56.



Szmukler GI, Burgess P, Herrman H, Benson A, Colusa S, Bloch S. Caring for relatives with serious mental illness: the development of the Experience of Caregiving Inventory. *Soc Psychiatry Psychiatr Epidemiol.* 1996;31(3-4):137-148.

Question 6. The methodological difficulties in conceptualizing and measuring caregiver burden could be mentioned at some point. (Schene AH, Tessler RC, Gamache GM. Caregiving in severe mental illness: conceptualization and measurement. In: Knudsen HC, Thornicroft G, editors. *Mental Health Service Evaluation*. Cambridge, England: Cambridge University Press; 1996. p. 296-316.).

Answer to question 6. This point has now been clarified in the Limitations section with the following statements:

“Furthermore, another criticism must be reported. There are many methodological difficulties in conceptualizing and measuring caregiver burden (Schene et al., 1996). Relevantly, the concept of caregivers burden has been viewed as multidimensional although caregivers burden has been generally divided in objective and subjective burden by Hoenig and Hamilton (Hoenig and Hamilton, 1966)”.

Question 7. Some idea about how the extent and pattern of caregiver burden in bipolar disorder compares with that in other disorders such as schizophrenia, would be helpful in gaining a better perspective on caregiver burden in bipolar disorder.

Answer to question 7. Now within the Discussion section, we discussed, as suggested, the burden on caregivers of patients with schizophrenia. We also reported findings from studies comparing the impact and implications of burden of care on caregivers of patients with both schizophrenia and bipolar disorder.

In detail, the following statements have been added:

“The burden experienced by caregivers of persons/patients with bipolar disorder has been associated with increased caregiver psychiatric conditions, and mental health service utilization.

Investigating the impact of caregivers burden in other chronic psychiatric conditions such as schizophrenia could be, in our opinion, helpful to understand the caregiver burden in bipolar disorder. Caregivers of patients



with schizophrenia experience a huge burden and are considered as a potential high risk group for developing psychiatric disorders (Lasebikan and Ayinde, 2013). Tan et al. (2012) found in a convenient sample of 150 caregivers of outpatients with schizophrenia that high levels of burden due to several factors like other commitments, lack of resources, low financial support, education level and ageing. Kate et al. (2013) suggested that caregiving burden, in particular tension is associated with dysfunctional coping strategies, poor quality of life and psychological morbidity in caregivers.

Burden of care for caregivers of patients with schizophrenia may be considered as a complex construct generally defined by its emotional, psychological, physical and economic impact on the quality of life of caregivers (Awad and Voruganti, 2008). Many studies measured the burden of care in schizophrenia whereas only some studies measured the burden experienced by the caregivers of patients with bipolar disorder. To date, few studies have compared the degree of burden on the caregivers of patients with schizophrenia and bipolar disorders. Some authors (Grover et al., 2012) reported that caregivers of schizophrenia patients experience caregiving more negatively compared with those of bipolar disorders patients. The authors suggested that caregivers of patients with schizophrenia and bipolar affective disorder experience a relevant burden while caring their patients.

There are also studies suggesting that caregivers of patients with schizophrenia and bipolar disorders experience similar levels of burden using similar coping strategies to deal with it (Chadda et al., 2007). Similarly, Nehra et al. (2005) found high levels of patient dysfunction and caregiver burden in both bipolar disorders and schizophrenia, with no significant differences between the two groups. Although the caregiving experience has been extensively investigated in some chronic severe mental disorders, more methodologically and culturally relevant studies are needed in order to understand the differential aspects of emotional and psychological burden on caregivers of patients with schizophrenia and bipolar disorders."

References

Lasebikan VO, Ayinde OO. Family Burden in Caregivers of Schizophrenia Patients: Prevalence and Socio-demographic Correlates. *Indian J Psychol Med.*2013;35(1):60-6.



Tan SC, Yeoh AL, Choo IB, Huang AP, Ong SH, Ismail H, Ang PP, Chan YH. Burden and coping strategies experienced by caregivers of persons with schizophrenia in the community. *J Clin Nurs*.2012;21(17-18):2410-8

Kate N, Grover S, Kulhara P, Nehra R. Relationship of caregiver burden with coping strategies, social support, psychological morbidity, and quality of life in the caregivers of schizophrenia. *Asian J Psychiatr*. 2013;6(5):380-8.

Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoeconomics*. 2008;26(2):149-62.

Grover S, Chakrabarti S, Aggarwal M, Avasthi A, Kulhara P, Sharma S, Khehra N. Comparative study of the experience of caregiving in bipolar affective disorder and schizophrenia. *Int J Soc Psychiatry*.2012;58(6):614-22.

Chadda RK, Singh TB, Ganguly KK. Caregiver burden and coping: a prospective study of relationship between burden and coping in caregivers of patients with schizophrenia and bipolar affective disorder. *Soc Psychiatry Psychiatr Epidemiol*.2007;42(11):923-30.

Nehra R, Chakrabarti S, Kulhara P, Sharma R. Caregiver-coping in bipolar disorder and schizophrenia--a re-examination. *Soc Psychiatry Psychiatr Epidemiol*. 2005;40(4):329-36.

Question 8. The interventions to reduce burden could be grouped under simple interventions, which can be offered at the level of the clinician (e.g. enquiring about burden, education and support), and the more complex interventions such as family interventions.

Answer to question 8. Thank you for this suggestion, in the revised version of the manuscript the following statements have been added to focus on this point: "It was found that parents of persons/patients with BD may benefit from a variety of interventions. Generally, the interventions to reduce caregivers burden could be grouped under simple interventions at clinician's level (e.g. enquiring about burden, psychoeducational and support interventions), and the more complex interventions such as family interventions. It has been suggested that identifying and modifying burdensome aspects may help to reduce the



level of burden and their negative effects on the caregivers also improving patients outcome (Reinares et al., 2006).

Studies evaluating interventions on caregivers showed to improve caregiver quality of life (Corring, 2002; Cuijpers, 1999). However, although interventions may be associated with reduced burden (Dixon et al., 2001), and to a stronger family competence (Johnson, 2000) generally few caregivers seek out support for themselves.

Caregivers of persons/patients with bipolar disorder can benefit from psychoeducational interventions designed to provide information, support and stress management skill building (Nadkarni & Fristad, 2012). It has been demonstrated in randomized controlled trials that Psychoeducational approach can improve outcomes for both patients and families (Fristad, 2006; Fristad, Goldberg-Arnold, & Gavazzi, 2003). The ways of intervention has to be investigated with further studies, but what is sure at this time is that professionals and non-professional care-givers should work together to make support of people with affective disorder more efficient.

Perlick et al. (2010) suggested that caregivers treated with a psychoeducational and cognitive-behavioral approach in the Family-Focused Treatment-Health Promoting Intervention condition reported a significant reduction in depressive symptoms and improvement in health behaviors when compared to caregivers who received education alone. They also experienced significant reductions in subjective burden associated with the patients' symptoms and role dysfunction during the course of treatment.

There are also potential short-term interventions that can be provided at the time of hospitalization for families of patients with mood disorders and are associated with an improvement of caregiver's burden (Heru & Ryan 2004).

Considering that male caregivers dropped out at higher rates than female caregivers, specific engagement strategies could be required to engage younger male caregivers experiencing high level of burden and distress (Perlick et al., 2001)."

References

Reinares M, Vieta E, Colom F, Martínez-Arán A, Torrent C, Comes M, Goikolea JM, Benabarre A, Daban C, Sánchez-Moreno J. What really matters



to bipolar patients' caregivers: sources of family burden. *J Affect Disord.* 2006;94(1-3):157-163.

Corring, D., 2002. Quality of life: perspectives of people with mental illnesses and family members. *Psychiatric Rehabilitation Journal* 25 (4), 350 – 359;

Cuijpers, P., 1999. The effects of family intervention on relatives' burden: a meta-analysis. *Journal of Mental Health* 8, 275 – 285.

Dixon L, Stewart B, Burland J, Delahanty J, Licksted A, Hoffman M. Pilot study of the effectiveness of the family-to family education program. *Psychiatric Services* 2001;52:965–967.

Johnson E.D. Differences among families coping with serious mental illness: a qualitative analysis. *American Journal of Orthopsychiatry* 2000;70(1):126–134.

Perlick DA, Miklowitz DJ, Lopez N, Chou J, Kalvin C, Adzhishvili V, Aronson A. Family-focused treatment for caregivers of patients with bipolar disorder. *Bipolar Disord.* 2010;12 (6):627-37.

Heru AM, Ryan CE. Burden, reward and family functioning of caregivers for relatives with mood disorders: 1-year follow-up. *J Affect Disord.* 2004 Dec;83(2-3):221-225).

Perlick DA, Rosenheck RR, Clarkin JF, Raue P, Sirey J. Impact of family burden and patient symptom status on clinical outcome in bipolar affective disorder. *Journal of Nervous and Mental Disease* 2001;189(1):31 –37.

Question 9. The authors could add a table listing the studies, which were included for this review and those which were excluded.

Answer to question 9. In the revised version of the manuscript, we added Figure 1 describing the main steps of the search strategy used for selecting studies (identification, screening, eligibility, inclusion in the systematic review). Specifically, we included a new paragraph about study design (we adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines to achieve a high standard of reporting and in the first lines of Results section we described the number of studies selected in the present review.

The following paragraphs have been added:

Study design and eligibility criteria

To achieve a high standard of reporting we have adopted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher



et al., 2009). The PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram for reporting in systematic reviews and meta-analyses.

Number of studies selected

The combined search strategies yielded a total of 227 articles of which, after a complete analysis, 96 full-text articles were screened and 131 were excluded. We excluded articles not published in peer-reviewed journals and not in English language, articles without abstracts, abstracts that did not explicitly mention caregivers burden in patients/persons with bipolar disorder and articles with a publication date before 1963. Forty-eight full-text articles were assessed for eligibility but twenty-eight full-text articles were excluded due to low-relevance to the main theme, including unclear data regarding materials and methods, and number of patients analyzed.

Reference

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2535.

Question 10. Positive aspects of caregiving

Answer to question 10. Thank you for this suggestion, the following statements have been added to focus on the positive aspects of caregiving as suggested.

“Existing studies on family caregivers of persons/patients with psychiatric disorders have been traditionally conducted on negative aspects of caregiving focusing on caregivers burden. However, it’s also important to describe the potential rewards and positive aspects of caregiving.

Veltman et al. (Veltman A, Cameron J, Stewart DE. The experience of providing care to relatives with chronic mental illness. *J Nerv Ment Dis.* 2002;190(2):108-114) investigated caregivers' perspectives on both the negative and positive aspects of caregiving. Interestingly, even beneficial effects such as feelings of gratification, love, and pride have been reported by caregivers. Specifically, caregivers described the importance of life lessons learned, love, and caring for persons/patients with psychiatric conditions. Helping to identify the rewards of caregiving, may improve caregiving abilities to face distress and challenging situations reducing the global caregiver burden.



Also, Bauer et al. (Bauer R, Koepke F, Sterzinger L, Spiessl H. Burden, rewards, and coping--the ups and downs of caregivers of people with mental illness. *J Nerv Ment Dis.* 2012;200(11):928-34) examined using semistructured interviews the potential rewards of caregiving and coping strategies of 60 caregivers of people with psychiatric disorders. They identified 413 individual statements of rewards, the items with the highest factor loading are the increase in self-confidence, inner strength, maturity, and life experience. The authors highlighted the importance of providing an adequate knowledge about caregivers burdens.

References

Veltman A, Cameron J, Stewart DE. The experience of providing care to relatives with chronic mental illness. *J Nerv Ment Dis.* 2002;190(2):108-114.

Bauer R, Koepke F, Sterzinger L, Spiessl H. Burden, rewards, and coping--the ups and downs of caregivers of people with mental illness. *J Nerv Ment Dis.* 2012;200(11):928-34.

Reviewer 3.

Comments to Authors: This work deals with the burden of the caregivers who take care of bipolar patients. While it is a very important and actual issue, the manuscript requires a thorough revision.

Detailed comments:

Question 1. Introduction, first sentence: it is not clear how that special year, 1999 was selected for reporting and why was a more than ten years earlier time point so important. It would be more appropriate reporting data from the previous year or for a longer period.

Answer to Question 1. Thank you for this suggestion, the sentence has been now revised and the requested details have been added.



Question 2. Introduction, second paragraph, fourth sentence states: 'BD is indeed the sixth cause of disability among all medical conditions' As this statement is not generally true for all countries in the world, I recommend explicitly indicate the country where this data has come from.

Answer to Question 2. In the revised version of the manuscript, the mentioned statement has been corrected.

Question 3. Introduction, fifth paragraph, first sentence: there is an extra 'that' in the sentence.

Answer to Question 3. Thank you for this suggestion, the sentence has been revised.

Question 4. Methods, subheading: singular is better for 'identification'.

Answer to Question 4. We have revised the subheading as suggested.

Question 5. Study period is differently defined in the Abstract and Method section. Please correct it.

Answer to Question 5. In the revised version of the manuscript, the study period within the Method section has been corrected as suggested.

Question 6. Quality assessment, first paragraph, last sentence: instead of 'caregivers of bipolar disorders patients', caregivers of patients with bipolar disorder, or caregivers of bipolar patients would be better.

Answer to Question 6. Thank you for this suggestion, now we revised the mentioned statement.

Question 7. Caregivers burden section, sixth paragraph, forth sentence: '-this is not a discussion. -this is not a discussion. This is a continuation of the review. These statements do not belong to the Discussion section, as well as many



statements below' is not appropriate there. It seems to be a comment from a reviewer.

Answer to Question 7. We deleted the suggested statements in the revised version of the paper.

Question 8. The structure of the review is a bit confused. Certain issues are discussed more than one times in different parts of the manuscript making the text difficult to follow (e.g.: violence towards the caregiver was discussed in 'Caregivers burden in BD' section as well as in 'Caregivers relationship with the patient' section.). Create a separate chapter for violence may solve this problem.

Answer to Question 8. Now, this specific topic "Violence towards the caregiver" has been inserted as a new separate section within the manuscript structure as suggested.

Question 9. In 'Caregivers relationship with the patient' section, fifth paragraph, third sentence can hardly be understood: 'When ill, the patient became may be irritable.' Please correct it.

Answer to Question 9. In the revised version of the manuscript, the suggested statement has been re-written in the following way: "In the acute phase of his/her illness, the patient may become more irritable, distant and difficult to manage".

Question 10. Discussion, second paragraph: 'non-biological caregivers'. What does it mean? In the same sentence: 'Axis I and anxiety diagnoses'. As I know, anxiety diagnoses also belong to the Axis I group. The discussion part is a continuation of the results section, drawing conclusions from the findings is missing.

Answer to Question 10. The two mentioned inconsistencies have now been corrected. In detail, "non-biological caregivers" has been changed in "non-



biological relatives" and "Axis I and anxiety diagnoses" has been replaced with: "DSM-III-R Axis I diagnoses".

Question 11. English style also requires an extensive revision preferably by a native speaker.

Answer to Question 11. Thank you for this suggestion, now the manuscript has been reviewed by a native English speaker for the quality of language.

Given efforts of the Publisher to work with the attached revised manuscript, the authors hereby convey transfers and otherwise assigns all copyright ownership to the Publisher in the event that this work is published. The manuscript contains nothing, to the best of our knowledge, that is unlawful or that might infringe on the rights of any other person, or any copyright.

My coauthors and I hope you will find the revised MS sufficiently improved as to be suitable for timely appearance in World Journal of Psychiatry, which continues to seem ideally suited for this material.

Sincerely yours,

Maurizio Pompili, M.D. , Ph.D.