ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2017 August 26; 5(4): 80-123

Published by Baishideng Publishing Group Inc

WJMA World Journal of Meta-Analysis

A peer-reviewed, online, open-access journal of clinical pediatrics

Editorial Board

2013-2018

The *World Journal of Meta-Analysis* Editorial Board consists of 380 members, representing a team of worldwide experts in clinical medicine. They are from 39 countries, including Argentina (2), Australia (3), Austria (1), Belgium (5), Brazil (10), Canada (16), Chile (2), China (116), Croatia (1), Egypt (1), Finland (4), France (2), Germany (9), Greece (9), Hungary (1), India (12), Iran (2), Ireland (1), Israel (2), Italy (39), Japan (5), Lithuania (1), Netherlands (8), New Zealand (1), Norway (1), Peru (1), Poland (3), Portugal (6), Romania (1), Saudi Arabia (5), Singapore (3), South Korea (7), Spain (8), Sri Lanka (2), Switzerland (2), Thailand (3), Turkey (3), United Kingdom (23), and United States (59).

Jian-Sheng Li, *Zhengzhou*
Jun-Sheng Li, *Nanjing*
Xiao-Ping Li, *Chengdu*
Yan-Yan Li, *Nanjing*
Hua Liu, *Nanchong*
Tong Liu, *Tianjin*
Ai-Ping Lu, *Hong Kong*
Ying Luo, *Kunming*
Chao Ma, *Shanghai*
Dan Xing Ma, *Tianjin*
Jie Ma, *Xi'an*
Yan-Lei Ma, *Shanghai*
Wei Nie, *Shanghai*
Wen-Quan Niu, *Shanghai*
Wen-Sheng Pan, *Hangzhou*
Shi-Qiang Shen, *Wuhan*
Xiang-Chun Shen, *Guiyang*
Ke-Qing Shi, *Wenzhou*
Rui-Hua Shi, *Nanjing*
Yong-Bing Shi, *Suzhou*
Zhi-Yuan Song, *Chongqing*
Qing-Min Sun, *Nanjing*
Yihong Sun, *Beijing*
Shi-Qiao Tan, *Chengdu*
Jiu-Lai Tang, *Hefei*
Na-Ping Tang, *Shanghai*
Yong Tang, *Tianjin*
Yang Tian, *Changchun*
Jian-Cheng Tu, *Wuhan*
Bin Wang, *Beijing*
Cong-Xia Wang, *Xi'an*
Dao-Rong Wang, *Yangzhou*
Fu-Zhou Wang, *Nanjing*
Hong-Xia Wang, *Shanghai*
Jing Wang, *Changshu*
Na Wang, *Shijiazhuang*
Shukui Wang, *Nanjing*
Wei Wang, *Wuxi*
Xing-Huan Wang, *Wuhan*
Xi-Shan Wang, *Harbin*
Yu-Ting Wang, *Chengdu*
Zhen-Ning Wang, *Shenyang*
Bing Xia, *Wuhan*
Zi-Qiang Xin, *Beijing*
Jun Xiong, *Nanchang*
Lin Xu, *Nanjing*
Xi-Ping Xu, *Guangzhou*
Zhuo-Qun Xu, *Wuxi*
Hui-Ping Xue, *Shanghai*
Feng Xie Yang, *Shanghai*
Shuan-Ying Yang, *Xi'an*
Yi-Cong Ye, *Beijing*
Yan-Wei Yin, *Beijing*
Yong-Mei Yin, *Nanjing*
Zi Yin, *Guangzhou*
Bin Yu, *Guangzhou*
Yun-Xian Yu, *Hangzhou*
Bei-Bei Zhang, *Chengdu*
Jian Zhang, *Shanghai*
Jun-Hua Zhang, *Tianjin*
Li-Li Zhang, *Chongqing*
Ling Zhang, *Beijing*
Qiu Zhang, *Heifei*
Shuo Zhang, *Shenyang*
You-Cheng Zhang, *lanzhou*
Yu-Rong Zhang, *Xi'an*
Zhong-Heng Zhang, *Jinhua*
Hai-Tao Zhao, *Beijing*
Pan Zhao, *Beijing*
Yu-Lan Zhao, *Shanghai*
GQ Zheng, *Wenzhou*
Cui-Hong Zheng, *Wuhan*
Jie-Jiao Zheng, *Shanghai*
Ming-Hua Zheng, *Wenzhou*
Xue-Sheng Zheng, *Shanghai*
Jian-Hong Zhong, *Nanning*
Lai-Ping Zhong, *Shanghai*
Peng Zhou, *Shanghai*
Ping Zhou, *Wuhan*
Tian-Biao Zhou, *Guangzhou*
Kun-Ju Zhu, *Guangdong*

Croatia

Miljenko Franic, *Zagreb*

Egypt

Ashraf F Nabhan, *Cairo*

Finland

Jouni JK Jaakkola, *Oulu*
Ville Kyto, *Turku*
Jouko Miettunen, *Oulu*
Reginald Quansah, *Oulu*

France

Alain Braillon, *Amiens*
Julie Dubourg, *Lyon*

Germany

Tonio Ball, *Freiburg*
Robert Bergholz, *Hamburg*
Jan S Brunkwall, *Cologne*
Holger Cramer, *Essen*
Joseph P Kambeitz, *Munich*
Sascha Meyer, *Homburg*
Thomas Nickl-Jockschat, *Aachen*
Martin Pinquart, *Marburg*
Robert Schier, *Cologne*

Greece

Vangelis G Alexiou, *Athens*
Stefanos Bonovas, *Athens*
Dimitrios Daoussis, *Patras*
John K Goudakos, *Thessaloniki*
Savas Grigoriadis, *Thessaloniki*
Pagona Lagiou, *Athens*
Athanasios G Papatsoris, *Athens*
Theodoros N Sergentanis, *Athens*
Sotirios Tsiodras, *Athens*

Hungary

Balazs Gyorffy, *Budapest*

India

Ritesh Agarwal, *Chandigarh*
Giridhara R Babu, *Bangalore*
Subho Chakrabarti, *Chandigarh*
Yennapu Madhavi, *New Delhi*
Tanu Midha, *Kanpur*
Kaushal K Prasad, *Chandigarh*
Kameshwar Prasad, *New Delhi*
Singh Rajender, *Lucknow*
Vinod Ravindran, *Kozhikode*
Vijay D Shetty, *Mumbai*
R.Umaya Suganthi, *Bangalore*
Krishna Undela, *Mysore*

Iran

Nejat Mahdieh, *Tehran*
Ramin Sadeghi, *Mashhad*

Ireland

Ian Conrick-Martin, *Dublin*

Israel

Uri Kopylov, *Ramat Gan*
Meir Lotan, *Kfar-Saba*

Italy

Umberto Aguglia, *Catanzaro*
Fabio Aiello, *Palermo*
Alessandro Antonelli, *Pisa*
Annalisa Blasetti, *Chieti*
Francesco Brigo, *Verona*
Emanuele Cereda, *Pavia*
Roberto Cirocchi, *Terni*
Bernardo Cortese, *Milano*
Alessandro Cucchetti, *Bologna*
Gianfranco Damiani, *Rome*
Fabrizio D'Ascenzo, *Turin*
Massimo Del Fabbro, *Milano*
Valeria Fadda, *Arezzo*
Alessandro Fancellu, *Sassari*
Giuseppe Ferrante, *Milan*
Virginia Festa, *Rome*
Francesco Fiorica, *Ferrara*
Guglielmo Giraldi, *Rome*
Jenny Guidi, *Bologna*
Lorenzo Loffredo, *Rome*
Andrea Messori, *Firenze*
Eliano P Navarese, *Bydgoszcz*
Stefano Omboni, *Solbiate Arno (Varese)*

Alvisa Palese, *Udine*
Stefano Palomba, *Reggio Emilia*
Carlo Perricone, *Rome*
Mario Petretta, *Naples*
A Pezzini, *Brescia*
Gianluca Pontone, *Milan*
Palo E Puddu, *Rome*
Andrea Rognoni, *Novara*
Giuseppe Scalabrino, *Milan*
Fabrizio Sgolastra, *L'Aquila*
Maria L Specchia, *Rome*
Fabio Tine, *Palermo*
Nereo Vettoretto, *Chiari (BS)*
Alberto Vianello, *Perugia*
Luigi Zorcolo, *Cagliari*

Japan

Nguyen T Huy, *Nagasaki*
Hiroharu Kamioka, *Setagayaku*
Koji Kawakami, *Kyoto*
Keitaro Matsuo, *Nagoya*
Kazushi Okamoto, *Nagoya*

Lithuania

Edmundas Kadusevicius, *Kaunas*

Netherlands

Joost de Winter, *Delft*
Dimitra Dodou, *Delft*
Daniel Haverkamp, *Amsterdam*
Vassilios Koussoulas, *Drachten*
Bart J Polder, *Nijmegen*
Theo Stijnen, *Leiden*
Michel PJ van den Bekerom, *Amsterdam*
RNM Weijers, *Amsterdam*

New Zealand

Shaofeng Li, *Auckland*

Norway

Eivind Berge, *Oslo*

Peru

Rafael Bolanos-Díaz, *Lima*

Poland

Maciej Banach, *Lodz*
Krzysztof Jonderko, *Sosnowiec*
Jolanta Lissowska, *Warsaw*

Portugal

Daniel Caldeira, *Lisbon*
Joao P Costa, *Lisbon*
Ana Miguel, *Coimbra*
Manuel Morgado, *Covilha*
Bárbara Peleteiro, *Porto*
Rui M Torres, *Porto*

Romania

Ovidiu C Fratila, *Oradea*

Saudi Arabia

Hazem M Al-Mandeel, *Riyadh*
Ezzeldin M Ibrahim, *Jeddah*
Mutahir A Tunio, *Riyadh*
Alaine N Umubyeyi, *Pretoria*
Hayfaa A Wahabi, *Riyadh*

Singapore

Nikos LD Chatzisarantis, *Singapore*
Roger CM Ho, *Singapore*
Edwin CW Lim, *Singapore*

South Korea

Jung-Hee Kim, *Cheonan*
Hyangsook Lee, *Seoul*
Myeong S Lee, *Daejeon*
Chi-Un Pae, *Bucheon*
Jae H Seo, *Seoul*
Byung-Cheul Shin, *Yangsan*
Yong S Song, *Seoul*

Spain

Pablo Avanzas, *Oviedo*
Joan Cid, *Barcelona*
Joaquin De Haro, *Madrid*
Joan Guardia-Olmos, *Barcelona*
Nabil Halaihel, *Zaragoza*
Jose A Monge-Argiles, *Alicante*
Raul Moreno, *Madrid*
Inés Velasco, *Aracena*

Sri Lanka

Priyanga Akilen, *Colombo*
Ranil Jayawardena, *Colombo*

Switzerland

Jay P Singh, *Zurich*
Giorgio Treglia, *Bellinzona*

Thailand

Manop Pithukpakorn, *Bangkok*
Surasak Saokaew, *Phayao*
Piyamitr Sritara, *Bangkok*

Turkey

Nese Demirturk, *Afyonkarahisar*
Nilufer Ozabaci, *Eskisehir*
Ilke Sipahi, *Istanbul*

United Kingdom

Omar M Aboumarzouk, *Wales*
Abeer Al-Namankany, *London*
Lesley A Anderson, *Belfast*
Ernest A Azzopardi, *Cardiff*
Umberto Benedetto, *Papworth*
Joanne Brooke, *London*
Noriko Cable, *London*
David SY Chan, *Cardifff*
Ying Cheong, *Southampton*
Andrew Currie, *Harrow*
Valentina Gallo, *London*
Gianpiero Gravante, *Leicester*
Peter N Lee, *Sutton*
Ghulam Nabi, *Dundee*
Igho Onakpoya, *Oxford*
Michael A O'Rorke, *Belfast*
Evridiki Patelarou, *London*
Ashish Pradhan, *Huntingdon*
Yousef Shahin, *Hull*
Jian-Qing Shi, *Newcastle*
Surendra P Singh, *Wolverhampton*
Natalie Taylor, *Leeds*
Zheng Ye, *Cambridge*

United States

Olusola O Adesope, *Pullman*
Mike Allen, *Milwaukee*
Bhupinder Anand, *Houston*
Stephen C Aronoff, *Philadelphia*
KoKo Aung, *San Antonio*
William L Baker, *Eagleville*
Matthew L Bechtold, *Columbia*
Atul Bhardwaj, *Hershey*
Somjot S Brar, *Los Angeles*
Hui Cai, *Nashville*
Subhash Chandra, *Towson*
Wen-Pin Chang, *Omaha*
Yong Chen, *North Wales*
Myunghan Choi, *Phoenix*
John H Coverdale, *Houston*
Prakash C Deedwania, *Fresno*
Eugene Demidenko, *Hanover*
Hong-Wen Deng, *New Orleans*
Eric M Deshaies, *Syracuse*
Ali El-Solh, *Buffalo*
Tao Fan, *Whitehouse Station*
Janvier Gasana, *Miami*
Kaveh Hajifathalian, *Boston*
Mohammad O Hoque, *Baltimore*
Larissa RB Huber, *Charlotte*
Imran H Iftikhar, *Columbia*

WJMA World Journal of Meta-Analysis

Contents

Bimonthly Volume 5 Number 4 August 26, 2017

MINIREVIEWS

SYSTEMATIC REVIEWS

Contents

World Journal of Meta-Analysis
Volume 5 Number 4 August 26, 2017

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Bimonthly

World Journal of Meta-Analysis
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
August 26, 2017

World Journal of Meta-Analysis

Submit a Manuscript: http://www.f6publishing.com

World J Meta-Anal 2017 August 26; 5(4): 80-84

DOI: 10.13105/wjma.v5.i4.80

ISSN 2308-3840 (online)

MINIREVIEWS

Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale

Claudio Luchini, Brendon Stubbs, Marco Solmi, Nicola Veronese

Claudio Luchini, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, 37134 Verona, Italy

Claudio Luchini, Surgical Pathology Unit, Santa Chiara Hospital, 38122 Trento, Italy

Brendon Stubbs, Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom

Brendon Stubbs, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience King's College London, De Crespigny Park, London Box SE5 8AF, United Kingdom

Brendon Stubbs, Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford CM1 1SQ, United Kingdom

Marco Solmi, Department of Neurosciences, University of Padova, 35122 Padova, Italy

Marco Solmi, Nicola Veronese, Institute for Clinical Research and Education in Medicine, IREM, 35122 Padova, Italy

Nicola Veronese, National Research Council, Neuroscience Institute, Aging Branch, 35131 Padova, Italy

Author contributions: Luchini C and Solmi M wrote the manuscript; Stubbs B and Veronese N critically evaluated the manuscript; all the authors approved the final form and the submission.

Conflict-of-interest statement: None to declare.

Manuscript source: Invited manuscript

Correspondence to: Claudio Luchini, MD, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, 37134 Verona, Italy. claudio.luchini@univr.it
Telephone: +39-45-8124842
Fax: +39-45-8027136

Received: January 13, 2017
Peer-review started: January 16, 2017
First decision: February 17, 2017
Revised: May 18, 2017
Accepted: June 6, 2017
Article in press: June 8, 2017
Published online: August 26, 2017

Abstract

One of the most important points in the meta-analyses is certainly represented by the assessment of the quality of the studies included in such research. The meta-analyses are considered the highest level of evidence in science. Also for this reason, the quality of the studies included should be accurately evaluated by standardized tools. The overall results of the meta-analysis depend indeed also on a rigorous evaluation of the studies quality. Among all the possible tools for this complex evaluation, the Newcastle Ottawa Scale (NOS) is one of the most used worldwide, above all for observational studies. In this review, we will discuss the strengths and limitation of the NOS, also on the basis of the branch of science in which it has been applied.

Key words: Quality; Meta-analysis; Newcastle Ottawa Scale

Core tip: To assess the quality of a meta-analysis is a remarkable point. In this review, we summarize the current evidence regarding the use of the Newcastle Ottawa Scale, one of the most used tool for evaluating

quality in meta-analyses of observational studies. Taking also our works as example, we found that, even standardized and quick in its application, it suffers from some limitations, particularly when evaluating cross-sectional studies.

Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017; 5(4): 80-84 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i4/80.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i4.80

INTRODUCTION

The quality assessment of studies included in systematic reviews and meta analyses is essential to enable a clear understanding of the evidence base. There are several sources of biases in meta-analyses including inaccurate selection of participants, data collection, analysis and selective reporting of study results[1]. Many of these biases derive directly from the studies which are included in the meta-analysis. However, since systematic reviews and meta-analyses are considered the highest level of evidence in science[2], the quality of the studies included should be accurately evaluated by validated and standardized tools.

For randomized controlled trials (RCTs), numerous tools are available to assess the risk of bias and methodological quality. Among the most commonly used, the Cochrane Collaboration's tool[3] seems one of the most accurate, since it accounts for the main features of the RCTs. However, other tools (such as the Jadad's scale[4]) are commonly used.

There are less methodological quality assessment tools available for the meta-analyses of observational studies. Some authors (including our group[5,6]) have used reporting checklists for detailing the quality of included studies (such as STROBE[7-9]). Whilst this method has several strengths, it may be seen as a simple reporting checklist. Such tools are not validated for assessing the quality of studies included in meta-analyses[1]. For this reason, other tools are commonly used for assessing quality and risk of bias in observational (both cross-sectional and longitudinal) studies. Among these, the Newcastle Ottawa Scale (NOS)[10] is one of the most used worldwide.

Given the rising number of meta analyses of observational studies in the scientific literature, it is mandatory that the tools used to assess study quality in such endeavors are appraised. In this review, we will discuss the strengths and limitation of the NOS and its application, taking as example the branches of pathology and psychiatry, also with reference to some meta-analyses from our group of research.

REVIEW AND DISCUSSION

NOS: Definition

The NOS can be used for both case-control and longitudinal (prospective studies). Typically, cross-sectional studies are evaluated as case control studies. The NOS evaluates three quality parameters (selection, comparability, and outcome) divided across eight specific items, which slightly differ when scoring case control and longitudinal studies[10]. Each item on the scale is scored from one point, except for comparability, which can be adapted to the specific topic of interest to score up to two points. Thus, the maximum for each study is 9, with studies having less than 5 points being identified as representing at high risk of bias[11].

In order to minimize the subjective interpretation of bias from scoring the NOS typically two independent authors should score each paper. However, in our opinion, the most important as well as critical point in the NOS scoring and filling in is certainly represented by the specific field in which the meta-analysis has been conducted. Each field of science has indeed intrinsic aspects with consequent implications: Here we present these differences and both the advantages and the limitations of NOS scale in some of the most important branches of science.

NOS for meta-analyses in pathology

The pathologists' role in the era of modern medicine is based on performing an accurate as well as precise diagnosis, using standardized parameters, fixed cut-offs and thresholds. This standard strategy should be applied from the gross sampling to the pathology report[12,13]. The perfect tool for modern surgical pathologists to reach a consensus on the parameters to be reported in the diagnosis (when, how and why) is certainly represented by meta-analysis. With this statistical method the best standard and significant parameters, that can guide the pathologists during the diagnostic activity, can be documented. The meta-analysis can be thus applied to three of the main aspects of surgical pathology: (1) the prognostic impact of the mutation status of particular genes in cancer[14,15]; (2) the prognostic role of macro- or microscopic features of cancers[16-25]; and (3) the diagnostic utility of some morphological, immunohistochemical and/or molecular parameters[26]. Regarding the specific points of NOS scale for pathologists, an important topic is represented by the selection of the right method for ascertainment of exposure. If the meta-analysis regards a morphological aspect or an immunohistochemical staining, the classical microscopic exam should be preferred. Conversely, if the investigation regards a molecular aspect, the best standard molecular approach for the specific parameter should be applied, knowing that two of the most important are Sanger Sequencing[27]

Table 1 Strengths and weaknesses of the Newcastle Ottawa Scale

Strengths	Weaknesses
Quick and adaptable	Not validation for cross-sectional studies
Validated	Poor agreement
Moderator	Lack of comprehensive manuals

and Next Generation Sequencing[28-30]. For the outcome of interest, it is important specifying that this point is very subjective and may vary more than other points among different meta-analyses. In prognostic meta-analyses, however, we suggest to consider the disease-specific survival or the recurrence-free survival as the right parameter, being the overall survival the most common parameter in prognostic studies and thus not an index of quality. The point of NOS scale represented by the control for important factor or additional factor is obviously very important, since it can give two stars, determining a significant part of the quality's evaluation. In this case the choice of the right parameters it is even more important. Knowing that data from multivariate analysis are more reliable, this merit should be acknowledge using this index, for example giving a star to a study that presents hazard ratios and an additional star if this data are obtained considering at least two or more potential confounders. For meta-analysis in pathology, at last, it has to be highlighted that a standard length for the follow-up of patients is 60 mo (5 years). A point of strength of this scale is that these parameters are not fixed and adaptable on the basis of the specific analysis. For example, a meta-analysis on the survival of patients with glioblastomas, a tumor with a very poor prognosis generally no longer than 2 years, will reach a star for smaller period (18 mo for example) than the classical 60 mo. The adaptability of NOS scale in this sense represents surely a point of strength. A limitation of this scale in pathology is that it may be very difficult, or even impossible, considering every possible source of bias in this scale, or highlighting every point of strength of the analyzed studies with this multi-stars system. The expertise and a consensus meeting among the authors is the best way to choose the right parameters for this scale.

NOS for meta-analyses in psychiatry

Psychiatry is different from pathology and other branches of medicine, since diagnoses, response, and remission are defined exclusively on clinical evaluation. Thus, the selection and exposure or outcome NOS items, which assess whether cases are diagnosed through reliable and independent validation or through self-report instead, is fundamental in establishing research quality. Moreover, among the main diagnostic systems, namely DSM-V[31] and ICD, some differences are evident[32] and there remains a great debate about diagnosis in general. Also, a control group defined as free from a specific mental disease in the general population, has a lower odds of having other psychiatric comorbidity compared to a control population of inpatients, due to frequent medical comorbidity among patients with severe psychiatric conditions[33,34]. Furthermore, remission and response definitions need specific psychopathologic scales' cut-offs to be defined, and self-report or no description of such criteria need to be accounted for from a quality assessment scale, which is the case of NOS. Finally, treatment adherence is a substantial problem in psychiatry, and results are often affected by rates of completers and subjects lost at follow-up; again outcome NOS items account for such a variable. Thus authors encourage the use of NOS scale in the field of psychiatry, as has already been done in both observational[35,36] and interventional[37] studies' meta-analyses.

Strengths of the NOS

The NOS is one of the most known scale for assessing quality and risk of bias in observational studies for several reasons[38], as reported in Table 1. The first one is that this tool is relatively quick to do, although it requires the right attention. Second, as already explained, the adaptability of its indexes on the basis of the investigated topic is very important. Furthermore, differently from other checklists and tools, it is validated for case-control and longitudinal studies[10]. Finally, differently from other tools, NOS gives a score between 0 and 9 and so it is possible to use it as potential moderator in meta-regression analyses[11,39].

Weaknesses of the NOS

The NOS suffers from several weaknesses, however (Table 1). First, some domains are not univocal and one author should usually adapt this scale modifying some items. It is particularly true for cross-sectional studies for which the NOS should be adapted from the scheme of the case-control studies. Regarding the longitudinal investigations, the points usually adapted by the authors are the number and type of adjustments in the multivariate analyses, the duration of follow-up (not univocal follow-up is in fact given) and the outcome of interest not present at the baseline.

Another point of weakness is the low agreement between two independent reviewers in making the NOS. In the work proposed by Hartling *et al*[40], the agreement between the two reviewers was moderate/poor as shown by the *k*-value (< 0.50 for eight of the nine questions on the NOS). This is particularly true in case of low experience by the authors in meta-analysis/systematic reviews[41] suggesting that a training with a more expert author is needed.

Finally, the lack of comprehensive manuals could be interpreted as another limitation[42].

CONCLUSION

The NOS is a tool commonly used in medicine for

the assessment of quality. Although it is a validated instrument and with a long history of reliability it suffers from several limitations. Other tools (tailored for cross-sectional studies and with more univocal items for other observational studies) are probably needed.

REFERENCES

1 **Dreier M**. Quality Assessment in Meta-analysis. In: Doi SAR, Williams GM, editors. Methods of Clinical Epidemiology. Berlin, Heidelberg: Springer Berlin Heidelberg, 2013: 213-228

2 **Burns PB**, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg* 2011; **128**: 305-310 [PMID: 21701348 DOI: 10.1097/PRS.0b013e318219c171]

3 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]

4 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [PMID: 8721797]

5 **Solmi M**, Veronese N, Correll CU, Favaro A, Santonastaso P, Caregaro L, Vancampfort D, Luchini C, De Hert M, Stubbs B. Bone mineral density, osteoporosis, and fractures among people with eating disorders: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2016; **133**: 341-351 [PMID: 26763350 DOI: 10.1111/acps.12556]

6 **Veronese N**, Bano G, Bertozzo G, Granziera S, Solmi M, Manzato E, Sergi G, Cohen AT, Correll CU. Vitamin K antagonists' use and fracture risk: results from a systematic review and meta-analysis. *J Thromb Haemost* 2015; **13**: 1665-1675 [PMID: 26179400 DOI: 10.1111/jth.13052]

7 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344-349 [PMID: 18313558 DOI: 10.1016/j.jclinepi.2007.11.008]

8 **Solmi M**, Veronese N, Sergi G, Luchini C, Favaro A, Santonastaso P, Vancampfort D, Correll CU, Ussher M, Thapa-Chhetri N, Fornaro M, Stubbs B. The association between smoking prevalence and eating disorders: a systematic review and meta-analysis. *Addiction* 2016; **111**: 1914-1922 [PMID: 27206671 DOI: 10.1111/add.13457]

9 **Solmi M**, Veronese N, Favaro A, Santonastaso P, Manzato E, Sergi G, Correll CU. Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies. *Psychoneuroendocrinology* 2015; **51**: 237-252 [PMID: 25462897 DOI: 10.1016/j.psyneuen.2014.09.031]

10 **Wells GA**, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses, 2012. Available from: URL: http://wwwohrica/programs/clinical_epidemiology/oxfordasp

11 **Veronese N**, Cereda E, Solmi M, Fowler SA, Manzato E, Maggi S, Manu P, Abe E, Hayashi K, Allard JP, Arendt BM, Beck A, Chan M, Audrey YJ, Lin WY, Hsu HS, Lin CC, Diekmann R, Kimyagarov S, Miller M, Cameron ID, Pitkälä KH, Lee J, Woo J, Nakamura K, Smiley D, Umpierrez G, Rondanelli M, Sund-Levander M, Valentini L, Schindler K, Törmä J, Volpato S, Zuliani G, Wong M, Lok K, Kane JM, Sergi G, Correll CU. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538 elderly subjects. *Obes Rev* 2015; **16**: 1001-1015 [PMID: 26252230 DOI: 10.1111/obr.12309]

12 **Luchini C**, Parcesepe P, Nottegar A, Parolini C, Mafficini A, Remo A, Chilosi M, Manfrin E. CD71 in Gestational Pathology: A Versatile Immunohistochemical Marker With New Possible Applications. *Appl Immunohistochem Mol Morphol* 2016; **24**: 215-220 [PMID: 25906120 DOI: 10.1097/PAI.0000000000000175]

13 **Luchini C**, Parcesepe P, Mafficini A, Nottegar A, Parolini C, Veronese N, Remo A, Manfrin E. Specific expression patterns of epithelial to mesenchymal transition factors in gestational molar disease. *Placenta* 2015; **36**: 1318-1324 [PMID: 26459371 DOI: 10.1016/j.placenta.2015.09.012]

14 **Luchini C**, Veronese N, Solmi M, Cho H, Kim JH, Chou A, Gill AJ, Faraj SF, Chaux A, Netto GJ, Nakayama K, Kyo S, Lee SY, Kim DW, Yousef GM, Scorilas A, Nelson GS, Köbel M, Kalloger SE, Schaeffer DF, Yan HB, Liu F, Yokoyama Y, Zhang X, Pang D, Lichner Z, Sergi G, Manzato E, Capelli P, Wood LD, Scarpa A, Correll CU. Prognostic role and implications of mutation status of tumor suppressor gene ARID1A in cancer: a systematic review and meta-analysis. *Oncotarget* 2015; **6**: 39088-39097 [PMID: 26384299 DOI: 10.18632/oncotarget.5142]

15 **Luchini C**, Veronese N, Yachida S, Cheng L, Nottegar A, Stubbs B, Solmi M, Capelli P, Pea A, Barbareschi M, Fassan M, Wood LD, Scarpa A. Different prognostic roles of tumor suppressor gene BAP1 in cancer: A systematic review with meta-analysis. *Genes Chromosomes Cancer* 2016; **55**: 741-749 [PMID: 27223342 DOI: 10.1002/gcc.22381]

16 **Luchini C**, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Veronese N. Significance of the prognostic stratification of extranodal extension in colorectal cancer. *Ann Oncol* 2016; **27**: 1647 [PMID: 27069013 DOI: 10.1093/annonc/mdw173]

17 **Luchini C**, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Veronese N. Extranodal extension is an important prognostic parameter for both colonic and rectal cancer. *Ann Oncol* 2016; **27**: 955-956 [PMID: 26802150 DOI: 10.1093/annonc/mdw034]

18 **Luchini C**, Nottegar A, Solmi M, Sergi G, Manzato E, Capelli P, Scarpa A, Veronese N. Prognostic implications of extranodal extension in node-positive squamous cell carcinoma of the vulva: A systematic review and meta-analysis. *Surg Oncol* 2016; **25**: 60-65 [PMID: 26394825 DOI: 10.1016/j.suronc.2015.09.005]

19 **Luchini C**, Veronese N, Pea A, Sergi G, Manzato E, Nottegar A, Solmi M, Capelli P, Scarpa A. Extranodal extension in N1-adenocarcinoma of the pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. *Eur J Gastroenterol Hepatol* 2016; **28**: 205-209 [PMID: 26566063 DOI: 10.1097/MEG.0000000000000520]

20 **Luchini C**, Wood LD, Cheng L, Nottegar A, Stubbs B, Solmi M, Capelli P, Pea A, Sergi G, Manzato E, Fassan M, Bagante F, Bollschweiler E, Giacopuzzi S, Kaneko T, de Manzoni G, Barbareschi M, Scarpa A, Veronese N. Extranodal extension of lymph node metastasis is a marker of poor prognosis in oesophageal cancer: a systematic review with meta-analysis. *J Clin Pathol* 2016 Jul 7; epub ahead of print [PMID: 27387986 DOI: 10.1136/jclinpath-2016-203830]

21 **Nottegar A**, Veronese N, Senthil M, Roumen RM, Stubbs B, Choi AH, Verheuvel NC, Solmi M, Pea A, Capelli P, Fassan M, Sergi G, Manzato E, Maruzzo M, Bagante F, Koç M, Eryilmaz MA, Bria E, Carbognin L, Bonetti F, Barbareschi M, Luchini C. Extranodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis. *Eur J Surg Oncol* 2016; **42**: 919-925 [PMID: 27005805 DOI: 10.1016/j.ejso.2016.02.259]

22 **Veronese N**, Fassan M, Wood LD, Stubbs B, Solmi M, Capelli P, Pea A, Nottegar A, Sergi G, Manzato E, Carraro S, Maruzzo M, Cataldo I, Bagante F, Barbareschi M, Cheng L, Bencivenga M, de Manzoni G, Luchini C. Extranodal Extension of Nodal Metastases Is a Poor Prognostic Indicator in Gastric Cancer: a Systematic Review and Meta-analysis. *J Gastrointest Surg* 2016; **20**: 1692-1698 [PMID: 27412320 DOI: 10.1007/s11605-016-3199-7]

23 **Veronese N**, Luchini C, Nottegar A, Kaneko T, Sergi G, Manzato E, Solmi M, Scarpa A. Prognostic impact of extra-nodal extension in thyroid cancer: A meta-analysis. *J Surg Oncol* 2015; **112**: 828-833 [PMID: 26493240 DOI: 10.1002/jso.24070]

24 **Veronese N**, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Luchini C. Prognostic

impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. *Ann Oncol* 2016; **27**: 42-48 [PMID: 26483050 DOI: 10.1093/annonc/mdv494]

25 **Nottegar A**, Veronese N, Solmi M, Luchini C. Tumor suppressor gene ARID1A in cancer: recent advances and future perspective. *J Carinog Mutagene* 2016; **7**: 255 [DOI: 10.4172/2157-2518.100255]

26 **Luchini C**, Nottegar A, Solmi M, Veronese N. Meta-Analysis in Pathology. *J Pathol & Microbiol* 2016; **1**: 1002-1003

27 **Simbolo M**, Mafficini A, Agostini M, Pedrazzani C, Bedin C, Urso ED, Nitti D, Turri G, Scardoni M, Fassan M, Scarpa A. Next-generation sequencing for genetic testing of familial colorectal cancer syndromes. *Hered Cancer Clin Pract* 2015; **13**: 18 [PMID: 26300997 DOI: 10.1186/s13053-015-0039-9]

28 **Mafficini A**, Simbolo M, Parisi A, Rusev B, Luchini C, Cataldo I, Piazzola E, Sperandio N, Turri G, Franchi M, Tortora G, Bovo C, Lawlor RT, Scarpa A. BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing. *Oncotarget* 2016; **7**: 1076-1083 [PMID: 26745875 DOI: 10.18632/oncotarget.6834]

29 **Yachida S**, Wood LD, Suzuki M, Takai E, Totoki Y, Kato M, Luchini C, Arai Y, Nakamura H, Hama N, Elzawahry A, Hosoda F, Shirota T, Morimoto N, Hori K, Funazaki J, Tanaka H, Morizane C, Okusaka T, Nara S, Shimada K, Hiraoka N, Taniguchi H, Higuchi R, Oshima M, Okano K, Hirono S, Mizuma M, Arihiro K, Yamamoto M, Unno M, Yamaue H, Weiss MJ, Wolfgang CL, Furukawa T, Nakagama H, Vogelstein B, Kiyono T, Hruban RH, Shibata T. Genomic Sequencing Identifies ELF3 as a Driver of Ampullary Carcinoma. *Cancer Cell* 2016; **29**: 229-240 [PMID: 26806338 DOI: 10.1016/j.ccell.2015.12.012]

30 **Luchini C**, Capelli P, Fassan M, Simbolo M, Mafficini A, Pedica F, Ruzzenente A, Guglielmi A, Corbo V, Scarpa A. Next-generation histopathologic diagnosis: a lesson from a hepatic carcinosarcoma. *J Clin Oncol* 2014; **32**: e63-e66 [PMID: 24493719 DOI: 10.1200/JCO.2012.47.5855]

31 **Chan CB**, Abe M, Hashimoto N, Hao C, Ifor R, Brewster AS, Wang G, Yu X, William B, Brewster AS, Wang G, Yu X, William B, Tjajadi M, Klein MG, Chen XS. Correction for Chan et al., Mice lacking asparaginyl endopeptidase develop disorders resembling hemophagocytic syndrome. *Proc Natl Acad Sci USA* 2009; **106**: 6023 [DOI: 10.1073/pnas.0901254106]

32 **Hyland P**, Shevlin M, McNally S, Murphy J, Hansen M, Elklit A. Exploring differences between the ICD-11 and DSM-5 models of PTSD: Does it matter which model is used? *J Anxiety Disord* 2016; **37**: 48-53 [PMID: 26618238 DOI: 10.1016/j.janxdis.2015.11.002]

33 **Vancampfort D**, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 2015; **14**: 339-347 [PMID: 26407790 DOI: 10.1002/wps.20252]

34 **Stubbs B**, Vancampfort D, De Hert M, Mitchell AJ. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. *Acta Psychiatr Scand* 2015; **132**: 144-157 [PMID: 25943829 DOI: 10.1111/acps.12439]

35 **Zaninotto L**, Solmi M, Toffanin T, Veronese N, Cloninger CR, Correll CU. A meta-analysis of temperament and character dimensions in patients with mood disorders: Comparison to healthy controls and unaffected siblings. *J Affect Disord* 2016; **194**: 84-97 [PMID: 26803780 DOI: 10.1016/j.jad.2015.12.077]

36 **Solmi M**, Zaninotto L, Toffanin T, Veronese N, Lin K, Stubbs B, Fornaro M, Correll CU. A comparative meta-analysis of TEMPS scores across mood disorder patients, their first-degree relatives, healthy controls, and other psychiatric disorders. *J Affect Disord* 2016; **196**: 32-46 [PMID: 26897455 DOI: 10.1016/j.jad.2016.02.013]

37 **Fornaro M**, Stubbs B, De Berardis D, Perna G, Valchera A, Veronese N, Solmi M, Ganança L. Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials. *Int J Mol Sci* 2016; **17**: 241 [PMID: 26891297 DOI: 10.3390/ijms17020241]

38 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

39 **Veronese N**, Carraro S, Bano G, Trevisan C, Solmi M, Luchini C, Manzato E, Caccialanza R, Sergi G, Nicetto D, Cereda E. Hyperuricemia protects against low bone mineral density, osteoporosis and fractures: a systematic review and meta-analysis. *Eur J Clin Invest* 2016; **46**: 920-930 [PMID: 27636234 DOI: 10.1111/eci.12677]

40 **Hartling L**, Milne A, Hamm MP, Vandermeer B, Ansari M, Tsertsvadze A, Dryden DM. Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. *J Clin Epidemiol* 2013; **66**: 982-993 [DOI: 10.1016/j.jclinepi.2013.03.003]

41 **Oremus M**, Oremus C, Hall GB, McKinnon MC; ECT & Cognition Systematic Review Team. Inter-rater and test-retest reliability of quality assessments by novice student raters using the Jadad and Newcastle-Ottawa Scales. *BMJ Open* 2012; **2**: e001368 [PMID: 22855629 DOI: 10.1136/bmjopen-2012-001368]

42 **Sterne JA**, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919 [PMID: 27733354 DOI: 10.1136/bmj.i4919]

P- Reviewer: Francisco G, Treglia G **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Lu YJ

World Journal of Meta-Analysis

Submit a Manuscript: http://www.f6publishing.com

World J Meta-Anal 2017 August 26; 5(4): 85-102

DOI: 10.13105/wjma.v5.i4.85

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Remission endpoints in ulcerative colitis: A systematic review

Maki Jitsumura, Rory Frederick Kokelaar, Dean Anthony Harris

Maki Jitsumura, Rory Frederick Kokelaar, Dean Anthony Harris, Colorectal Department, Singleton Hospital, Abertawe Bro Morgannwg, University Health Board, Swansea SA2 8QA, United Kingdom

Author contributions: Jitsumura M and Harris DA conceptualised and designed the study; Jitsumura M and Kokelaar RF conducted the systematic review of the literature; Jitsumura M performed data analysis; Jitsumura M, Kokelaar RF and Harris DA contributed to the drafting and revision of the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: There is no financial conflict of interest to declare for any of the authors.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at dean.a.harris@wales.nhs.uk. No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Dean Anthony Harris, MD, FRCS, MB ChB, Honorary Clinical Professor, Colorectal Department, Singleton Hospital, Abertawe Bro Morgannwg, University Health Board, Sketty Lane, Swansea SA2 8QA, United Kingdom. dean.a.harris@wales.nhs.uk
Telephone: +44-0179-2285459

Received: January 27, 2017
Peer-review started: February 12, 2017
First decision: March 8, 2017
Revised: May 3, 2017
Accepted: May 12, 2017
Article in press: May 15, 2017
Published online: August 26, 2017

Abstract

AIM

To summarize the current consensus on the definition of remission and the endpoints employed in clinical trials.

METHODS

A bibliograraphic search was performed from 1946 to 2016 sing online databases (National Library of Medicine's PubMed Central Medline, OVID SP MEDLINE, OVID EMBASE, the Cochrane Library and Conference Abstracts) with key words: ("ulcerative colitis") AND ("ulcerative colitis endoscopic index of severity" OR "UCEIS") AND ("remission") as well as ("ulcerative colitis") AND ("ulcerative colitis disease activity index") OR "UCDAI" OR "UC disease activity index" OR "Sutherland index") AND ("remission").

RESULTS

The search returned 37 and 116 articles for the UCEIS and UCDAI respectively. For the UCEIS, 12 articles were cited in the final analysis of which 9 validation studies have been identified. Despite the UCEIS has been more extensively validated in all three aspects (validity, responsiveness and reliability), it has been little employed to monitor disease in randomised clinical trials. For the UCDAI, 37 articles were considered for the final analysis. Although the UCDAI is only partially validated, 29 randomised clinical trials were acknowledged to use the UCDAI to determine endpoints and disease remission, though no clear protocol was identified.

CONCLUSION

Although the UCEIS has been more widely validated than the UCDAI, it has not been reflected in the monitoring of disease activity in clinical trials. Conversely, the UCDAI has been used in numerous large clinical trials to define their endpoints and disease remission, however, it is challenging to determine the best possible outcomes due to a lack of homogeneity of the clinical

trial protocols. Before determining a gold standard index, international agreement on remission is urgently needed to advance patient care.

Key words: Ulcerative colitis; Remission; Ulcerative colitis endoscopic index of severity; Ulcerative disease activity index

Core tip: Despite the decades of discussion, disease remission for ulcerative colitis has yet to be fully defined. Instead, numerous indices that measure a large variety of endpoints had been developed, each claiming to be accurate and informative. This systematic review aimed to summarise the issues related to the uncertain definition of disease remissions in clinical trial studies by focusing on two indices ulcerative colitis endoscopic index of severity and ulcerative disease activity index. We recommend that an international consensus of remission should be sought before establishing a gold standard outcome measurement to untangle this confusion.

Jitsumura M, Kokelaar RF, Harris DA. Remission endpoints in ulcerative colitis: A systematic review. *World J Meta-Anal* 2017; 5(4): 85-102 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i4/85.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i4.85

INTRODUCTION

How do we determine remission as an endpoint in ulcerative colitis (UC) clinical trials when we design a study? There is no universally agreed definition of remission as an endpoint in UC clinical trials as of date, despite much discussion and urge for the standardisation. Currently, it is chosen to reflect the purpose of the studies, rather than long-term clinical outcomes or controlling bothersome symptoms that patients often suffer from. Furthermore, a lack of homogeneity of the clinical trial protocols makes comparison of such studies more difficult to comprehend.

UC is a chronic relapsing-remitting inflammatory bowel disease, affecting mucosa of the large bowel. Patients with UC often present with debilitating symptoms such as abdominal pain and rectal bleeding. Although the aetiology of UC is believed to be multifactorial involving dysregulated immune system, intestinal mucosal disturbance and genetic predisposition, natural history of the disease is poorly understood[1]. There is no curative treatment at present, thus the aim of management is induction and maintenance of remission with immunosuppressive agents, permitting individuals to carry on their daily life. The failure of medical therapy or refractory disease often require colorectal surgery, and there is an increased risk of colorectal cancer[2].

Since the first disease activity outcome measurement was developed in 1955, the Truelove and Witts Index, numerous outcome measure instruments have been developed[3]. Not only has the number of these instruments been growing, but also the assessed disease components have been expanding. Traditionally, disease activity has been assessed by a clinical and symptom scoring system, with or without a combined endoscopic assessment. A recent review counted seventeen clinical disease activity indices which evaluate symptoms, of which eight do so without endoscopic or biomarker assessment[4]. The purpose of these disease activity indices is to provide an objective measurement of the disease activity by employing typical symptoms such as stool frequency and rectal bleeding. Endoscopic assessment is another dimension of the disease that is mandated by the Food and Drug Administration (FDA)[5] and at least thirty-one instruments were proposed[6]. Many of these endoscopic indices, such as Mayo score and ulcerative colitis disease activity index (UCDAI), evaluate the macroscopic appearance of large bowel, together with symptomatic disease activity. Recently, the prognostic potential of histological assessment in UC has been highlighted in several studies[7-9], although histological remission has yet to be proposed as a therapeutic endpoint for clinical trials or practice, twenty-six histological activity indices have been developed thus far. It is important to note that there is considerable disparity between visual endoscopic assessment and histological disease activity[9], although confusingly these terms are used interchangeably[9]. In addition to symptomatology, endoscopic, and histological scoring systems, radiological outcome instruments as well as new biochemical markers are an additional developing dimension of disease assessment[4].

In addition to these objective indices, we cannot neglect patient subjective outcome measurement tools and quality of life (QoL) questionnaires. The aim of these tools is to evaluate the patients' emotional, social or professional well-being so that their ideas, concerns, and expectations can be a part of the objective medical decision-making process. Patients often have different expectations of treatment and remission from those of physicians, and symptoms used in established scoring tools may be of relatively little concerns to some individuals. Establishing an understanding of chronicity is also important in assessing a patient's disease, especially when reconciling the long term treatment goals with a patients' concerns regarding how quickly embarrassing, troublesome and physical symptoms can be resolved with minimal side effects[10]. Furthermore, we cannot underestimate the power of the internet and smartphone use in medicine; many patients often seek online diagnosis of their symptoms before they are formally assessed by a clinician, and may already be either well informed or misguided when discussing management. Patients often use "remission" and "flare-ups" informally to describe their disease activity without reference to formal assessments of such, and

thus misunderstandings may occur when discussing assessment and treatment. A few self-reporting assessment tools (smartphone apps) are available, allowing patients to monitor their disease activity on daily basis in a more objective manner[11]. Whether these patient-reported measurement instruments show a good correlation with true disease activity by other measures appears to be almost irrelevant. Many patients with asymptomatic UC do not feel the need of continuing medications in the absence of discernible symptoms, especially when they give side effects, making the negotiation more challenging for clinicians. A good rapport and the ability to reach negotiated consensus with patients is an integral skill for clinicians managing complex UC patients.

The overall picture is that there are numerous indices that measure a large variety of endpoints, each claiming to be accurate and informative regarding one or other management goal. Confusingly, these indices share similar names or are often referred to by multiple names or abbreviations, such as the UCDAI which is also referred to as the Sutherland Index. Unfortunately, no single scoring system provides comprehensive assessment of disease activity, and the majority of these indices lack robust clinical validation. Most clinical trials, from which the scoring systems are derived, choose disease outcome measures and endpoints reflecting the purpose of the studies, rather than long-term clinical outcomes or real-world symptom control for patients. Furthermore, each clinical trial defines remission differently, making comparison between different trials difficult.

The consequence of the complexity in UC outcome measurements and the huge variety in competing scoring systems is that many patients with UC may receive suboptimal therapy and poor long-term disease control.

This systematic review will reassess and summarise the current consensus on the definition of remission and the endpoints employed in clinical trials by focusing on two most validated and well-used indices, the ulcerative colitis endoscopic index of severity (UCEIS) and UCDAI, in order to address the issues with the standardisation of clinical trial protocols.

The current target of disease remission endoscopically is mucosal healing although it has not been fully validated or no standardised definition of mucosal healing[12,13]. Yet, this appears to be the goal for many clinical practice as well as drug trials.

The recent draft guideline released by the FDA[5] states the ideal primary efficacy assessment instrument in clinical trials should consist of (1) a signs and symptoms assessment scale - best measured by a patient-reported outcome instrument. If not, an observer-reported outcome instrument; and (2) an endoscopic and histological assessment scale.

Thus, endoscopic assessment tools with comprehensive clinical symptom assessment components that come from patients would be a reasonable choice to argue remission and endpoints employed in clinical trials.

Amongst numerous endoscopic indices claiming to measure disease activity, the UCEIS is one of the most widely validated indices to date. It would be interesting to see any impact of the quality of validation for defining remission and endpoints compared with the index, such as the UCDAI, that has not been fully validated yet being widely employed in clinical trials. For these reasons, these two indices were chosen for this systematic review.

UCEIS

The UCEIS proposed by Travis *et al*[14] in 2012 is the only validated endoscopic index in ulcerative colitis to date[15]. It was developed to minimise variation in endoscopic assessment, thus it could be widely applied as a reliable outcome measure in clinical trials as well as clinical settings.

The first stage of development of the UCEIS demonstrated the significant inconsistency in endoscopic assessment amongst specialists by 10 specialists scoring the severity of UC using the Baron score[16] in colonoscopy videos. The greatest correlation was found in the "severe" level of the Baron score, demonstrating a 76% agreement, however, only 27% agreement was achieved for a normal mucosa (Baron score 0) and 37% agreement for moderate friability (Baron score 2).

The second part of the study further quantifies intra- and inter-observer variation on common descriptors on endoscopic assessments (Table 1). For intra-observer variation, 60 repeat pair assessment of 36 different videos were scored and assessed by κ statistics. For inter-observer variation, 30 new investigators were randomly allocated to score 25 videos, thus each video was assessed by 10-12 investigators.

Both intra- and inter-observer variation showed good agreement to assess erosions and ulcers, vascular pattern and bleeding, which were subsequently chosen for descriptors of a newly developed endoscopic assessment tool, the UCEIS (Table 2).

The authors also proposes definition of remission using the UCEIS, which is when all three descriptors were level 1 (no visible bleeding or erosions or ulceration, but some blurring or loss of capillary margins with a recognisable vascular pattern is allowed).

UCDAI

The UCDAI (also called UC Disease Activity Index, and Sutherland Index) was introduced by Sutherland *et al*[17] to assess efficacy of 5-aminosalicylic acid enema in the treatment of distal UC in its randomized, double-blind clinical trial in 1987.

The index was used for objective assessment during this drug trial and considers four variables of UC - stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity (Table 3). Unlike the UCEIS, the UCDAI was developed without any validated study. Although the authors described that the index incorporates many of the subscales used by

Table 1 Descriptors and intra- and inter-observer variation

Descriptor	Likert scale anchor points	Intra-observer variation (a weighted *k*)	Inter-observer variation (a weighted *k*)
Vascular pattern	Normal (1) Patchy loss (3) Obliterated (5)	0.61	0.42
Mucosal erythema	None (1) Light red (3) Dark red (5)	0.43	0.35
Mucosal surface (Granularity)	Normal (1) Granular (3) Nodular (5)	0.45	0.34
Mucosal oedema	None (1) Probable (3) Definite (5)	0.43	0.31
Mucopus	None (1) Some (3) Lots (5)	0.47	0.4
Bleeding	None (1) Mucosal (2) Luminal mild (3) Luminal moderate (4) Luminal severe (5)	0.57	0.37
Incidental friability	None (1) Mild (2) Moderate (3) Severe (4) Very severe (5)	0.49	0.4
Contact friability	None (1) Probable (3) Definite (5)	0.34	0.3
Erosions and ulcers	None (1) Erosions (2) Superficial ulcer (3) Deep ulcer (4)	0.65	0.45
Extent of erosions or ulcers	None (1) Limited (2) Substantial (3) Extensive (4)	0.6	0.42

other investigators and demonstrated efficacy as an overall index and individual component subscale, they failed to demonstrate this with any form of statistical assessment. Furthermore, they also compared between the overall index and the physician's global assessment by this drug trial study physician and concluded that the UCDAI demonstrates good correlation with the physician's assessment (P = 0.0001). This conclusion fails to demonstrate objectivity although the authors' fundamental aim of designing this index was to provide objective assessment.

The UCEIS was developed based on components to minimise the variation identified in previous endoscopic assessment instruments. It has been validated from various angles at the time of designing, making it more reliable than traditional instruments. Conversely, the UCDAI was designed without any validated evidence to assess efficacy of a drug for treatment of UC. Yet, it has been widely used in numerous clinical trials for decades and even recommended by the FDA as one of the endoscopic assessment tools.

Table 2 The ulcerative colitis endoscopic index of severity descriptors (maximum score = 8, Scoring is based on the most severe area)

Descriptors	Likert Scale anchor point	Definition
Vascular pattern	0: Normal	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	1: Patchy obliteration	
	2: Complete obliteration	Complete obliteration
Bleeding	0: None	
	1: Mucosa	Some spots or streaks of coagulated blood on the surface of the mucosa
	2: Luminal mild	Some free liquid blood in the lumen
	3: Luminal moderate or severe	Frank blood in the lumen ahead of endoscope or visible oozing from a haemorrhagic mucosa
Erosions and Ulcers	0: None	None
	1: Erosions	Tiny < 5 mm defects in the mucosa, of white or yellow colour with a flat edge
	2: Superficial ulcer	Larger > 5 mm defect in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	3: Deep ulcer	Deeper excavated defects in the mucosa, with a slightly raised edge

Table 3 Ulcerative colitis disease activity index (maximum score = 12)

Variables	Score	Items
Stool frequency	0	Normal
	1	1-2 stools/d more than normal
	2	3-4 stools/d more than normal
	3	> 4 stools/d more than normal
Rectal bleeding	0	None
	1	Streaks of blood
	2	Obvious blood
	3	Mostly blood
Endoscopic appearance	0	Normal
	1	Mild friability
	2	Moderate friability
	3	Exudation, spontaneous bleeding
Physician global assessment	0	Normal
	1	Mild
	2	Moderate
	3	Severe

MATERIALS AND METHODS

A systematic bibliographic search was performed between 10th and 14th November 2016 of the following online databases: OVID SP MEDLINE (1946 to present),

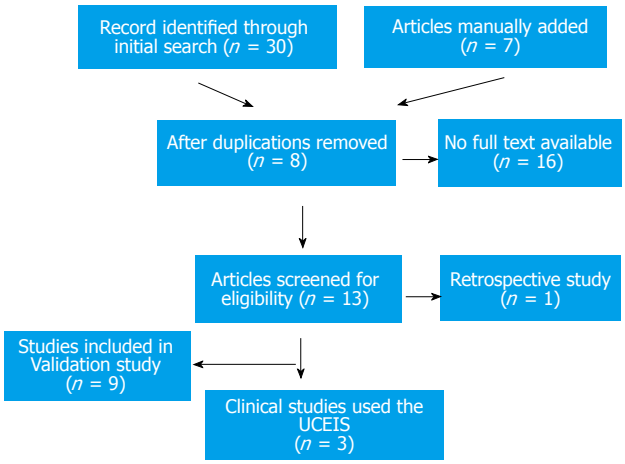

Figure 1 PRISMA flow diagram for ulcerative colitis endoscopic index of severity. UCEIS: Ulcerative colitis endoscopic index of severity.

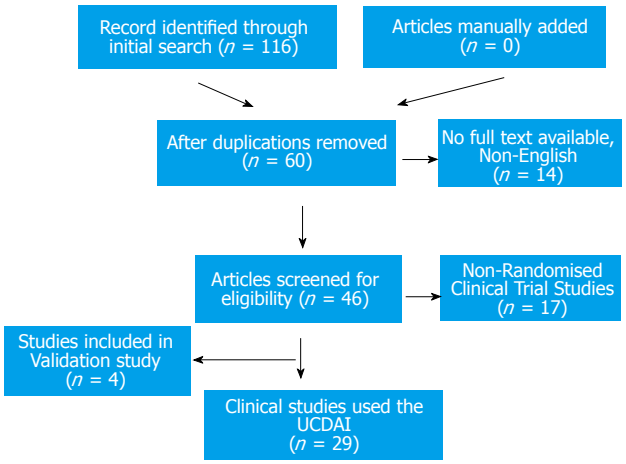

Figure 2 PRISMA flow diagram for ulcerative colitis disease activity index. UCDAI: Ulcerative colitis disease activity index.

OVID EMBASE (1974 to present), National Library of Medicine's PubMed Central MEDLINE (1950 to present), the Cochrane Library, using the key heading-words strategy set below and the medial subject heading. The bibliographies of recovered systematic review, meta-analysis, and review articles were also searched for additional articles.

Each database was searched for the following headings: (1) Ulcerative colitis endoscopic index of severity: ("ulcerative colitis") AND ("ulcerative colitis endoscopic index of severity" OR "UCEIS") AND ("remission"); and (2) Ulcerative Colitis Disease Activity Index: ("ulcerative colitis") AND ("Ulcerative colitis disease activity index" OR "UC disease activity index" OR "UCDAI" OR "Sutherland index") AND ("remission")

Non-English articles, studies pertaining to paediatric subjects, and non-human subjects were excluded. Studies presenting data of patient populations already included in other publication (duplicates) were excluded. No abstract publications without subsequent full-text published data were used. Disagreements about inclusion were resolved in a consensus meeting.

RESULTS

Ulcerative colitis endoscopic index of severity

A total of 37 articles were returned using the initial search. After applying exclusion criteria and eliminating duplication, 12 articles screened for relevance and manual search of articles referenced in the retrieved articles was performed. Nine articles were included in the final analysis for validation assessment of UCEIS and 3 articles were evaluated for the UCEIS use in clinical trials (Figure 1).

UCDAI

A total of 116 articles were returned using the initial search, which was down to 37 articles after considering exclusion criteria and duplication. Four articles were identified for the final analysis of validation assessment and 29 articles were included to evaluate defining remission and endpoints of clinical trials (Figure 2).

What do we need in outcome measurement instruments?

The definition of disease remission has not yet been validated or standardised. Inevitably, implementing clinical scoring tools based on a broad definition of remission results in inaccuracy of outcomes, and a reduction in the utility of a derived tool. The gold standard for disease activity in UC must be a diagnostic tool that truly quantifies the disease activity and can accurately assess and therefore guide future disease managements and outcome. A robust and standardised outcome measurement instrument is vital for clinical trials and establishment of medical therapy, although many instruments are not fully validated.

In this systematic review, validation of UCEIS and UCDAI studies were described by dividing into validity, reproducibility and responsiveness (Table 4).

Validity: The diagnostic and prognostic validity of an assessment tool is defined as evidence that variations in UC disease activity causally produce variations in the measurement outcomes. This must be demonstrated by qualitative assessment and evidence of indices measuring disease activity adequately and sufficient reflection of true disease. The development of these indices should be supported by a robust systematic review of literature. Statistical studies of agreement between the indices and disease activity should be assessed including sensitivity and specificity. Validity of the correlation between an index score and objective assessment score including clinical disease activity index scores or physician global assessment of severity should be measured. Although there are many indices have been proposed the degree of validity for these indices vary, and many indices are not fully validated. In this study, UCEIS and UCDAI, one of the best validated indices and most widely used indices in drug trials

Table 4 Validation studies of ulcerative colitis endoscopic index of severity and ul-cerative colitis disease activity index

	Ref.	Patient number	Outcomes
UCEIS			
Validity	Corte *et al*[18]	89	Correlation between UCEIS and outcomes The UCEIS score was directly proportional to requirement of rescue therapy UCEIS ⩾ 5 was significantly linked to requiring colectomy 18/54 (33%) patients with UCEIS ⩾ 5 compared to 3/33 (9%) with UCEIS ⩽ 4 No definition of remission
	Fernandes *et al*[19]	108	Prediction of outcomes in acute severe colitis UCEIS was applied to score of the rectum and sigmoid, seg-UCEIS Seg-UCEIS predicted to develop steroid-refractory disease and the likelihood of colectomy (seg-UCEIS = 14 had a 17 times higher risk of steroid-refractory disease and a 25 times higher risk of requiring colectomy) Every 1 point increase in the UCEIS or Seg-UCEIS increased the need of colectomy by 2.78 and 1.79 respectively Mayo score did not predict these No definition of remission
	Arai *et al*[20]	285	Reflection of true UC activity and remission The recurrence rate was directly proportional to the UCEIS score (5.0% for UCEIS = 0, 22.4% for UCEIS = 1, 27.0% for UCEIS = 2, 35.7% for UCEIS = 3, 75% for UCEIS = 4-5) The absence of bleeding and mucosal damage were independent factors for continued clinical remission UCEIS ranged from 0 to 5 when clinical remission, Mayo ⩽ 1 UCEIS ⩽ 1 for clinical remission, which showed sensitivity of 68% and specificity 57% The expected duration of recurrence is also prolonged when UCEIS ⩽ 1
	Kucharski *et al*[21]	49	Assessment of 9 endoscopic indices correlate well with (1) clinical indices; and (2) histological Geboes Index[22] The UCEIS showed the strongest correlation with the Geboes Index (the coefficient: 0.434 to 0.629) Recommends the UCEIS for the best overall correlations with both clinical and histological indices
Responsiveness	Ikeya *et al*[23]	41	The ability to detect to change after Tacrolimus remission induction treatment for moderate to severe UC Although Mayo endoscopic score is easy to use, it does not distinguish depth of ulcers unlike UCEIS Despite UCEIS score improved from 7 to 4, Mayo endoscopic score remained at 3 (severe) An improvement of UCEIS ⩾ 3 showed close correlation with clinical remission, colectomy-free and relapse free rates Proposed remission (score 0-1), mild (2-4), moderate (5-6), severe (7-8) UCEIS 1 in remission is only from vascular pattern
	Menasci *et al*[24]	80	Comparison of the global UCEIS score from 5 segments and a traditional method of UCEIS score The regular method of the UCEIS is to score the most inflamed segment of the bowel This was compared with the sum of the score of five colonic segments A very good correlation (Spearman's r = 0.86, P < 0.0001) for disease with UCEIS score ⩽ 5 Less correlation (r = 0.48, P < 0.01) for disease with UCEIS > 5
Reliability	Travis *et al*[15]		Investigation of intra- and inter-observer consistency assessment 25 readers evaluated 28 videos including 4 duplicates to assess intra-reader reliability The intra and inter-reader reliability ratios for the UCEIS were 0.96 and 0.88 respectively The USCEI revealed a strong correlation with overall assessment of severity without being influenced by knowledge of clinical information No definition of remission
	Feagan *et al*[25]	281	The effect of centralized review of images on inter-observer variations Patients with UCDAI ⩾ 2 were randomised to evaluate the efficacy of delayed mesalamine treatment (4.8 g/d for 10 wk)
	Travis *et al*[26]		UCEIS was used as a part of inter-observer agreement study and showed interclass correlation coefficient of 0.83 amongst 7 central readers, which is superior to UCDAI Clinical information influences UCEIS score 40 readers evaluated 28 of 44 videos No discrepancy between blinded and unblended readers Intra- and inter-reader variability demonstrated moderate to substantial agreement (κ = 0.47 to 0.74 and κ = 0.40 to 0.50 respectively) UCEIS correlated well with patient-reported symptoms - rectal bleeding, stool frequency and patient functional assessment (rank correlation = 0.76 to 0.82)
UCDAI			
Validity	Higgins *et al*[27]	66	Finding endpoints in disease activity indices for remission and improvement in UC UCDAI < 2.5 for remission, which had a sensitivity and specificity of 0.82 and 0.89 Remission in this study was defined by patients
	Poole *et al*[28]	126	Establish the relationship between the UCDAI and patient reported EQ-5D The UCDAI with or without endoscopy assessment demonstrated a good correlation with EQ-5D Endoscopy assessment may not link with the disease activity

	Kucharski *et al*[21]	49	Assessment of 9 endoscopic indices correlate well with (1) clinical indices; and (2) histological Geboes Index (22) The UCDAI showed strong correlations with all 9 endoscopic indices (the coefficient in a range of 0.712 to 0.790) The UCDAI showed the highest correlation amongst clinical activity indices with the Geboes Index (the Spearman's coefficient 0.478) Compared to UCEIS, the UCDAI is less correlated with the Geboes Index
Reliability	Feagan *et al*[25]	281	The effect of centralized review of images on inter-observer variations Patients with UCDAI ⩾ 2 were randomised to evaluate the efficacy of delayed mesalamine treatment (4.8 g/d for 10 wk) 31% of patients with UCDAI ⩾ 2 enrolled in the RCT initially were considered ineligible by the central readers Inter-observer agreement amongst 7 central readers was good (interclass correlation coefficient: 0.78)

UC: Ulcerative colitis; UCEIS: Ulcerative colitis endoscopic index of severity; Seg-UCEIS: The sum of the rectal and sigmoid segmental UCEIS score; UCDAI: Ulcerative colitis disease activity index; EQ-5D: EuroQol Five Dimensions Questionnaire; RCT: Randomised control trial.

respectively, were studied for their evidence of validity.

The UCEIS is one of the well validated indices in many aspects. The authors have studied difficulties in standardisation of the disease activity indices and defining remission in systematic reviews as well as reviews of literature prior to the development of the UCEIS[29,30]. The authors attempted to develop an index that minimises this variation by validating variation in endoscopic assessment of disease activity, which was described in 2.1. The study also suggested remission might be defined as no obliteration of vascular pattern, no rectal bleeding and no erosion or ulceration, although this has not been fully validated.

Since the UCEIS was published in 2012, there are nine studies attempted to validate the UCEIS, of which four studies are focusing on validity.

Corte *et al*[18] validated whether the UCEIS predicts clinical outcomes of acute severe colitis. 98 Patients with the UCEIS score from 3 to 8 were included in this study. It showed when UCEIS ⩾ 5, 33% (18/54) of acute colitis patients required colectomy 18/54 (33%) whereas only 9% (3/33) of patients with UCEIS ⩽ 4 required surgical interventions. When the UCEIS score is above 7 at the time of admission, almost all patients required medical therapy more than hydrocortisone, such as infliximab or ciclosporin. It concluded that the higher UCEIS score is associated with higher requirement of rescue therapy, surgical intervention and readmission.

Fernandes *et al*[19] identified patients with poor response to optimal therapy with 108 patients who are defined as acute severe colitis based on the Truelove and Witts criteria (the score ⩾ 2). All the patients received intravenous prednisolone 40-60 mg/d, methylprednisolone 60 mg or hydrocortisone 400 mg/d. Patients who had not responded to the initial therapy within 3 d received salvage therapy, and their UCEIS scores ranged from 2 to 8. The study also divided the UCEIS scoring system to segmental bowel - rectum and sigmoid, which demonstrated a strong correlation between higher UCEIS score and unfavourable outcomes especially the UCEIS-segmental score predicted refractoriness to steroid therapy. The UCEIS was significantly better at predicting clinical outcomes than the Mayo endoscopic sub-score.

Arai *et al*[20] attempted to foresee the prognosis of patients with UC who are in clinical remission. 285 patients who are in clinical remission (partial Mayo score of ⩽ 1) were included in the study. The UCEIS score of these patients with clinical remission ranged from 0 to 5, of which 92% received a UCEIS score of 2 or 3. These scores are higher than a suggested score for clinical remission. The study demonstrated the recurrence risk is direct proportional to the UCEIS score - the recurrence rate of 5.0% for UCEIS = 0, 22.4% for UCEIS = 1, 27.0% for UCEIS = 2, 35.7% for UCEIS = 3, 75% for UCEIS = 4-5. The study also highlighted the absence of bleeding and mucosal damage being independent factors for clinical remission. The duration of recurrence was also significantly prolonged in patients with lower UCEIS score. The study presented validity of the UCEIS with its predictability of clinical outcomes. Furthermore, it suggests UCEIS ⩽ 1 for clinical remission based on the direct correlation between the recurrence rate and the UCEIS, which showed sensitivity of 68% and specificity 57%.

Kucharski *et al*[21] assessed correlations between 9 endoscopic indices and 11 clinical activity indices. The author also assessed correlations between those endoscopic indices and the histological Geboes index[22]. Nine endoscopic indices used are Baron score[16], Powell-Tuck Score[31], Schroeder Score[32], UCDAI, Rachmilewitz Endoscopic Index[33], LÖtberg Score[34], Lemann Endoscopic Index[35], Feagan Score[36] and UCEIS. Eleven clinical activity indices are Truelove and Witts Severity Index[3], Powell-Tuck Index[31], Schroeder Score[32], UCDAI, Rachmilewitz Index[33], Lichtiger Index[37], Seo Score[38], Walmsley Index[39], Improvement Based on Individual Symptom Scores (IBOISS)[40], Feagan Score[36] and Montreal Classification of Severity of Ulcerative Colitis[41].

The correlations between clinical and endoscopic indices were evaluated using Spearman's ranking correlation coefficient. The Rachmilewitz Index showed strong correlations with 5 clinical activity indices (UCDAI,

Truelove and Witts, Schroeder Score, IBOISS and Feagan Index) with the correlation coefficient ranging in 0.710-0.788. The UCEIS also showed high correlations with the UCDAI, Schroeder Score, IBOISS and Feagan Index, the coefficient ranging from 0.722 to 0.761. When the correlations between clinical indices and the Geboes Index were assessed, all clinical indices showed low correlations, whereas all endoscopic indices showed better correlations with the histological Geboes Index. To evaluate correlations with endoscopic indices, all endoscopic indices were scored at four colonic segments right colon, transverse colon, left colon and rectum. The highest correlations were seen with the UCEIS at all four segments (the coefficient ranging from 0.434 to 0.629). The authors conclude that the UCEIS is the most effective endoscopic outcome measure instrument when considering correlations of both clinical and histological indices. In contrast, the UCDAI showed moderate correlations with rectal and transverse colonic segment with the Geboes Index with 0.651 and 0.534 respectively, though the correlations with other two segments were low with 0.428 for left colon and 0.459 for right colon.

Although the UCDAI has been widely used especially in multiple and large clinical trials, the study focused on validation of this index is much less compared to the UCEIS. The UCDAI was developed to assess the efficacy and safety of 5-aminosalicylic acid enema use for patients with UC[17]. The UCDAI claim to assess disease activity from four descriptors - stool frequency, rectal bleeding, mucosal appearance and physician's global assessment of the disease. Although the description of each scoring system is simple to understand, it cannot avoid subjectivity without clear definition of each item. In particular, physician's global assessment is far from being objective. Furthermore, the supposedly objective endoscopic assessment is scored based on severity of "friability". Yet again, this friability without clear definition cannot avoid subjectivity, meaning it is exposed to greater inter- and intra-observer variability.

Higgins *et al*[27] defined objective end points in disease activity indices including UCDAI for remission and improvement in UC. This study was conducted on 66 patients with UC and their subjective dichotomous assessment of remission and regulatory remission were compared with the UCDAI. Regulatory remission was defined as (1) no more than grade Ⅰ or Ⅱ changes on a Feagan endoscopic score; and (2) absence of visible rectal bleeding in this study. It suggests the cut off point for clinical remission of the UCDAI is below 2.5, offering good statistical power - sensitivity and specificity is 0.82 and 0.89 for patient defined remission and 0.92 and 0.93 for regulatory remission. Patient-defined dichotomous end points may be over-simplification, however, as it is clinically significant outcomes that determines if therapies are perceived as beneficial by patients. Regardless of physicians' objective assessment, patients with the disease are those that must agree with it in order to gain benefit in receiving therapies.

Poole *et al*[28] designed a new patient-reported disease assessment instrument, EuroQoI Five Dimensions Questionnaire (EQ-5D), for which the UCDAI was used to validate the instrument. Although validation of the UCDAI was not the aim of this study, the correlation between physician-rated and patient-rated instruments was elaborated. The study concluded that the abbreviated UCDAI (without endoscopic assessment component) and EQ-5D showed reasonable consistency when severity of the disease was measured in two randomised studies (PINCE[42] and PODIUM[43]). Goodness of fit was verified by the mean square error for mean predicted utility score. This showed patients in remission was 0.939, 0.944 and 0.940 mean utility units for estimated-PINCE, observed-PINCE and PODIUM.

Comparison of these two very different outcome measure instruments highlighted two incomparable benefits when they are chosen for clinical trials. The UCEIS is extensively validated and development of the index is based on robust studies, whereas the UCDAI is deigned based on expert opinion on the disease. However, the UCDAI is more widely used in clinical trials. This makes the choice of an index for future clinical trial studies more difficult when the clinical benefit was considered. In this systematic review, only two indices are compared. With current inconsistent use of measurement instruments and non-standardised definition of remission, the choice is almost impossible.

Responsiveness: Responsiveness is assessed in this systematic review as the ability to detect changes after a treatment that has known efficacy.

Ikeya *et al*[23] investigated true evaluation of UC severity and outcome after Tacrolimus remission induction therapy using the UCEIS as well as Mayo endoscopic subscore (Mayo ES) with 41 patients who are known to have moderate to severe disease.

In this study, clinical remission was defined as clinical activity index (CAI) $\leqslant$ 4 and a reduction of CAI score more than 4 was defined as clinical response. On the contrary, an increase of CAI score more than 4 was defined as relapse.

After 12 wk from the treatment, 31 patients (75.6%) successfully achieved clinical remission [defined as clinical activity index (CAI) $\leqslant$ 4] and 3 patients did not respond. Overall the UCEIS and Mayo ES showed close correlations, however, when the Mayo ES was 3, there was prominent discrepancy between the two indices. The UCEIS score equivalent to Mayo ES 3 ranged from 5 to 8 pre-treatments and 3 to 7 post-treatments. This was believed to be due to a lack of ability to distinguish characteristics of ulcers, vascular patterns or bleeding with the Mayo ES. For instance, ulcers and erosions often become smaller and shallower in the early phases of mucosal healing. Since the Mayo ES does not distinguish the size and depth of ulcers, it tends to stay with the same score, meaning the Mayo ES score is 3 for all types of ulcers. Furthermore, the Mayo ES combine all those macroscopic findings of ulcers,

vascular pattern and bleeding into four different overall grades. This means if there are ulcerations of any shape, the Mayo ES score becomes 3, even if vascular pattern disturbance is resolved.

The study also demonstrated significantly better relapse-free and colectomy-free rates when the UCEIS score was improved by more than 3. In addition, improvement by a UCEIS score of more than 3 was strongly associated with achieving clinical remission group (23 out of 41 patients).

Menasci *et al*[24] evaluated to see whether the global score of the sum of 5 colonic segments (rectum, sigmoid, descending, transverse, and ascending colon), abbreviated as tU score, would alter the outcome score when it is compared with the regular method of UCEIS scoring, which is to score the most inflamed colonic segment. The two scores showed a good correlation with Spearman's $r = 0.86$ and P value less than 0.0001 for less severe disease UCEIS $\leqslant 5$. However, correlation is substantially decreased for severe disease (UCEIS > 5) with Spearman's $r = 0.48$ and $P < 0.01$. Moreover, when these two scoring methods were applied to assess patients with a flare-up at 1 year, *tU* score was more sensitive than the regular UCEIS score with area under ROC curve = 0.688 ± 0.06 *vs* 0.60 ± 0.07 and $P < 0.01$. The tU score was also significantly higher when patients with and without a flare-up at 1 year were assessed, whereas the regular UCEIS score did not differ (25.3 ± 8.2 *vs* 20.1 ± 6, $P < 0.005$). This concluded that the evaluation of disease by full colonoscopy with multiple segments may provide the more accurate method to evaluate disease activity.

Overall, the study concluded that the UCEIS confirmed better responsiveness than the UCDAI, and it is superior to describe accurate endoscopic findings in patients with severe UC. This responsiveness can be crucial in clinical trials since duration of primary endpoints in many clinical trials is approximately 12 wk[44]. Thus, indices that allow to capture small but vital improvement that reflects on disease outcome is essential to clinical trials.

Reliability: Despite mucosal healing becoming the goal for management for UC, the most critical limitation of endoscopic assessment is its inherent intra- and inter-observer variations[6,45-47]. Reliability is evaluated with inter- and intra-observer reliability as well as internal consistency. The leading author of the UCEIS led another study to investigate reliability in different aspects.

The first study published in 2013 investigated intra- and inter-observation reliability[15]. Twenty-five readers from 14 countries were recruited in this study, who evaluated 28 videos. To quantify intra-observer reliability, 4 duplicated videos were included. For inter-observer reliability, all readers were trained to ensure consistent understanding and use of the scoring system. Internal consistency was measured using the Cronbach's coefficient alpha, which was 0.863 for the overall UCEIS - bleeding 0.80, vascular pattern 0.83, and ulcers and erosions 0.79.

The study found that the intra and inter-observer reliability ratios for the UCEIS were 0.96 and 0.88 respectively. Intra-observer agreement static was calculated with kappa, which was 0.72, with individual descriptors ranging from 0.47 (for bleeding) to 0.87 (for vascular pattern). Inter-observer agreement statistic was slightly lower at 0.50, with individual descriptors ranging from 0.48 (bleeding) to 0.54 (vascular pattern). Additionally, these observer reliabilities were compared with readers who were given clinical information at the time of the video readings, which determined no apparent bias by clinical information.

To evaluate the impact of clinical information on UCEIS scores, the author also undertook another study in 2015[26]. The study invited 40 readers from various countries who were experienced with endoscopic assessment. Each reader was divided into two groups (with and without clinical information) and conducted evaluation of a random 28 from 44 videos, which had not been used in the previous study. Furthermore, 4 videos included misleading information in order to ensure disparity between endoscopic assessment and clinical information.

This study showed there is no impact of clinical information on mean UCEIS scores. They were almost identical whether readers had knowledge of patient's clinical information and the median SD was 0.94 for blinded and 0.93 for unblinded. The SD was low for videos with severe disease.

Intra- and inter-observer agreement of the blinded and unblinded readers was also evaluated. Intra-observer agreements for bleeding and vascular pattern were very similar for the two groups, whereas that for erosions and ulcers just reached to statistical significance with kappa of 0.47 for blinded and 0.74 for unblinded.

The study also extended to compare the UCEIS with other indices and patient-reported symptom scoring systems. The full Mayo Clinic Score (MC)[32], partial MC (excluding endoscopic subscore)[48], patient-reported stool frequency and rectal bleeding subscore, patient functional assessment score and Feagan score were compared with the UCEIS as well as Feagan Score[36]. This showed the UCEIS is significantly superior to the Feagan Score including patient-reported symptom subscore. This implies that the UCEIS alone may be sufficient for outcome measurement in clinical trials.

The only inter-observer and central reader variations study on UCDAI also referred to UCEIS[25]. The authors investigated the role of central readers to minimise inter-observer variations, which may contribute to false responses to placebo in UC trials. They conducted a 10-wk randomised double-blinded placebo-controlled study on patients with UC who scored UCDAI $\geqslant 2$.

Three hundreds and forty-three patients, who were initially assessed by site investigators, were enrolled to the randomised clinical trials. Clinical remission (UCDAI,

Table 5 Definitions of remission in ulcerative colitis

Guidelines	Definition
FDA[5]	Clinical remission
	Mayo score of ⩽ 2 with no individual subscore > 1
	Rectal Bleeding subscore = 0
	Stool Frequency subscore = 0 (at least one point decrease in Stool Frequency subscore from baseline and achieved 1 is considered)
	Endoscopy subscore = (Mayo score: 0 or 1, UCDAI = 0)
	Clinical response
	Reduction in Mayo score ⩾ 3 and ⩾ 30% from baseline with Rectal Bleeding subscore ⩽ 1
	Corticosteroid-free remission
	Clinical remission in patients using oral corticosteroids at baseline who have discontinued them and are in clinical remission at the end of the study
World Gastroenterology Organisation	Clinical remission
	UCDAI ⩽ 2 (2010 World Gastroenterology Organisation Practice Guideline)[50]
	Corticosteroid-free remission
	Decreasing the frequency and severity of recurrence and reliance on corticosteroids
International Organisation for the Study of IBD	End points = induction of remission = mucosal healing[12]
	The absence of friability, blood, erosions and ulcers in all visible segments
	No mention of clinical symptoms
American College of Gastroenterology	No clear definition[51]
British Society of Gastroenterology	No clear definition[52]
European Crohn's and Colitis Organisation	Remission[53]
	A complete resolution of symptoms and endoscopic mucosal healing
	Not been a fully validated definition of remission
	Suggest the best way forward is a combination of
	Stool Frequency ⩽ 3
	No rectal bleeding
	Normal or quiescence mucosa at endoscopy
	Clinical response
	Clinical and endoscopic response depending on the activity index
	Generally, a decrease in the activity index > 30% plus a decrease in the rectal bleeding and endoscopic subscores

UCDAI: Ulcerative colitis disease activity index; IBD: Inflammatory bowel disease; FDA: Food and Drug Administration.

stool frequency and bleeding scores of 0) was achieved by 30.0% of patients treated with mesalamine and 20.6% of those with placebo. However, when those 343 were re-assessed by 7 central-readers, 31% of those patients were in fact ineligible as they scored lower than 2. Furthermore, this altered the remission rate to 29.0% and 13.8% in the mesalamine and placebo groups respectively. In conclusion, this study suggests robust methodology for future clinical trials in UC to avoid misleading results.

The authors also extended the study to quantify the inter-observer variation amongst 7 central readers using UCDAI, UCEIS, Feagan score, visual analogue scale. Of those indices, UCEIS demonstrated the highest interclass correlation coefficient with 0.83 and UCDAI was 0.79. The authors concluded that this might be attributed to no friability assessment in UCEIS, which is the commonest source of disagreement between central and site readers in this study.

What is remission in UC?

Definition of remission: Remission rates can vary by more than two-fold depending on the definition of remission used for data analysis[49]. In addition to uncertainty about standardisation of disease activity measurement, disease remission has also never been conclusively defined or validated. Defining disease remission should be the fundamental starting point of studying therapeutic efficacy and disease monitoring, before standardising how to measure disease activity.

Definitions of remission in UC vary depending on users, settings and the purpose of monitoring the disease activity. The definition of remission used in clinical practice and by the patient is often different from that used in clinical trials. Remission, clinical remission, complete remission, partial remission, clinical response, mucosal healing or remission, corticosteroid-free remission, registration remission are frequently employed terms used in clinical practice by healthcare professionals and patients, although these terms are used interchangeably and variably without strict definition, including in clinical trials.

Table 5 is a summary of definitions of remissions in UC defined by large regulatory bodies and guidelines. All guidelines mention remission to manage disease, however, few guidelines explicitly define remission. The American College of Gastroenterology is no exception, though it controversially states that, "practical therapeutic end point, endoscopic demonstration of mucosal healing is not usually necessary for a patient who achieves clinical remission". The FDA recommends a primary endpoint of clinical remission, and clinical remission is defined

Table 6 Clinical studies measured with the ulcerative colitis endoscopic index of severity

Ref.	Year	Type of study	Drug/subject of study	Entry criteria	Primary endpoint	Secondary endpoint	Remission/clinical improvement	Length of study
Hartman *et al*[54]	2016	Randomised, double-blind, placebo-controlled study	AVX-470, oral	36 patients with Mayo score 5-12 and Mayo ES ⩾ 2	Not set, but implies clinical response at week 4	Not set	Remission was not defined. Clinical response Mayo reduction ⩾ 3	4 wk
Lin *et al*[55]	2015	Prospective, multi-centre study	Faecal calprotectin	52 patients with UC	N/A	N/A	Endoscopic remission: UCEIS < 3	N/A
Magro *et al*[56] ACERTIVE study	2016	Cross-sectional multi-centre study	Faecal calprotectin/ lipocalin	371 patients Mayo partial score < 2, montreal classification < 2			Remission: UCEIS ⩽ 1 Mucosal healing: Mayo ES = 0	

UCEIS: Ulcerative colitis endoscopic index of severity; UC: Ulcerative colitis; ES: Endoscopic subscore; N/A: Not available.

as follows[5]: Rectal Bleeding subscore = 0: (1) Stool Frequency subscore = 0 (or stool frequency subscore 1 is considered if at least one point improvement in Stool Frequency subscore from baseline); and (2) Endoscopy subscore 0 on UCDAI.

It also describes mucosal healing should not be supported from macroscopic appearance of the mucosa through endoscopy. However, the FDA further describes that there are no criteria for histological assessment of mucosal healing due to a lack of validated gold standard histological scoring systems.

The European Crohn's and Colitis Organisation (ECCO) more realistically states in their guidelines for patients in UC that there is no fully validated definition of remission.

How indices are used in clinical trials and defining remission endpoints: Since there is no gold-standard outcome measurement instruments in UC, many clinical trials have employed instruments depending on its application. Classic disease activity measurement instruments have been recently challenged by the FDA because of the significant effect of their subjective components affecting reproducibility. Even the traditionally promoted indices used by the FDA (Mayo Score and UCDAI) contain physician global assessment, which is highly sensitive to bias. The FDA suggests the primary endpoint should be achieved by endoscopic as well as clinical outcome, however, the difficulty in this is that these symptoms do not necessarily occur simultaneously with symptom control, especially where stool frequency and abdominal pain are considered. Nevertheless, these symptoms affect patients' quality of life. There are therefore further hurdles to overcome before standardisation of endpoint definition in UC[44].

In this systematic review, remission endpoints were investigated by studying the application of the UCEIS and UCDAI in clinical research and therapeutic trials (Tables 6 and 7). There are only three clinical research identified which applied the UCEIS for disease outcome measure and defined remission. Furthermore, only one randomised clinical trial has chosen the index for its outcome measurement instrument so far[54].

The trial was the first-in-human trial of AVX-470, which is a bovine-derived, orally-administered, anti-tumour necrosis factor (TNF) antibody, that works to intestinal mucosal tissue with minimal systematic effects. TNF is upregulated in the colonic mucosa in UC and believed to play a pathological role by loss of mucosal barrier integrity[57]. AVX-470 reduces levels of TNF protein in mice models, thus correcting immune dysregulation. In this study, the UCEIS was used to assess endoscopic response to treatment along with the total Mayo score and sub-scores.

This study successfully correlates between UCEIS scores and TNF immunohistochemistry scores at baseline. Further, it found that TNF staining was significantly reduced in proximal and distal segments of bowel, whereas the UCEIS changes were more apparent in proximal segments than distal ones. Although the study described achieving clinical remission, this was never defined.

The UCEIS was used for endoscopic assessment in a prospective study to quantify faecal calprotectin in patients with UC[55]. The authors used Quantum Blue Calprotectin High Range Rapid Test (Buhlmann laboratories AG, Schonenbuch, Switzerland) for faecal calprotectin measurement tools in this study. Interestingly, the authors defined endoscopic remission when the UCEIS < 3. They also concluded that faecal calprotectin and CRP were both well correlated with the UCEIS (the Spearman correlation coefficient is 0.696 and 0.581 respectively). Moreover, they concluded that when a cut-off faecal calprotectin of 191 μg/g is set, this could predict endoscopic remission and mucosal remission (UCEIS < 3) with 88% sensitivity and 75% specificity. However, when UCEIS < 1 clinical remission proposed by other authors[14,23] is applied, faecal calprotectin would be lower than 191 μg/g. This could lead to underestimate patients who should be treated.

The largest patient population study that used the UCEIS is a cross-sectional, multi-centre study, ACERTIVE study[56]. The aim of this study was to evaluate potential applications of biomarkers (faecal calprotectin and neutrophil gelatinase B-associated lipocalin) as disease activity measuring instrument

Table 7 Randomised clinical trials measured with the ulcerative colitis disease activity index

Ref.	Year	Drug	Entry criteria	Primary endpoint	Secondary endpoint	Remission/clinical improvement	Length of study
Randomised clinical trials - to induce remission Mesalazine (5-ASA)							
Marteau *et al*[58]	2005	Pentasa (PR + PO *vs* PO alone)	UCDAI: 3-8	Remission at week 4	Remission rate at week 8 Improvement at week 4 and 8	Remission: UCDAI ⩽ 1 Clinical improvement: A decrease of UCDAI ⩾ 2	8 wk
D'Haens *et al*[59]	2006	SPD476 - MMX mesalazine	UCDAI: 4-10 + endoscopic score ⩾1 PGA score ⩽ 2	Remission	Change in UCDAI, FS, histology at week 8 Change in symptoms	Remission: UCDAI ⩽ 1 (with RB 0, SF ⩽ 1) at week 8	8 wk
Sandborn *et al*[60]	2007	MMX Multi Matrix System mesalazine	UCDAI: 4-10 + endoscopic score ⩾1 PGA score ⩽ 2	Clinical/endoscopic remission at 8 wk	Proportion of clinical improvement Proportion of patients as treatment failure Change in: RB, SF, FS	Clinical remission: UCDAI ⩽ 1 Endoscopic remission: UCDAI endoscopic subscore ⩽ 1 Clinical improvement: A decrease of UCDAI ⩾ 3 Treatment failure: Unchanged or worsened UCDAI	8 wk
Lichtenstein *et al*[61]	2007	SPD476 - MMX mesalazine OD *vs* BD	UCDAI: 4-10	Clinical and endoscopic remission at week 8	Comparison of remission rate at week 8	Clinical remission: UCDAI ⩽ 1 with RB/SF/EI = 0	8 wk
Kamm *et al*[62,63] MEZAVANT study	2007 2009	MEZAVANT MMX Mesalamine	Mild - mod UC: UCDAI 4-10 + endoscopic subscore ⩾ 1, PGA ⩽ 2	Clinical + Endoscopic remission at week 8	Clinical remission Clinical improvement Change in UCDAI	Clinical + endoscopic remission: UCDAI ⩽ 1 + subscore RB/SF = 0, No mucosal friability + a ⩾ 1 reduction in EI Clinical improvement: Decrease in UCDAI ⩾ 3	8 wk
Ito *et al*[64]	2010	Asacol *vs* PentasaTime-dependent *vs* pH dependent Mesalamine	UCDAI: 3-8 and blood stool score ⩾ 1	To demonstrate Asacol over Pentasa AND the decrease in UCDAI	Macroscopic changes	Remission: UCDAI ⩽ 2 and no blood diarrhoea Clinical improvement: UCDAI decreased by ⩾ 2	8 wk
Hiwatashi *et al*[65]	2010	Mesalazine - dose study	UCDAI: 6-8	Change in UCDAI at week 8	Remission, improvement, efficacy	Remission: UCDAI ⩽ 1 Efficacy: Decrease of UCDAI ⩾ 2	8 wk
Flourié *et al*[66] MOTUS study	2013	Mesalazine, Pentasa OD or BD in total of 4 g/d	UCDAI: 3-8	UCDAI ⩽ 1 after 8 wk	Complete remission (UCDAI = 0) at 8 wk UCDAI decreased by ⩾ 2 at 8 wk Clinical remission at week 4, 8, 12 Mucosal healing at 8 wk	Complete remission: UCDAI = 0 Endoscopic remission: UCDAI endoscopic subscore: 0 or 1 Clinical remission: UCDAI ⩽ 1	12 wk
Probert *et al*[42] PINCE study	2013	Mesalazine (pentasa) enema	UCDAI: 3-8	Remission rate (UCDAI < 2) at 4 wk	Remission rate at 8 wk, improvement at week 2, 4 and 8 Time to cessation of RB QoL (EQ-5D)	Remission: UCDAI ⩽ 1 Clinical improvement: UCDAI decreased by ⩾ 2	8 wk
Sun *et al*[67]	2016	Mesalazine (modified-release *vs* enteric-coated tablets)	UCDAI: 3-8 + bloody stool score > 1	The decrease in UCDAI	Remission rate Efficacy rate	Remission: UCDAI ⩽ 2 + bloody stool 0 Clinical improvement: A decrease of UCDAI ⩾ 2	8 wk
Suzuki *et al*[68]	2016	pH dependent release mesalamine, asacol dose	UCDAI: 6 - 10 Rectal bleeding score ⩾ 1	Decrease in UCDAI		Remission: UCDAI ⩽ 2 Rectal bleeding score: 0 Improvement UCDAI decreased by ⩾ 2	8 wk
Thiazole compounds							
Mantzaris *et al*[69]	2004	Azathioprine alone (2.2 mg/kg) *vs* combination with olsalazine (0.5 g TID)	Steroid-dependent remission	Relapse rate	Time to relapse Time to discontinuation Severity of relapse	Remission: UCDAI ⩽ 1 Relapse: New symptoms + UCDAI > 3	2 yr

Schreiber *et al*[70]	2007	Tetomilast - Thiazole compound	UCDAI: 4-11	Clinical improvement: UCDAI decreased by ⩾ 3 at 8 wk	Remission Clinical improvement at week 4 IBDQ-32 score Proportion of pts with improved Flexible Sigmoidscopy score Time to clinical improvement Time to remission	Clinical improvement: UCDAI decreased by ⩾ 3 Remission: UCDAI ⩽ 1	8 wk
Steroids							
Travis *et al*[71] CORE Ⅱ study	2012	Budesonide MMX	UCDAI: 4-10	Clinical/endoscopic remission at week 8	Clinical improvement Endoscopic improvement at week 8	Clinical/endoscopic Remission: UCDAI ⩽ 1 + RB/SF/EI = 0 Clinical improvement: A decrease of UCDAI ⩾ 3 Endoscopic improvement: A decrease of EI ⩾ 1	8 wk
Probiotics							
Vernia *et al*[72]	2000	Sodium Butyrate	Mild-moderate UC	Remission or marked improvement		Remission: UCDAI ⩽ 2 Positive response: Decrease of UCDAI ⩾ 2	6 wk
Mahmood *et al*[73]	2005	Human recombinant trefoil factor 3 enema	UCDAI: >3	Remission at week 2	Clinical significant improvement in clinical and histological scores at 2 and 4 wk	Remission: UCDAI ⩽ 1 without RB Clinical improvement: A decrease of UCDAI >3	4 wk
Lichtenstein *et al*[74]	2007	Bowman-Birk inhibitor concentrate - soy extract with high protease inhibitor activity	UCDAI: 4-10	Remission at week 8		Remission: UCDAI ⩽ 1 + no RB or SF Clinical improvement: UCDAI decrease ⩾ 1	
Tursi *et al*[75]	2009	VSL #3 (probiotic)	UCDAI 3-8, endoscopic subscore ⩾ 3	Decrease in UCDAI of ⩾ 50%	Activity of relapsing UC Remission Improvement Change in objective and subjective symptoms	Remission: UCDAI ⩽ 2	8 wk
Sood *et al*[76]	2009	VSL #3 probiotic	UCDAI 3-9 with endoscopic subscore ⩾ 2	Clinical improvement at week 6	Clinical remission	Clinical remission: UCDAI ⩽ 2 Clinical improvement: A decrease UCDAI by 50%	12 wk
Tamaki *et al*[77]	2016	Bifidobacterium longum 536 (probiotic)	UCDAI 3-9	Change in UCDAI	Remission Improvement of Objective and subjective symptoms Endoscopic improvement in Mayo subscore	Remission: UCDAI ⩽ 2	8 wk
Helminth therapy Garg *et al*[78]	2014	Helminth Trichuris suis ova	UCDAI of ⩾ 4	Clinical improvement	Clinical remission	Clinical improvement: Decrease in the UCDAI of ⩾ 4 Clinical remission: UCDAI of ⩽ 2	12 wk
Nicotine therapy							
Ingram *et al*[79]	2005	Nicotine enema 6 mg/d	Confirmed UC with inflamed mucosa grade > 2	Clinical remission	Improvement in the UCDAI	Clinical remission: UCDAI EI ⩽ 1 and No RB for 1 wk	6 wk
Randomised clinical trials - to maintain remission							
Lichtenstein *et al*[80-82] and Zakko *et al*[83]	2010 2012 2015 2016	Mesalamine granules 1.5 g/d, OD	Previously achieved remission with steroids for > 1 mo and < 12 mo	Percentage of patients relapse-free at 6 mo	Mean changes from baseline at month 6	Relapse: UCDAI RB ⩾ 1 and EI ⩾ 2 Remission: UCDAI RB = 0, EI < 2	6 mo
Bokemeyer *et al*[43] and Dignass *et al*[84]	2009 2011	Mesalazine, Pentasa OD or BD in total of 2 g/d	Clinical remission: UCDAI < 2	To demonstrate OD is not inferior to BD	Time to relapse between 2 groups UC-DAI total and subscores between 2 groups	Remain in remission UCDAI ⩽ 2	12 mo

RB: Rectal bleeding; SF: Stool frequency; EI: Endoscopic index/subscore; OD: Once daily; BD: Twice daily; TID: Three times daily; UCDAI: Ulcerative colitis disease activity index; QoL: Quality of life.

in patients with asymptomatic UC. The UCEIS and Geboes index[22] were applied for macroscopic and

microscopic assessment respectively. Nine percent of the asymptomatic patients had active disease with UCEIS > 2. Twenty-one percent of the asymptomatic patients presented with Geboes index > 3. One point fifteen percent and 5% of the patients presented with focal and diffuse basal plasmacytosis, respectively. Patients with asymptomatic disease indeed showed presence of macroscopic as well as microscopic disease. Furthermore, 50% of patients who scored a UCEIS < 2 and 15% of patients who were considered to have achieved mucosal healing (Mayo ES = 0) had diffuse basal plasmacytosis. These results support the previous published notion that macroscopic findings are not sufficient to define remission or endpoint[9].

Both biomarkers predicted mucosal healing as well as histological remission with satisfactory probability of 75%-93%. The authors proposed a cut-off figures of 150-250 μg/g for faecal calprotectin and 12 μg/g for lipocalin. This range of cut-off level for faecal calprotectin is due to the application of two faecal calprotectin measurement tools (Quantum Blue Calprotectin High Range Rapid Test and Automated Fluroimmunoassay-EliA Test) from stool samples. Although this proposed cut-off point for faecal calprotectin for clinical remission is a similar value with the Taiwan group[55], the defined remission show variance as the Taiwan group set UCEIS < 3 for remission whereas ACERTIVE study used UCEIS $\leqslant$ 1. Although it is only one score difference, this can be of significance for disease outcome. As Arai *et al*[20] concluded, the recurrence rate was directly proportional to the UCEIS score. The recurrence rate for UCEIS 1 disease is 22.4%, whereas UCEIS 2 disease increases to 27.0%. As the authors state validation of the proposed cut-off values is required before introducing them in clinical setting. Moreover, caution should be applied when introducing biomarkers especially when their intention is to replace endoscopic assessment.

Table 6 shows the summary of the randomised clinical trials that utilised the UCDAI for disease activity assessment, defining remission and endpoints. The studies were divided into introduction and maintenance of disease remission.

Most of the studies investigated the efficacy of introducing remission set clinical remission as UCDAI $\leqslant$ 1, however some studies defined as UCDAI $\leqslant$ 2 for remission. It appears that many studies have taken advantage of defining their own remission, clinical response and endpoints with the UCDAI as it is not clearly defined in previous guidelines. The studies with probiotics appear to choose higher remission cut-off point, which could interpret that it is undemanding to achieve clinical remission so that it would satisfy requirements of regulatory bodies such as the FDA. The previous validation study suggested UCDAI score < 2.5 for clinical remission[65], meaning UCDAI $\leqslant$ 2 is still within the range of remission.

Another point to note is that many studies have their own additional criteria with a specific patient-reported symptom scoring system to measure rectal bleeding and stool frequency to define remission or clinical response. This is likely attributed to the guideline published by the FDA, which encourages to assess patient-reported outcome measurement on rectal bleeding and stool frequency in addition to the macroscopic assessment with endoscopy as an endpoint for clinical trials. This is also reflected on their definition of clinical remission on Table 5.

If a more stringent primary endpoint is enforced the clinical utility of therapeutics may be harder to demonstrate, potentially limiting the number of agents available in the marketplace. Furthermore, drug development for UC faces bigger challenge due to the unknown natural history of UC, unpredictable relapse and remission patterns as well as response to medications with known efficacy. If the stringent remission and endpoint was forced by regulatory bodies, the pharmaceutical industry may choose drugs that have cheaper development cost.

Although the FDA supports the use of UCDAI for measuring primary endpoints, UCDAI has limitations. As it is highlighted in the previous section, one of the weakness is a lack of validation and vulnerability to observer bias. Adding inconsistent definition of remission and endpoint for each clinical trial hinders providing optimal management to patients with the disease.

DISCUSSION

Homogeneity of the clinical trials in UC has been discussed amongst experts for decades. Despite a desire for a single gold-standard disease activity index, the number of indices has been steadily increasing. Disease remission is yet to be fully defined, thus trial outcomes vary and limit the utility of these studies depending on the purpose of its clinical use. Most trials chose individual endpoints which are not necessarily clinically pertinent. Clinicians, on the other hand are constantly negotiating with patients to provide the best possible management for this chronic condition, regardless of an index score. This variation makes the comparison amongst clinical trials extremely difficult, hindering drug development.

So far, many review studies summarised and evaluated currently available indices on different assessments. The majority of these studies highlighted the wide variation of endpoints by different indices and emphasised the importance of having a gold-standard index to assess the efficacy of the interventions. This has led to development of more indices rather than choosing a gold-standard index, adding more choices and fuelling confusion amongst researchers and clinicians. This systematic review proposes to emphasise on a universal consensus on UC remission before developing any more indices. Futher more this systematic review would assist scientists and clinicians to have a better understanding of confusing definitions and disease activity indices that have been used interchangeably.

This systematic review was conducted to evaluate the definition and evidence for remission endpoints in ulcerative colitis from the point of view of two particular indices. The UCDAI has been widely used in clinical studies compared to the UCEIS. Although the UCEIS has been extensively validated, only one randomised clinical trial has employed the UCEIS as their outcome measurement instrument of date. The reason may be threefold. Firstly, other traditional disease activity measurement instruments have been widely used in previous clinical trials, making comparison with those trials more straightforward, although less robust. Secondary, if clinical trials were conducted for drug development, they would more likely choose the disease activity indices as recommended by regulatory bodies such as the FDA or equivalent. Finally, the UCEIS was recently developed thus there is no surprise that the number of clinical trials using this scoring system is still low.

The other two studies that used the UCEIS are not randomised clinical trials, though they demonstrated how multiple definitions of remission used in the evaluation of biomarker, calprotectin, to monitor disease activity could alter the outcomes. Without a universal definition of remission, researchers can freely define the UCEIS score for a remission endpoint, making evaluation of calprotectin use in clinical practice very difficult.

Furthermore, regulatory bodies such as the FDA recommend measuring endpoints in terms of clinical remission with particular indices, although they still do not convey the ideal length of clinical trial to achieve a primary endpoint or the duration of clinical remission before relapsing. This diversity of clinical protocols was also emphasised in this systematic review.

One of the criticisms for traditional outcome measurement instruments has been insufficient validation. The UCEIS has designed to overcome from this problem and to take a step forward for establishing a gold standard outcome measurement instrument. Yet, this systematic review highlighted that validation is not necessarily an issue for employing an outcome measurement instrument for clinical trials. Although we focused on developing new ideal indices, a new index may not be a solution to establish a gold standard outcome measurement instrument.

A lack of understanding in aetiology and natural history of ulcerative colitis may contribute to this confusion. In order to untangle this confusion, we recommend that an international consensus of remission should be sought as a matter of urgency before establishing a gold standard outcome measurement. Once a universal consensus for remission is reached and defined, establishing a gold-standard index, which can measure true symptoms and is transferable and meaningful to clinical practice, can be determined. That would lead to standardisation of clinical trial protocols for advancing patient care.

COMMENTS

Background

The current target of disease remission endoscopically is mucosal healing although it has not been fully validated or no standardised definition of mucosal healing. Yet, this appears to be the goal for many clinical practice as well as drug trials. The recent draft guideline released by the FDA states the ideal primary efficacy assessment instrument in clinical trials should consist of (1) a signs and symptoms assessment scale - best measured by a patient-reported outcome instrument. If not, an observer-reported outcome instrument; and (2) an endoscopic and histological assessment scale. Thus, endoscopic assessment tools with comprehensive clinical symptom assessment components that come from patients would be a reasonable choice to argue remission and endpoints employed in clinical trials.

Research frontiers

The authors believe this has been mentioned everywhere in the paper that definition of ulcerative colitis endpoint has been introducing ambiguity especially when different clinical trial studies are compared. The authors also mentioned in the summary that a lack of understanding in aetiology and disease natural history may contribute to this confusion, which needs to be addressed in the future research.

Innovations and breakthroughs

The authors added to emphasize the differences from other similar studies.

Applications

The authors added "This systematic review would assist scientists and clinicians to have a better understanding of confusing definitions and disease activity indices that have been used interchangeably".

Peer-review

This is a comprehensive review of remission endpoints in ulcerative colitis, the paper is well written and is very useful for both clinical practice and teaching purposes.

REFERENCES

1 **Ungaro R**, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2017; **389**: 1756-1770 [PMID: 27914657 DOI: 10.1016/S0140-6736(16)32126-2]

2 **Andrew RE**, Messaris E. Update on medical and surgical options for patients with acute severe ulcerative colitis: What is new? *World J Gastrointest Surg* 2016; **8**: 598-605 [PMID: 27721922 DOI: 10.4240/wjgs.v8.i9.598]

3 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656]

4 **Walsh AJ**, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 567-579 [PMID: 27580684 DOI: 10.1038/nrgastro.2016.128]

5 **U.S. Department of Health and Human Services Food and Drug Administration C for DE and R (CDER)**. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. USA: U.S. Department of Health and Human Services Food and Drug Administration C for DE and R (CDER), 2016

6 **Samaan MA**, Mosli MH, Sandborn WJ, Feagan BG, D' Haens GR, Dubcenco E, Baker KA, Levesque BG. A systematic review of the measurement of endoscopic healing in ulcerative colitis clinical trials: recommendations and implications for future research. *Inflamm Bowel Dis* 2014; **20**: 1465-1471 [PMID: 24831558 DOI: 10.1097/MIB.0000000000000046]

7 **Lichtenstein GR**, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 338-346 [PMID: 19637362 DOI: 10.1002/ibd.20997]

8 **Popp C**, Stăniceanu F, Micu G, Nichita L, Cioplea M, Mateescu RB, Voiosu T, Sticlaru L. Evaluation of histologic features with potential

prognostic value in ulcerative colitis. *Rom J Intern Med* 2014; **52**: 256-262 [PMID: 25726628]
9 **Bryant RV**, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis* 2014; **8**: 1582-1597 [PMID: 25267173 DOI: 10.1016/j.crohns.2014.08.011]
10 **Gray JR**, Leung E, Scales J. Treatment of ulcerative colitis from the patient's perspective: a survey of preferences and satisfaction with therapy. *Aliment Pharmacol Ther* 2009; **29**: 1114-1120 [PMID: 19222412 DOI: 10.1111/j.1365-2036.2009.03972.x]
11 **Van Deen WK**, van der Meulen-de Jong AE, Parekh NK, Kane E, Zand A, DiNicola CA, Hall L, Inserra EK, Choi JM, Ha CY, Esrailian E, van Oijen MG, Hommes DW. Development and Validation of an Inflammatory Bowel Diseases Monitoring Index for Use With Mobile Health Technologies. *Clin Gastroenterol Hepatol* 2016; **14**: 1742-1750.e7 [PMID: 26598228 DOI: 10.1016/j.cgh.2015.10.035]
12 **D'Haens G**, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; **132**: 763-786 [PMID: 17258735 DOI: 10.1053/j.gastro.2006.12.038]
13 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]
14 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lémann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Bernhardt CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012; **61**: 535-542 [PMID: 21997563 DOI: 10.1136/gutjnl-2011-300486]
15 **Travis SP**, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Schnell P, Bernhardt CA, Mary JY, Sandborn WJ. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013; **145**: 987-995 [PMID: 23891974 DOI: 10.1053/j.gastro.2013.07.024]
16 **Baron JH**, Connell AM, Lennard-Jones JE. VariationA between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92 [PMID: 14075156]
17 **Sutherland LR**, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, Martin T, Sparr J, Prokipchuk E, Borgen L. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987; **92**: 1894-1898 [PMID: 3569765]
18 **Corte C**, Fernandopulle N, Catuneanu AM, Burger D, Cesarini M, White L, Keshav S, Travis S. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015; **9**: 376-381 [PMID: 25770163 DOI: 10.1093/ecco-jcc/jjv047]
19 **Fernandes SR**, Santos P, Miguel Moura C, Marques da Costa P, Carvalho JR, Isabel Valente A, Baldaia C, Rita Gonçalves A, Moura Santos P, Araújo-Correia L, Velosa J. The use of a segmental endoscopic score may improve the prediction of clinical outcomes in acute severe ulcerative colitis. *Rev Esp Enferm Dig* 2016; **108**: 697-702 [PMID: 27701881 DOI: 10.17235/reed.2016.4470/2016]
20 **Arai M**, Naganuma M, Sugimoto S, Kiyohara H, Ono K, Mori K, Saigusa K, Nanki K, Mutaguchi M, Mizuno S, Bessho R, Nakazato Y, Hosoe N, Matsuoka K, Inoue N, Ogata H, Iwao Y, Kanai T. The Ulcerative Colitis Endoscopic Index of Severity is Useful to Predict Medium- to Long-Term Prognosis in Ulcerative Colitis Patients with Clinical Remission. *J Crohns Colitis* 2016; **10**: 1303-1309 [PMID: 27194529 DOI: 10.1093/ecco-jcc/jjw104]
21 **Kucharski M**, Karczewski J, Mańkowska-Wierzbicka D, Karmelita-Katulska K, Grzymisławski M, Kaczmarek E, Iwanik K, Rzymski P, Swora-Cwynar E, Linke K, Dobrowolska A. Applicability of endoscopic indices in the determination of disease activity in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2016; **28**: 722-730 [PMID: 26894632 DOI: 10.1097/MEG.0000000000000601]
22 **Geboes K**, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000; **47**: 404-409 [PMID: 10940279]
23 **Ikeya K**, Hanai H, Sugimoto K, Osawa S, Kawasaki S, Iida T, Maruyama Y, Watanabe F. The Ulcerative Colitis Endoscopic Index of Severity More Accurately Reflects Clinical Outcomes and Long-term Prognosis than the Mayo Endoscopic Score. *J Crohns Colitis* 2016; **10**: 286-295 [PMID: 26581895 DOI: 10.1093/ecco-jcc/jjv210]
24 **Menasci F**, Pagnini C, Di Giulio E. Disease Extension Matters in Endoscopic Scores: UCEIS Calculated as a Sum of the Single Colonic Segments Performed Better than Regular UCEIS in Outpatients with Ulcerative Colitis. *J Crohns Colitis* 2015; **9**: 692-693 [PMID: 25975267 DOI: 10.1093/ecco-jcc/jjv088]
25 **Feagan BG**, Sandborn WJ, D'Haens G, Pola S, McDonald JW, Rutgeerts P, Munkholm P, Mittmann U, King D, Wong CJ, Zou G, Donner A, Shackelton LM, Gilgen D, Nelson S, Vandervoort MK, Fahmy M, Loftus EV Jr, Panaccione R, Travis SP, Van Assche GA, Vermeire S, Levesque BG. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. *Gastroenterology* 2013; **145**: 149-157.e2 [PMID: 23528626 DOI: 10.1053/j.gastro.2013.03.025]
26 **Travis SP**, Schnell D, Feagan BG, Abreu MT, Altman DG, Hanauer SB, Krzeski P, Lichtenstein GR, Marteau PR, Mary JY, Reinisch W, Sands BE, Schnell P, Yacyshyn BR, Colombel JF, Bernhardt CA, Sandborn WJ. The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS]. *J Crohns Colitis* 2015; **9**: 607-616 [PMID: 25956538 DOI: 10.1093/ecco-jcc/jjv077]
27 **Higgins PD**, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005; **54**: 782-788 [PMID: 15888785 DOI: 10.1136/gut.2004.056358]
28 **Poole CD**, Connolly MP, Nielsen SK, Currie CJ, Marteau P. A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. *J Crohns Colitis* 2010; **4**: 275-282 [PMID: 21122516 DOI: 10.1016/j.crohns.2009.11.010]
29 **Travis SP**, Higgins PD, Orchard T, Van Der Woude CJ, Panaccione R, Bitton A, O'Morain C, Panés J, Sturm A, Reinisch W, Kamm MA, D'Haens G. Review article: defining remission in ulcerative colitis. *Aliment Pharmacol Ther* 2011; **34**: 113-124 [PMID: 21615435 DOI: 10.1111/j.1365-2036.2011.04701.x]
30 **Walsh A**, Travis S. Assessing disease activity in patients with ulcerative colitis. *Gastroenterol Hepatol* (N Y) 2012; **8**: 751-754 [PMID: 24672411]
31 **Powell-Tuck J**, Day DW, Buckell NA, Wadsworth J, Lennard-Jones JE. Correlations between defined sigmoidoscopic appearances and other measures of disease activity in ulcerative colitis. *Dig Dis Sci* 1982; **27**: 533-537 [PMID: 6979471]
32 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]
33 **Rachmilewitz D**. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; **298**: 82-86 [PMID: 2563951]
34 **Löfberg R**, Ostergaard Thomsen O, Langholz E, Schiöler R, Danielsson A, Suhr O, Graffner H, Påhlman L, Matzen P, Møller-Petersen JF. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1994; **8**: 623-629 [PMID: 7696452]
35 **Lémann M**, Galian A, Rutgeerts P, Van Heuverzwijn R, Cortot A, Viteau JM, Elewaut A, Belaiche J, Froguel E, Modigliani R. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1995; **9**: 557-562 [PMID: 8580278]
36 **Feagan BG**, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Dubé R, Cohen A, Steinhart AH, Landau S, Aguzzi RA, Fox IH, Vandervoort MK. Treatment of ulcerative colitis with a humanized

antibody to the alpha4beta7 integrin. *N Engl J Med* 2005; **352**: 2499-2507 [PMID: 15958805 DOI: 10.1056/NEJMoa042982]
37 **Lichtiger S**, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet* 1990; **336**: 16-19 [PMID: 1973211]
38 **Seo M**, Okada M, Yao T, Ueki M, Arima S, Okumura M. An index of disease activity in patients with ulcerative colitis. *Am J Gastroenterol* 1992; **87**: 971-976 [PMID: 1642220]
39 **Walmsley RS**, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998: **43**:29-32 [PMID: 9771402 DOI: 10.1136/gut.43.1.29]
40 **Levine DS**, Riff DS, Pruitt R, Wruble L, Koval G, Sales D, Bell JK, Johnson LK. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 1398-1407 [PMID: 12094857 DOI: 10.1111/j.1572-0241.2002.05781.x]
41 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]
42 **Probert CS**, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. *J Crohns Colitis* 2014; **8**: 200-207 [PMID: 24012063 DOI: 10.1016/j.crohns.2013.08.007]
43 **Bokemeyer B**, Hommes D, Gill I, Broberg P, Dignass A. Mesalazine in left-sided ulcerative colitis: efficacy analyses from the PODIUM trial on maintenance of remission and mucosal healing. *J Crohns Colitis* 2012; **6**: 476-482 [PMID: 22398060 DOI: 10.1016/j.crohns.2011.10.006]
44 **D'Haens G**. Standardisation of Study Protocols - Pros and Cons. *J Crohns Colitis* 2016; **10** Suppl 2: S553-S559 [PMID: 27604980 DOI: 10.1093/ecco-jcc/jjw001]
45 **Regueiro M**, Rodemann J, Kip KE, Saul M, Swoger J, Baidoo L, Schwartz M, Barrie A, Binion D. Physician assessment of ulcerative colitis activity correlates poorly with endoscopic disease activity. *Inflamm Bowel Dis* 2011; **17**: 1008-1014 [PMID: 20812333 DOI: 10.1002/ibd.21445]
46 **Mazzuoli S**, Guglielmi FW, Antonelli E, Salemme M, Bassotti G, Villanacci V. Definition and evaluation of mucosal healing in clinical practice. *Dig Liver Dis* 2013; **45**: 969-977 [PMID: 23932331 DOI: 10.1016/j.dld.2013.06.010]
47 **Osada T**, Ohkusa T, Yokoyama T, Shibuya T, Sakamoto N, Beppu K, Nagahara A, Otaka M, Ogihara T, Watanabe S. Comparison of several activity indices for the evaluation of endoscopic activity in UC: inter- and intraobserver consistency. *Inflamm Bowel Dis* 2010; **16**: 192-197 [PMID: 19575359 DOI: 10.1002/ibd.21000]
48 **Lewis JD**, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008; **14**: 1660-1666 [PMID: 18623174 DOI: 10.1002/ibd.20520]
49 **Cooney RM**, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for Ulcerative Colitis: towards standardisation. *Trials* 2007; **8**: 17 [PMID: 17592647 DOI: 10.1186/1745-6215-8-17]
50 **Bernstein CN**, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, LeMair AW, Malfertheiner, Ouyang Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A, Watermeyer G. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis* 2010; **16**: 112-124 [PMID: 19653289 DOI: 10.1002/ibd.21048]
51 **Kornbluth A**, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
52 Chronic Management - Inflammatory Bowel Disease [Internet]. British Society of Gastroenterology. Available from: URL: http://www.bsg.org.uk/images/Commissioning_report/BSG_Chronic_Inflammatory_Bowel_Disease.pdf
53 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
54 **Hartman DS**, Tracey DE, Lemos BR, Erlich EC, Burton RE, Keane DM, Patel R, Kim S, Bhol KC, Harris MS, Fox BS. Effects of AVX-470, an Oral, Locally Acting Anti-Tumour Necrosis Factor Antibody, on Tissue Biomarkers in Patients with Active Ulcerative Colitis. *J Crohns Colitis* 2016; **10**: 641-649 [PMID: 26802087 DOI: 10.1093/ecco-jcc/jjw026]
55 **Lin WC**, Wong JM, Tung CC, Lin CP, Chou JW, Wang HY, Shieh MJ, Chang CH, Liu HH, Wei SC; Taiwan Society of Inflammatory Bowel Disease Multicenter Study. Fecal calprotectin correlated with endoscopic remission for Asian inflammatory bowel disease patients. *World J Gastroenterol* 2015; **21**: 13566-13573 [PMID: 26730169 DOI: 10.3748/wjg.v21.i48.13566]
56 **Magro F**, Lopes S, Coelho R, Cotter J, Dias de Castro F, Tavares de Sousa H, Salgado M, Andrade P, Vieira AI, Figueiredo P, Caldeira P, Sousa A, Duarte MA, Ávila F, Silva J, Moleiro J, Mendes S, Giestas S, Ministro P, Sousa P, Gonçalves R, Gonçalves B, Oliveira A, Chagas C, Torres J, Dias CC, Lopes J, Borralho P, Afonso J, Geboes K, Carneiro F; Portuguese IBD Study Group [GEDII]. Accuracy of Faecal Calprotectin and Neutrophil Gelatinase B-associated Lipocalin in Evaluating Subclinical Inflammation in UlceRaTIVE Colitis-the ACERTIVE study. *J Crohns Colitis* 2017; **11**: 435-444 [PMID: 27664275 DOI: 10.1093/ecco-jcc/jjw170]
57 **Leppkes M**, Roulis M, Neurath MF, Kollias G, Becker C. Pleiotropic functions of TNF-α in the regulation of the intestinal epithelial response to inflammation. *Int Immunol* 2014; **26**: 509-515 [PMID: 24821262 DOI: 10.1093/intimm/dxu051]
58 **Marteau P**, Probert CS, Lindgren S, Gassul M, Tan TG, Dignass A, Befrits R, Midhagen G, Rademaker J, Foldager M. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005; **54**: 960-965 [PMID: 15951542 DOI: 10.1136/gut.2004.060103]
59 **D'Haens G**, Hommes D, Engels L, Baert F, van der Waaij L, Connor P, Ramage J, Dewit O, Palmen M, Stephenson D, Joseph R. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. *Aliment Pharmacol Ther* 2006; **24**: 1087-1097 [PMID: 16984503 DOI: 10.1111/j.1365-2036.2006.03082.x]
60 **Sandborn WJ**, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007; **26**: 205-215 [PMID: 17593066 DOI: 10.1111/j.1365-2036.2007.03361.x]
61 **Lichtenstein GR**, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, Lees K, Joseph RE, Sandborn WJ. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007; **5**: 95-102 [PMID: 17234558 DOI: 10.1016/j.cgh.2006.10.025]
62 **Kamm MA**, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007; **132**: 66-75; quiz 432-433 [PMID: 17241860 DOI: 10.1053/j.gastro.2006.10.011]
63 **Kamm MA**, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K, Joseph R. Effect of extended MMX mesalamine therapy for acute, mild-to-moderate ulcerative colitis. *Inflamm Bowel Dis* 2009;

15: 1-8 [PMID: 18671232 DOI: 10.1002/ibd.20580]
64 **Ito H**, Iida M, Matsumoto T, Suzuki Y, Sasaki H, Yoshida T, Takano Y, Hibi T. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflamm Bowel Dis* 2010; **16**: 1567-1574 [PMID: 20049950 DOI: 10.1002/ibd.21193]
65 **Hiwatashi N**, Suzuki Y, Mitsuyama K, Munakata A, Hibi T. Clinical trial: Effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. *J Gastroenterol* 2011; **46**: 46-56 [PMID: 20878425 DOI: 10.1007/s00535-010-0308-3]
66 **Flourié B**, Hagège H, Tucat G, Maetz D, Hébuterne X, Kuyvenhoven JP, Tan TG, Pierik MJ, Masclee AA, Dewit O, Probert CS, Aoucheta D; MOTUS study investigators. Randomised clinical trial: once- vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. *Aliment Pharmacol Ther* 2013; **37**: 767-775 [PMID: 23451806 DOI: 10.1111/apt.12266]
67 **Sun J**, Yuan Y. Mesalazine Modified-Release Tablet in the Treatment of Ulcerative Colitis in the Active Phase: A Chinese, Multicenter, Single-Blind, Randomized Controlled Study. *Adv Ther* 2016; **33**: 400-409 [PMID: 26898569 DOI: 10.1007/s12325-016-0303-z]
68 **Suzuki Y**, Iida M, Ito H, Saida I, Hibi T. Efficacy and safety of two pH-dependent-release mesalamine doses in moderately active ulcerative colitis: a multicenter, randomized, double-blind, parallel-group study. *Intest Res* 2016; **14**: 50-59 [PMID: 26884735 DOI: 10.5217/ir.2016.14.1.50]
69 **Mantzaris GJ**, Sfakianakis M, Archavlis E, Petraki K, Christidou A, Karagiannidis A, Triadaphyllou G. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 1122-1128 [PMID: 15180735 DOI: 10.1111/j.1572-0241.2004.11481.x]
70 **Schreiber S**, Keshavarzian A, Isaacs KL, Schollenberger J, Guzman JP, Orlandi C, Hanauer SB. A randomized, placebo-controlled, phase II study of tetomilast in active ulcerative colitis. *Gastroenterology* 2007; **132**: 76-86 [PMID: 17241861 DOI: 10.1053/j.gastro.2006.11.029]
71 **Travis SP**, Danese S, Kupcinskas L, Alexeeva O, D'Haens G, Gibson PR, Moro L, Jones R, Ballard ED, Masure J, Rossini M, Sandborn WJ. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. *Gut* 2014; **63**: 433-441 [PMID: 23436336 DOI: 10.1136/gutjnl-2012-304258]
72 **Vernia P**, Monteleone G, Grandinetti G, Villotti G, Di Giulio E, Frieri G, Marcheggiano A, Pallone F, Caprilli R, Torsoli A. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. *Dig Dis Sci* 2000; **45**: 976-981 [PMID: 10795763]
73 **Mahmood A**, Melley L, Fitzgerald AJ, Ghosh S, Playford RJ. Trial of trefoil factor 3 enemas, in combination with oral 5-aminosalicylic acid, for the treatment of mild-to-moderate left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2005; **21**: 1357-1364 [PMID: 15932366 DOI: 10.1111/j.1365-2036.2005.02436.x]
74 **Lichtenstein GR**, Deren JJ, Katz S, Lewis JD, Kennedy AR, Ware JH. Bowman-Birk inhibitor concentrate: a novel therapeutic agent for patients with active ulcerative colitis. *Dig Dis Sci* 2008; **53**: 175-180 [PMID: 17551835 DOI: 10.1007/s10620-007-9840-2]
75 **Tursi A**, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, Forti G, Morini S, Hassan C, Pistoia MA, Modeo ME, Rodino' S, D'Amico T, Sebkova L, Sacca' N, Di Giulio E, Luzza F, Imeneo M, Larussa T, Di Rosa S, Annese V, Danese S, Gasbarrini A. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2010; **105**: 2218-2227 [PMID: 20517305 DOI: 10.1038/ajg.2010.218]
76 **Sood A**, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1202-1209, 1209.e1 [PMID: 19631292 DOI: 10.1016/j.cgh.2009.07.016]
77 **Tamaki H**, Nakase H, Inoue S, Kawanami C, Itani T, Ohana M, Kusaka T, Uose S, Hisatsune H, Tojo M, Noda T, Arasawa S, Izuta M, Kubo A, Ogawa C, Matsunaka T, Shibatouge M. Efficacy of probiotic treatment with Bifidobacterium longum 536 for induction of remission in active ulcerative colitis: A randomized, double-blinded, placebo-controlled multicenter trial. *Dig Endosc* 2016; **28**: 67-74 [PMID: 26418574 DOI: 10.1111/den.12553]
78 **Garg SK**, Croft AM, Bager P. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. *Cochrane Database Syst Rev* 2014; **(1)**: CD009400 [PMID: 24442917 DOI: 10.1002/14651858.CD009400.pub2]
79 **Ingram JR**, Thomas GA, Rhodes J, Green JT, Hawkes ND, Swift JL, Srivastava ED, Evans BK, Williams GT, Newcombe RG, Courtney E, Pillai S. A randomized trial of nicotine enemas for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2005; **3**: 1107-1114 [PMID: 16271342]
80 **Lichtenstein GR**, Gordon GL, Zakko S, Murthy U, Sedghi S, Pruitt R, Merchant K, Shaw A, Bortey E, Forbes WP. Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis - a 6-month placebo-controlled trial. *Aliment Pharmacol Ther* 2010; **32**: 990-999 [PMID: 20937044 DOI: 10.1111/j.1365-2036.2010.04438.x]
81 **Lichtenstein GR**, Zakko S, Gordon GL, Murthy U, Sedghi S, Pruitt R, Merchant K, Bortey E, Forbes WP. Mesalazine granules 1.5 g once-daily maintain remission in patients with ulcerative colitis who switch from other 5-ASA formulations: a pooled analysis from two randomised controlled trials. *Aliment Pharmacol Ther* 2012; **36**: 126-134 [PMID: 22617015 DOI: 10.1111/j.1365-2036.2012.05142.x]
82 **Lichtenstein GR**, Gordon GL, Zakko S, Murthy U, Sedghi S, Pruitt R, Barrett AC, Bortey E, Paterson C, Forbes WP. Long-Term Benefit of Mesalamine Granules for Patients Who Achieved Corticosteroid-Induced Ulcerative Colitis Remission. *Dig Dis Sci* 2016; **61**: 221-229 [PMID: 26563167 DOI: 10.1007/s10620-015-3866-7]
83 **Zakko SF**, Gordon GL, Murthy U, Sedghi S, Pruitt R, Barrett AC, Bortey E, Paterson C, Forbes WP, Lichtenstein GR. Once-daily mesalamine granules for maintaining remission of ulcerative colitis: pooled analysis of efficacy, safety, and prognostic factors. *Postgrad Med* 2016; **128**: 273-281 [PMID: 26861051 DOI: 10.1080/00325481.2016.1152876]
84 **Dignass AU**, Bokemeyer B, Adamek H, Mross M, Vinter-Jensen L, Börner N, Silvennoinen J, Tan G, Pool MO, Stijnen T, Dietel P, Klugmann T, Vermeire S, Bhatt A, Veerman H. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 762-769 [PMID: 19375519 DOI: 10.1016/j.cgh.2009.04.004]

P- Reviewer: Gurkan A, Lakatos P, Ribaldone DG
S- Editor: Song XX **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Meta-Analysis

Submit a Manuscript: http://www.f6publishing.com

World J Meta-Anal 2017 August 26; 5(4): 103-123

DOI: 10.13105/wjma.v5.i4.103

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors

Subho Chakrabarti

Subho Chakrabarti, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Author contributions: Chakrabarti S solely contributed to this paper.

Conflict-of-interest statement: No conflicts of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Subho Chakrabarti, MD, FAMS, FRCPsych, Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. subho@pgimer.edu.in
Telephone: +91-172-2756808
Fax: +91-172-2744401

Received: February 28, 2017
Peer-review started: March 2, 2017
First decision: April 18, 2017
Revised: May 31, 2017
Accepted: June 12, 2017
Article in press: June 13, 2017
Published online: August 26, 2017

Abstract

AIM

To conduct a systematic search for all studies examining rates and demographic and illness-related determinants of medication non-adherence in bipolar disorder (BD).

METHODS

A comprehensive literature search was undertaken of six English-language databases to identify published articles on medication non-adherence in BD from inception till December 2016. Any article, either a review or an original-research article was examined for its relevance to the subject. All such articles were manually searched to locate any further articles containing relevant information. Studies were included only if they had adequately described the patient sample, assessment methods and statistical procedures, presented their results systematically and their conclusions were congruent with the results.

RESULTS

The initial search yielded 249 articles on the subject; of these 198 articles were included. Of the 162 original-research studies, 132 had provided information on rates of medication non-adherence in BD. There was a wide variation in rates ranging from universal adherence (100%) to almost universal non-adherence (96%); this discrepancy was more due to methodological differences than true variations in rates. Notwithstanding the significant discrepancies in methodology, based on these 132 studies mean rates of 41.5%-43% and median rates of 40%-41% were obtained for medication non-adherence in BD. Rates of adherence with mood stabilizers were significantly lower than those for antipsychotics, or for medications of all classes. None of the demographic attributes were unequivocally linked to medication non-adherence in BD. Similarly, medication-related variables such as type of medications, doses, treatment regimens and side effects did not demonstrate consistent associations with non-adherence. Among clinical characteristics the presence of comorbid substance use disorder and absence of insight were the only two factors clearly linked to non-adherence in BD.

CONCLUSION

Medication non-adherence is prevalent in about a third

to half of patients with BD. Demographic, illness and treatment related factors do not predict non-adherence with certainty.

Key words: Medications; Demographics; Rates; Non-adherence; Illness characteristics; Treatment variables; Bipolar disorder

Core tip: Based on existing reviews non-adherence is estimated to be present in 25%-42% of patients with bipolar disorder (BD). The present, more comprehensive review comprising of 198 studies found mean rates of 41.5%-43% and median rates of 40%-41% for medication non-adherence in BD. Neither demographic characteristics nor medication-related variables were unequivocally linked to medication non-adherence in BD, while comorbid substance use disorder and absence of insight were the only two clinical factors consistently associated with non-adherence in BD. The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD.

Chakrabarti S. Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors. *World J Meta-Anal* 2017; 5(4): 103-123 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i4/103.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i4.103

INTRODUCTION

Bipolar disorder (BD) is prototypical of all chronic medical conditions with enduring symptoms, residual disability and the need for long-term care[1,2]. Like other such conditions, non-adherence with treatment is very common among patients with BD and associated with a range of adverse consequences such as poor clinical outcomes, functional impairment, impaired quality of life, increased health-service utilization and higher costs of care[2-4].

Several reviews on the subject have estimated non-adherence rates in BD to range from around 8% to 68% with mean rates varying from 25% to 40% across these reviews[5-8]. Despite this wide variation in rates the median rate of non-adherence, which is probably a more true measure of non-adherence, has been fairly stable at 40% to 42% in different reviews. However, it is somewhat surprising that despite there being over 100 studies on treatment non-adherence in BD, most of these reviews have not included more than a handful of studies. Moreover, the majority of reviews are somewhat dated and have not systematically and comprehensively searched the existing literature to identify all possible studies relating to non-adherence in BD. Those that have systematically reviewed the existing literature (*e.g.*, Busby and Sajatovic[3]) appeared to have used very stringent selection criteria limiting the number of studies they have included.

The correlates of non-adherence in BD have been traditionally categorized into patient-related, illness-related, treatment-related and physician-related factors[9-12]. The majority of studies have, however, examined demographic correlates like age, gender, marital status, or clinical features such as age of onset, longitudinal course, symptom-severity, insight and comorbidity, or medication-related variables such as the class of medications, number and doses of medications and side effects associated with treatment[3,13,14]. However, results of these studies have been largely inconsistent, leading to considerable uncertainty regarding which of these factors truly influence non-adherence in BD[8,13]. Consequently, there is little consensus among reviews regarding the clinical, demographic and treatment-related determinants of medication non-adherence in BD. Moreover, similar to the reviews on the rates of non-adherence in BD, reviews examining correlates of non-adherence are based on a limited number of studies.

Given these drawbacks of existing reviews on rates and correlates of medication non-adherence in BD, the present review aimed to conduct a more comprehensive and systematic search for all possible studies of BD, which have investigated these aspects. The principal objective was to estimate rates of medication non-adherence in BD and examine its demographic, illness and medication related correlates based on a much wider selection and a larger number of studies than those that have been included as a part of earlier reviews.

MATERIALS AND METHODS

A comprehensive literature search was undertaken using the following six English-language databases: MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane and Google to identify published articles on medication non-adherence in BD from inception till December 2016. Search terms included BD, bipolar depression or mania used in conjunction with other terms including adherence, compliance, concordance, non-adherence, non-compliance, determinants, predictors, treatment and medication. Any article, either a review or an original research article (based on clinical trials or observational studies) was examined for its relevance to the subject. All such articles were manually searched to locate any further articles, which were judged to be containing information pertaining to the topic. In an effort to identify and include as many studies as possible the initial criteria for selection were broad and inclusive. Any article that had provided information on rates and/or demographic, clinical or treatment correlates of medication non-adherence in BD was included. Articles dealing with other forms of adherence, *e.g.*, appointment adherence or attendance for psychosocial interventions were considered only if they had provided

Table 1 Rates of medication non-adherence in bipolar disorder: Reviews

Ref.	Review based on	Non-adherence rates
Van Putten[20], 1975	7 studies	20%-30% (only lithium)
Jamison and Akiskal[21], 1983	10 studies	33%-50% (only lithium)
Cochran[5], 1986	13 studies from 1966-1986	9%-57% (only lithium)
Goodwin and Jamison[22], 1990	50 studies	18%-53% (only lithium)
Lingam and Scott[6], 2002	3 studies and 1 review	20%-66%, median 41%
Perlick *et al*[7], 2004	25 papers from 1979-2004	23%-68%, median 42%
Colom *et al*[4], 2005	6 studies	20%-64%, mean 25%
Gaudiano *et al*[18], 2008	3 reviews	20%-60%, mean 40%
Basco and Smith[8], 2009	9 studies	8%-64%
Busby and Sajatovic[3], 2010	6 studies	20%-60%
Foster *et al*[23], 2011	7 studies	21%-50%
Leclerc *et al*[12], 2013	27 studies(rates derived from 6 studies)	12%-64%
García *et al*[16], 2016	9 studies	23%-60% (only antipsychotics)

Other reviews have also estimated non-adherence rates to be in the range of 20%-68% with a median rate of 41%-42% in BD including Schou[24] (1988), Guscott and Taylor[25] (1994), Scott[26] (1995), Schou[19] (1997), Berk *et al*[17] (2004), Sajatovic *et al*[27] (2004), Byrne *et al*[28] (2006), Depp and Lebowitz[29] (2007), Depp *et al*[14] (2008), Pompili *et al*[10] (2009), Crowe *et al*[15] (2011) and Rakofsky *et al*[11] (2011). BD: Bipolar disorder.

information on medication adherence. Both quantitative and qualitative studies were included. Final selection, however, also depended on the quality of studies, which was assessed partly based on criteria used in previous reviews[12,15]. Studies were included only if they had adequately described the source and nature of the patient sample, the methods of ascertaining relevant variables and the statistical procedures followed. Additionally, for any study to be incorporated its results should have been presented systematically and the conclusions should have been congruent with the results of the study.

Statistical analysis

Statistical analyses consisted mainly of estimation of mean and median rates. Student's *t* test was used to compare the non-adherence rates among different classes of medications. This was approved by the bio-statistics department of the institution.

RESULTS

The initial search yielded 249 articles on the subject; 43 of these were reviews and 206 were original research articles. Of these 51 articles (7 reviews and 44 original research articles) were excluded. Though these 51 articles did deal with some aspect of treatment adherence in BD the principal reason for excluding them was the lack of information either on rates of medication non-adherence or on demographic, illness or treatment related correlates of non-adherence in BD. Thus, the final list included 198 articles; 36 of these were reviews and 162 were original research articles.

Rates of medication non-adherence in BD

Reviews: Table 1 lists the reviews on rates of non-adherence in BD. The most commonly quoted reviews are the ones by Lingam and Scott[6] and Perlick *et al*[7], both of which have found rates ranging from about 20% to 68% with median rates of about 41% to 42% for non-adherence in BD. Other reviews included in the table also indicate that non-adherence rates vary from 8%-64% with mean rates of 25% to 40% and median rates of 40% to 41% for all classes of medications. Reviews on lithium estimate non-adherence rates to lie between 9% to 57%, while one review found the rates to vary from 23%-60% among patients on antipsychotics[16]. The wide variation in rates (from 8% to 68%) was most likely to be due to differences in methodology adopted by individual studies[4]. Moreover, the number of studies, from which these rates are derived was quite small in most reviews. Only Pompili *et al*[10] have included 104 articles on mood disorders from 1975 to 2009, but the number of studies from which the non-adherence rate for BD was derived was not clear. Despite these disparities and limitations it was evident that about a quarter to half of the patients with BD were fully or partially non-adherent[15,17]. This rate was similar to other chronic medical disorders including psychiatric and physical disorders[1,4,18]. There appeared to be no substantial differences between rates of non-adherence for mood stabilizers (principally lithium carbonate) and those for antipsychotics[4]. Similarly, no differences in rates between older or newer medications were noted. Indeed, studies conducted decades apart have revealed that rates of non-adherence have remained the same over the years despite the availability of many new types of medications[4,6,10,13,19].

Studies: Tables 2-4 list the 132 studies of this review providing an estimate of medication non-adherence in BD. Studies spanned exactly four decades with the first study conducted by Bech *et al*[30] among patients on lithium in 1976. The number of studies with patients on all classes of medications (n = 69) was the highest followed by studies of patients on mood stabilizers (n = 46). There were 15 studies of patients on antipsychotics and only two of patients on antidepressants. The majority of the studies were conducted in Western settings with barely 20 studies from non-Western countries. Not surprisingly, there was a wide variation in rates from universal adherence (100%) to almost universal non-adherence (96%). This was obviously more as a result of methodological differences across studies rather than a true variation in rates. Studies differed in the number of patients included, the duration during which adherence was assessed and the

Table 2 Rates of medication non-adherence in bipolar disorder: Studies of all classes of medications

Ref.	Study	Non-adherence rates
Keck *et al*[47], 1996a	*n* = 101; duration-past month; clinical interview and serum levels	64% fully or partially non-adherent
Keck *et al*[48], 1998	*n* = 134; duration - 12 mo; clinical interview	53% fully or partially non-adherent
Strakowski *et al*[49], 1998	*n* = 109 (83 with BD); duration - 12 mo; clinical interviews	59% fully or partially non-adherent
Weiss *et al*[50], 1998	*n* = 44 with BD and SUD; cross-sectional study; clinical interviews	79% fully or partially non-adherent (35% took medications less than 67% of the time)
Colom *et al*[51], 2000	*n* = 200; duration 2 yr; clinical interviews with patients and relatives and serum levels for mood stabilizers	40% fully or partially non-adherent
Svarstad *et al*[52], 2001	*n* = 67; duration 12 mo; retrospective claims data	33% irregular use
Calabrese *et al*[53], 2000	*n* = 324 with RCBD; duration - 6 mo; clinical interview	34%
Greenhouse *et al*[54], 2000	*n* = 32: duration - 1 wk; self-report	25%
Lam *et al*[55], 2003	*n* = 52; duration - 6 mo; serum levels and self-reports	Serum levels - 7%-22%; self-report - 12%-33%
Calabrese *et al*[56], 2005	*n* = 254 with RCBD; duration - 30 mo; clinical interview	20%-28%
Coletti *et al*[57], 2005	*n* = 38 adolescents; duration - 1 mo; parent reports	66% fully or partially non-adherent
Fleck *et al*[58], 2005	*n* = 50; cross-sectional study; visual analogue scale	52% fully or partially non-adherent
Roy *et al*[33], 2005	*n* = 100 (42 with BD); cross-sectional study; clinical interview	91%
Sajatovic *et al*[46], 2005	*n* = 52; duration - 3 mo; self-reports and DAI-10	12%
Sajatovic *et al*[59], 2006a	*n* = 323; cross-sectional study; clinical interview	36% partially or fully non-adherent
Clatworthy *et al*[36], 2007	*n* = 16; cross-sectional study; self-report-qualitative data	81%
DelBello *et al*[60], 2007	*n* = 71 adolescents; duration 12 mo; clinical interviews	65% fully or partially non-adherent
Johnson *et al*[61], 2007	*n* = 469; cross-sectional study; web-based survey; self-report	30%
Montoya *et al*[62], 2007	*n* = 312; cross-sectional study; clinical interviews	40% fully or partially non-adherent
Sajatovic *et al*[63], 2007c	*n* = 205 with RCBD; duration - 6 mo; clinical interview	20%
Shabani and Eftekhar[64], 2007	n = 22; duration - 17 mo; clinical interview	38%
Strakowski *et al*[65], 2007	*n* = 96 (United States) and 46 (Taiwan); duration – 1 yr (Taiwan) to 8 yr (United States); clinical interviews	21% (Taiwan) - 41% (United States) followed up without full treatment adherence
Baldessarini *et al*[66], 2008a	*n* = 429; duration -last 10 d; self-report	34% (psychiatrists rated 6%-18% as non-adherent)
Copeland *et al*[67], 2008	*n* = 435; duration - past 4 d; self-report of missed dose and self-report-MMAS	27% on missed dose and 46% on MMAS
Sajatovic *et al*[40], 2008	*n* = 302; duration - 3 yr; clinical interview	12%
Zeber *et al*[68], 2008	*n* = 435; cross-sectional study; self-report and MMAS	Overall 30%; 23% (self-report) to 46% (MMAS)
Taj *et al*[69], 2008	*n* = 23; cross-sectional study; clinical interviews	26%
Azorin *et al*[70], 2009	*n* = 766; duration 2 yr; clinical interview	At baseline - 44% (pure mania) - 50% (mixed mania); at 2 yr - 8% (pure mania) - 16% (mixed mania)
Clatworthy *et al*[71], 2009	*n* = 223; cross-sectional study; self-report - MARS	30%
Martinez-Aran *et al*[74], 2009	*n* = 103; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	41%
Mazza *et al*[75], 2009	*n* = 131 (94 with BD); duration - 12 mo; serum levels and relatives' reports	22%
Sajatovic *et al*[72], 2009a	*n* = 140; cross-sectional study; self-report-TRQ	19%
Sajatovic *et al*[39], 2009b	*n* = 164; duration - 12 mo; self-report	19%
Sharifi *et al*[73], 2009	*n* = 76; duration - 8 wk; clinical interview	29%
Bates *et al*[76], 2010	*n* = 1052; cross-sectional study; web-based survey; self-report -MMAS	49.50%
Devulapalli *et al*[77], 2010	*n* = 140; duration - past month; self-report	19%
González-Pinto *et al*[78], 2010	*n* = 1831; duration - 24 mo; clinical interview	23%
Hou *et al*[79], 2010	*n* = 35; cross-sectional study; self-report -MMAS	54%
Jónsdóttir *et al*[80], 2010	*n* = 280 (114 with BD); duration- past week; self-report, MARS-5, serum levels	Serum levels - 34%; self-report - 16%
Gutiérrez-Rojas *et al*[81], 2010	*n* = 108; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	17%
Perlis *et al*[82], 2010	*n* = 3640; duration - 12 mo; self-reports and clinical interviews	54% fully or partially non-adherent (24% non-adherent on 20% or more study visits)
Cely *et al*[83], 2011	*n* = 124; cross-sectional study; self-report-MMAS	30%
Cruz *et al*[35], 2011	*n* = 17 elderly subjects; cross-sectional study; self-report-MMAS	88%
Hong *et al*[84], 2011	*n* =1341; duration - 21 mo; clinical interview	24%
Savaş *et al*[85], 2011	*n* = 147; duration - 12 mo; self-report	27%
Sajatovic *et al*[86], 2011b	*n*= 140; duration - 1 mo; TRQ	18%
Mahmood *et al*[87], 2011	*n* = 40; duration - 1 mo; clinical interview	62%
Barraco *et al*[88], 2012	*n* = 650; duration - 12 mo; self-report-SMAQ and DAI-10	60% at baseline; 31% at 9 mo; 33% at 12 mo
Eker and Harkin[89], 2012	*n* = 71; duration - 6 wk; ANT, self-report-MARS, TOS	60%-61% at baseline; 13%-76% at 6wk
Murru *et al*[90], 2012	*n* = 76 schizoaffective disorder-bipolar type; duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	41%
Miasso *et al*[91], 2012	*n* = 101; cross-sectional study; self-report-MMAS	63%
Sajatovic *et al*[92], 2012	*n* = 43; duration - 6 mo; self-report-TRQ, MMAS; Pill counts	TRQ - 48%-51% at baseline; 21%-25% at 6 mo - Pill counts - 58% at baseline

Vieta *et al*[93], 2012	*n* = 2448 psychiatrists; duration-3 mo; questionnaire survey	57% patients rated fully or partially non-adherent
Sharma *et al*[94], 2012	*n* = 127; cross-sectional study; self-report	40%
Belzeaux *et al*[95], 2013	*n* = 382; cross-sectional study; self-report - MARS and clinical interviews	25%
de Souza *et al*[96], 2013	*n* = 36 cross-sectional study; self-report - MMAS	78%
Gibson *et al*[97], 2013	*n* = 24; cross-sectional study; self-report	50%-77% fully or partially non adherent
Hibdye *et al*[98], 2013	*n* = 410; cross-sectional study; self-report - MMAS	51%
Jónsdóttir *et al*[99], 2013	*n* = 255 (109 with BD); duration - past week; self-report, serum levels	42% fully or partially non-adherent
Murru *et al*[100], 2013	schizoaffective disorder-bipolar type (*n* = 75) and BD (*n* = 151); duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	BD - 33%; schizoaffective disorder-bipolar type - 44%
Arvilommi *et al*[101], 2014	*n* = 168; duration 18 mo; clinical interview	> 50% non-adherent
Kassis *et al*[102], 2014	*n* = 76; cross-sectional study; questionnaire based	55%
Ghaffari-Nejad *et al*[103], 2015	*n* = 123; duration-6 mo; DAI = 10	61% fully or partially non-adherent
Hajda *et al*[104], 2015	*n* = 33; cross-sectional study; self-report - DAI-10	58%
Ibrahim *et al*[105], 2015	*n* = 358 (177 with BD); cross-sectional study; self-report-MMAS-8	46%
Levin *et al*[106], 2015	*n* = 65; duration-3 mo; self-report-TRQ	32%-59% at baseline; 10%-40% at 3 mo
Mert *et al*[107], 2015	*n* = 68; duration - 6 mo; self-reports; relatives' reports, medical records	45%
Azadforouz *et al*[108], 2016	*n* = 47; duration-6 mo; clinical interview	36%
Mousavi *et al*[32], 2016	*n* = 73 with BD and psychotic symptoms; cross-sectional study; clinical interviews	96%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance rating scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

techniques used to assess adherence. The majority of studies had sample sizes ranging from 100 to 500 patients (*n* = 51; 39%); but about a third had included 50 to 100 patients (*n* = 37; 28%), while 20% of the studies (*n* = 26) had less than 50 patients. Most studies were conducted over the period of 1 mo to 1 year (*n* = 56; 42%), but cross-sectional studies were also very common (*n* = 37; 28%), whereas about a quarter of the studies (*n* = 33; 25%) had extended beyond 1 year, often up to several years in some studies of mood stabilizers. About a third of the studies had used multiple measures to estimate adherence (*n* = 38; 29%), even as studies based only on self-reports (*n* = 37; 28%), or only on clinical interviews (*n* = 34; 26%) were equally common. Fifteen studies (11%) were based on analysis of claims data.

Rates were computed using the highest rate of non-adherence where multiple rates were mentioned and rates at baseline for longitudinal studies. Despite significant discrepancies in methodology across studies, when rates were computed from all the 132 studies the mean rate of non-adherence turned out to be 41.5% (41.52 ± 19.56) and the median rate was 40%. Rates of non-adherence were between 25% to 50% in 65 studies (49%) and greater than 50% in 42 of the 132 studies (32%).

Most studies with very high rates of non-adherence (> 80%) were either part of randomized-controlled trials[31], or had been conducted among inpatients or mental hospital populations[32-34], or were studies with qualitative designs[35,36]. Patient numbers were generally small in these studies. Similarly, studies with very low rates of non-adherence (< 20%) were either from specialized lithium clinics[37,38], or were derived from randomized-controlled trials[39-42]. Others studies with very low rates had relied either exclusively on patient reports to estimate non-adherence[43-45], or had used qualitative designs with small patient samples[46]. In contrast, the average rate of non-adherence in the 18 studies with large and more representative samples (naturalistic studies with > 500 patients) was higher at 49% (48.81 ± 14.13). The mean rate of adherence in the studies which had lasted more than 1 year was lower at 36% (36.36 ± 12.90). However, even after excluding the 21 studies with very high or very low rates, the mean rate of non-adherence in BD increased only to 43% (42.81 ± 14.66) and the median rate to 41%.

The average rate of non-adherence derived from studies where patients received all classes of medication was 45% (44.62 ± 19.61) with a median of 41%; after excluding 11 studies with very high or very low rates the mean rate was still 45% (44.94 ± 14.95), while the median rate increased to 43.5%. The mean rate of non-adherence among patients on mood stabilizers was 34% (34.16 ± 18.35) and the median rate was 31.5%. After excluding 9 studies with very high or very low rates the mean increased to 38% (37.82 ± 13.24) and the median to 34%. Rates derived from studies of antipsychotic medications were the highest with a mean of 51% (50.87 ± 15.87) and a median of 48%. After excluding one study with a very high rate the mean dropped to 48% (48.43 ± 13.44) and the median to 47%. Therefore, rates of non-adherence derived

Table 3 Rates of medication non-adherence in bipolar disorder: Studies of mood stabilizers

Ref.	Study	Non-adherence rates
Bech *et al*[30], 1976	*n* = 76 on lithium (49 with BD); duration - 2 yr; retrospective case record data and serum levels	24%
Jamison *et al*[9], 1979	*n* = 47 on lithium; cross-sectional study; self-report and psychiatrists' estimations	Patients - 47% non-adherent; psychiatrists - 35% non-adherent
Connelly *et al*[109], 1982	*n* = 48 on lithium; duration - 9 mo; serum levels and > 75% clinic attendance	25%
Connelly *et al*[110], 1984	*n* = 75 on lithium; duration - 6 mo; serum levels and > 75% clinic attendance	33%
Cochran[31], 1984	*n* = 28 on lithium; duration - 6 mo; self-report; case notes; clinical interview and serum levels	93% had major or minor non-adherence
Danion *et al*[111], 1987	*n* = 73 on lithium (36 with BD); duration - 2 yr; retrospective psychiatric assessments and serum levels	56% - subjective 19%; objective 56%
Aagaard *et al*[112], 1988 Maarbjerg *et al*[113], 1988	*n* =133 on lithium (47 with BD); duration - 6 mo; clinical interview	23%
Cochran and Gitlin[114], 1988	*n* = 48 on lithium (43 with BD); cross-sectional study; patient questionnaires	46% fully or partially non-adherent
Vestergaard and Schou[115], 1988	*n* = 480 on lithium (187 with BD); duration - 7 yr; medical records based on serum levels and clinical interviews	50% in first 6 mo; 25% per year during the first 2 yr; 10% per year after 4-5 yr
Lenzi *et al*[116], 1989	*n* = 67 women on lithium or carbamazepine; duration - 8 mo; self-report and serum levels	45%
Nilsson and Axelsson[117], 1989	*n* = 64 with mood disorders on lithium; duration - 7 yr; serum levels and medical records	25%
Aagaard and Vestergaard[118], 1990	*n* = 133 on lithium (61 with BD); duration - 2 yr; clinical interview	42%
Courtney *et al*[38], 1995	*n* = 15 on lithium; cross-sectional study; serum levels	0%
Lee *et al*[119], 1992	*n* = 50 on lithium; duration 12 mo; self-report; clinical interview; serum levels	30%
Berghöfer *et al*[120], 1996	*n* = 86 (55 with BD) on lithium; retrospective follow-up over a mean of 8.9 yr based on clinical interview and serum levels	24%
Keck *et al*[121], 1997	*n* = 140 on mood stabilizers; duration - 12 mo; clinical interview	51% fully or partially non-adherent
Maj *et al*[122], 1998	*n* = 402 on lithium; duration - 5 yr; clinical interview and serum levels	28%
Schumann *et al*[123], 1999	*n* = 75 (31 with BD) on lithium; duration-6 yr; retrospective medical records based on interviews and serum levels	55%
Wong *et al*[124], 1999	*n* = 80 with mood disorders on lithium (60 with BD cross-sectional study; self-reports; clinical interviews; serum levels	27.50%
Licht *et al*[125], 2001	*n* = 148 on mood stabilizers (132 on lithium): duration 24 mo; retrospective analysis of treatment charts, serum levels and clinical interviews	20%
McCleod and Sharp[37], 2001	*n* = 30 on lithium; cross-sectional study; self-reports, clinical ratings and serum levels	0%
Svarstad *et al*[52], 2001	*n* = 53 on lithium; duration 12 mo; retrospective claims data	26% irregular use
Scott[126], 2002	*n* = 98 (85 with BD) on mood stabilizers; cross-sectional study; self-reports-ROMI and TRQ	30% partially adherent
Scott and Pope[127], 2002a	*n* = 98 on mood stabilizers (78 with BD); duration- 24 mo; TRQ and serum levels	partial non-adherence - 47% over 2 yr; 32%over past month; 27% over past week; full non-adherence - 20% over 2 yr
Scott and Pope[128], 2002b	*n* = 98 on mood stabilizers (78 with BD); duration - 18 mo; TRQ and serum levels	TRQ - 32% partial adherence; serum levels - 36%
Dharmendra and Eagles[43], 2003	*n* = 411; duration - 3 yr; retrospective study based on self-reports and serum levels	15%
Pope and Scott[129], 2003	*n* = 72 on lithium (61 with BD); duration - 2 yr; self-report-RSM	46%
Bowden *et al*[130], 2005	*n* = 372 on lithium or valproate; duration - 52 wk; clinical interview	54%-75% premature discontinuations
Calabrese *et al*[56], 2005	*n* = 254 with RCBD on lithium or valproate; duration 20 mo; clinical interviews and serum levels	10%-28%
Patel *et al*[131], 2005	*n* = 32 adolescents on mood stabilizers; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 47%
Salloum *et al*[41], 2005	*n* = 59 with BD and alcohol dependence on lithium or lithium and valproate; duration - 24 wk; self-report and serum levels	13%-14%
Gonzalez-Pinto *et al*[132], 2006	*n* = 72; duration - 10 yr; clinical interviews and serum levels	22%
Drotar *et al*[133], 2007	*n* = 107 adolescents; on lithium and valproate; duration - 20 wk; serum levels, pill counts, self/parent report and clinical interview	16%-34% (average 17%) non-adherent on various measures
Kessing *et al*[134], 2007	*n* = 14277 on lithium; duration 6 yr; nation-wide register and pharmacy data	25% stopped lithium within 45 d
Manwani *et al*[135], 2007	*n* = 115 on mood stabilizers; duration - 10 mo; clinical interview	34% lifetime adherence in those with SUD 17% in those without SUD
Rosa *et al*[136], 2007	*n* = 106; cross-sectional study; self-report-MARS and serum and RBC levels	14% (based on levels) 33% (based on MARS)

Sajatovic *et al*[137], 2007a	*n* = 44637 on mood stabilizers; duration - 3 mo or more; retrospective claims data-MPR based	46% partially or fully non-adherent; took medications less than 50%-80% of the time
Baldessarini *et al*[138], 2008b	*n* = 2197 on single mood stabilizers; duration - 12 mo; national health plan claims data; MPR based	72% took medications less than 80% of the time
Vega *et al*[139], 2009	*n* = 72 on lithium; duration - 5 yr; clinical interviews and serum levels	8% (women)-39% (men)
Bauer *et al*[44], 2010	*n* = 312 on mood stabilizers; duration - 6 mo; self-report	11% partially or fully non-adherent
Sajatovic *et al*[86], 2011b	*n* = 136; duration - 1 mo; self-report-TRQ	18% in the past week or month
Scott *et al*[140], 2012	*n* = 81 on mood stabilizers; cross-sectional study; self-report -TRQ	26% - past month
Bauer *et al*[45], 2013a	*n* = 206 on mood stabilizers; duration 100 d; self-report	14% mean percent of days of missing doses
Arvilommi *et al*[101], 2014	*n* = 168 on mood stabilizers; duration 18 mo; clinical interview	40% fully or partially non-adherent
Sylvia *et al*[42], 2014	*n* = 283 on lithium; duration - 6 mo; self-report-TRQ	4.5%-7% reported missing at least 30% of their medications in the past week
Col *et al*[141], 2014	*n* = 78 on mood stabilizers; cross-sectional study; self-report-MARS	42%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

Table 4 Rates of medication non-adherence in bipolar disorder: studies of antipsychotics and antidepressants

Ref.	Study	Non-adherence rates
Antipsychotics		
Keck *et al*[142], 1996b	*n* = 77 on antipsychotics; duration - 6 mo; clinical interview	32%
Svarstad *et al*[52], 2001	*n* = 56 on antipsychotics; duration 12 mo; retrospective claims data	23% irregular use
Patel *et al*[131], 2005	*n* = 32 adolescents on antipsychotics; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 44%
Sajatovic *et al*[143], 2006b	*n* = 32993 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	48% partially or fully non-adherent; took antipsychotics less than 50%-80% of the time
Sajatovic *et al*[144], 2007b	*n* = 73964 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	39% among those > 60 yr and 50% in those < 60 yr took antipsychotics less than 50%-80% of the time
Hassan and Lage[145], 2009	*n* = 1973 on antipsychotics; duration - 12 mo; retrospective claims based data-MPR based	56% took antipsychotics less than 50% of the time and 73% less than 75% of the time
Lage and Hassan[146], 2009	*n* = 7,769 on antipsychotics; duration- 12 mo; retrospective claims data-MPR based	62% took antipsychotics less than 50% of the time and 79% less than 75% of the time
Lang *et al*[147], 2011	*n* = 9410 on antipsychotics; duration - 12 mo; retrospective claims data-MPR based	60% took antipsychotics less than 80% of the time
Rascati *et al*[148], 2011	*n* = 2446 on SGAs; duration - 18 mo; retrospective claims data-MPR based	42% took antipsychotics less than 80% of the time
Berger *et al*[34], 2012	*n* = 84 on SGAs: Duration-6 mo; retrospective claims data-MPR and CMG based	85% took antipsychotics less than 80% of times (50% according to CMGs)
Stephenson *et al*[149], 2012	*n* = 162 patients with BD on SGAs and 153 physicians; duration - 12 mo; retrospective claims data and physician survey	57% with low-moderate adherence; physicians overestimated adherence in 67% patients
Montes *et al*[150], 2013	*n* = 303; cross-sectional study; self-reports- DAI-10 and MMAS, CRS	69%
Kutzelnigg *et al*[151], 2014	Olanzapine alone or in combination with mood stabilizers; n = 891 at entry; 657 at 2 yr; clinical interview	33% at baseline; 20% at 2 yr
Arvilommi *et al*[101], 2014	*n* = 168 on SGAs; duration 18 mo; clinical interview	46% fully or partially non-adherent
Sajatovic *et al*[152], 2016	*n* = 1114 on lurasidone; duration- 27 mo; retrospective claims data-MPR based	67%took lurasidone less than 80% of the time
Antidepressants		
Svarstad *et al*[52], 2001	*n* = 22 on antidepressants; duration 12 mo; retrospective claims data	27% irregular use
Bauer *et al*[153], 2013b	*n* = 144 on antidepressants; duration - daily for 100 d; self-report	19% (missing/changing doses) to 41% (drug holidays)

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CMG: Cumulative medication gaps; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

from studies of mood stabilizers were significantly lower than rates among patients on all three classes of medications, or among those on antipsychotics ($P < 0.05$ or $P < 0.01$), while there were no differences between rates among patients on all classes of medications and those on antipsychotics.

Demographic correlates of medication non-adherence in BD

Reviews: The evidence that socio-demographic characte-

ristics of patients influence their medication taking behaviour is largely inconsistent among patients with BD[154]. Accordingly, most reviews of the subject have concluded that there is no strong support for anassociation between demographic variables and medication non-adherence in BD[4,6,8,17,22,26]. Though certain demographic characteristics of patients have been associated with non-adherence in some studies of BD, such associations have not been found in others. There is also some discrepancy between reviews about which demographic parameters might be associated with non-adherence in BD; some reviews have concluded that younger age[12,14,22,27,29] and male gender[11,15,22,27] are more likely to be associated with non-adherence,while others have found that being single or living alone[2,3,7,11,15], being less educated[3,12,14,15,17] or belonging to ethnic minorities[3,10,11] were among the most consistent risk factors for non-adherence in BD.

Studies: Table 5 list the studies, which have examined the demographic correlates of medication non-adherence in BD. In keeping with the reviews on demographic variables influencing non-adherence in BD, these studies also demonstrate that there is very little to support the notion that demographic attributes of patients have a significant influence on their medication taking behaviour. Firstly, a large number of studies (*n* = 29) have been unable to find an association between medication non-adherence and any demographic variable. Among individual variables young age has often been cited as a correlate of non-adherence in BD[12,14,22,27,29], but the number of studies which have found an association with young age (*n* = 22) was almost similar to those that have been unable to demonstrate such an association (*n* = 19). Studies that have found associations with male gender, single marital status, lower levels of education, unemployment or low socioeconomic status or income were fewer than those unable to find such as association, or those that have found the obverse association. There appeared to be some link with a general "social disadvantage" factor including ethnic minority status, homelessness and dysfunctional family atmospheres, but the aggregate number of studies finding a positive association (*n* = 25) was not substantially different from those finding no such association (*n* = 16).

Clinical correlates of medication non-adherence in BD

Reviews: The relationship between several clinical features and medication non-adherence has been examined in a number of studies of BD. Clinical characteristics, which have been explored have included overall severity of the illness, severity of manic, depressive and psychotic symptoms as well as variables such as age of onset, duration of illness or episode-length, episode polarity and subtypes of BD. The impact of factors such as cognitive impairment, lack of insight and comorbidity on treatment-adherence has also been examined. The overall conclusion of reviews on the subject is that non-adherence in BD is a complex phenomenon and the association with clinical variables is ambiguous. Not only are the results of such associations inconsistent and equivocal, but the causal direction of any positive associations, *i.e.*, whether the clinical variable in question led to non-adherence or vice-versa, is often unclear[4,8,15,28]. Overall severity of illness in terms of number of episodes, number of hospitalizations or suicidality has been found to be associated with non-adherence in a few studies, but this is not a consistent finding[2-4,6,7,12]. Similarly, severity of manic symptoms have been found to impact adherence negatively quite commonly, though not all studies have found this association[2-4,6,15,22,23]. The influence of depressive or mixed symptoms and psychotic symptoms have not been examined often enough to reach any firm conclusions about their effect on non-adherence in BD[2-4,12,18,27,28]. It is postulated that cognitive impairment may adversely affect adherence in BD, but the evidence for this appears to be derived from only a few studies[2-4,8,14]. The evidence linking other clinical variables such as age of onset, duration of illness or episode-length, polarity and bipolar subtypes with non-adherence in BD is limited[3,8,12]. The adverse effects of comorbid personality disorders and anxiety disorders on adherence in BD has also found mention, though the evidence seems limited to a few studies[2-4,8,15]. In contrast, almost every review on the subject has concurred in finding that the presence of comorbid substance use disorders (SUD) has a significant negative impact on adherence in BD[6,8,12,14,23]. Current rather than past substance abuse is more likely to be associated with non-adherence in BD[3,163-166]. Finally, lack of insight and denial of illness has been consistently found to be associated with non-adherence in BD, though studies finding an association between insight and adherence in BD are still few in number[2,11,12,167,168].

Studies: Table 6 include studies examining the clinical correlates of medication non-adherence in BD. As is evident from the two tables there was no evidence of a consistent association with non-adherence for the majority of the clinical variables examined. Certain studies did find positive associations between non-adherence and clinical variables such as early age of onset, shorter durations of illness, greater number of hospitalizations, higher number of total, manic, depressive or mixed episodes, rapid cycling course, bipolar *vs* unipolar disorders and bipolar Ⅰ *vs* bipolar Ⅱ disorders, polarity of episodes, overall severity of illness and severity of depressive, mixed and psychotic symptoms, family history of psychiatric disorders, co-morbid personality disorders and comorbid anxiety or hyperkinetic disorders. However, the number of studies, which were unable to find such associations either equalled or outnumbered those with positive associations. The exceptions to this trend were associations of more severe manic symptoms (21 studies with positive associations and 16 without) and cognitive impairment

Table 5 Studies of demographic correlates of medication non-adherence in bipolar disorder

Demographic correlates	Studies with positive associations	Studies without positive associations	Others
Any demographic variable		Jamison *et al*[9], 1979; Aagaard and Vestergaard[118], 1990; Maj *et al*[122], 1998; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Scott [126], 2002; Scott and Pope[127], 2002a; Kliendienst and Griel[156], 2004; Revicki *et al*[155], 2005; Yen *et al*[157], 2005; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Taj *et al*[69], 2008; Sajatovic *et al*[72], 2009a; Clatworthy *et al*[71], 2009; Martinez-Aran *et al*[74], 2009; Sharifi *et al*[73], 2009; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Murru *et al*[90], 2012; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Jónsdóttir *et al*[99], 2013; Col *et al*[141], 2014; Sylvia *et al*[42], 2014; Ghaffari-Nejad *et al*[103], 2015; Levin *et al*[106], 2015; Mert *et al*[107], 2015	
Young age	Frank *et al*[158], 1985; Kleindienst and Greil[156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Copeland *et al*[67], 2008; Mazza *et al*[75], 2009; Bates *et al*[76], 2010; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Lang *et al*[147], 2011; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Hajda *et al*[104], 2015; Levin *et al*[106], 2015; Mousavi *et al*[32], 2016	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Coletti *et al*[57], 2005; Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Rosa *et al*[136], 2007; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007 c; Zeber *et al*[68], 2008; Savaş *et al*[85], 2011; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Murru *et al*[100], 2013; Kutzelnigg *et al*[151], 2014; Azadforouz *et al*[108], 2016	Both young and old age- Kessing *et al*[134], 2007 Old age - Lehman and Rabins[159], 2006; Rascati *et al*[148], 2011; Sharma *et al*[94], 2012
Male gender	Frank *et al*[158], 1985; Aagaard *et al*[112], 1988; Vestergaard and Schou[115], 1988; McCleod and Sharp[37], 2001; Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Vega *et al*[139], 2009; Savaş *et al*[85], 2011; Mousavi *et al*[32], 2016	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Licht *et al*[125], 2001; Gonzalez-Pinto *et al*[132], 2006; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Mazza *et al*[75], 2009; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Rascati *et al*[148], 2011; Sajatovic *et al*[86], 2011b; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Hibdye *et al*[98], 2013; Montes *et al*[150], 2013; Kutzelnigg *et al*[151], 2014; Hajda *et al*[104], 2015; Azadforouz *et al*[108], 2016	Female gender - Keck *et al*[142], 1996b; Keck *et al*[121], 1997; Jose *et al*[161], 2003; Sajatovic *et al*[46], 2005; Kessing *et al*[134], 2007; Copeland *et al*[67], 2008; Zeber *et al*[68], 2008; Bates *et al*[76], 2010; Belzeaux *et al*[95], 2013; Murru *et al*[100], 2013
Not married	Frank *et al*[158], 1985; Aagaard *et al*[112], 1988; Connelly *et al*[109], 1982; Connelly *et al*[110], 1984; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[137], 2007a; Vega *et al*[139], 2009; Perlis *et al*[82],2010; Sajatovic *et al*[162], 2011a; Hajda *et al*[104], 2015	Lenzi *et al*[116], 1989; Licht *et al*[125], 2001; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Zeber *et al*[68], 2008; Mazza *et al*[75], 2009; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Murru *et al*[100], 2013; Azadforouz *et al*[108], 2016; Mousavi *et al*[32], 2016	
Poorly educated	Frank *et al*[158], 1985; Connelly *et al*[110], 1984; Danion *et al*[111], 1987; Johnson *et al*[61], 2007; Sajatovic et al[63], 2007c; Bates et al[76], 2010; Savaş et al[85], 2011; Hajda *et al*[104], 2015; Mousavi *et al*[32], 2016	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Gonzalez-Pinto *et al*[132], 2006; Zeber *et al*[68], 2008; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013	
Unemployment	Aagaard *et al*[112], 1988; Perlis *et al*[82], 2010; Hibdye *et al*[98], 2013; Montes *et al*[150], 2013	Sajatovic *et al*[63], 2007c; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Murru *et al*[100], 2013; Hajda *et al*[104], 2015	
Low socioeconomic status or income	DelBello *et al*[60], 2007; Perlis *et al*[82], 2010	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Aagaard and Vestergaard[118], 1990; Johnson *et al*[61], 2007; Zeber *et al*[68], 2008; Savaş *et al*[85], 2011; Sharma *et al*[94], 2012	
Ethnic minority status	Keck *et al*[121], 1997; Strakowski *et al*[49], 1998; Kleindienst and Greil[156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Johnson *et al*[61], 2007; Copeland *et al*[67], 2008; Zeber *et al*[68], 2008; Perlis *et al*[82], 2010; Rascati *et al*[148], 2011; Sajatovic *et al*[162] 2011a; Sajatovic *et al*[92], 2012	Fleck *et al*[58], 2005; Patel *et al*[131], 2005; Drotar *et al*[133], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bates *et al*[76], 2010; Hibdye *et al*[98], 2013; Kutzelnigg *et al*[151], 2014	
Living alone/homeless	Lenzi *et al*[116], 1989; Kleindienst and Greil [156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b	Zeber *et al*[68], 2008; Montes *et al*[150], 2013; Murru *et al*[100], 2013; Hajda *et al*[104], 2015	

Family factors: Dysfunction, poor social support, negative attitudes	Aagaard *et al*[112], 1988; Drotar *et al*[133], 2007; Cely *et al*[83], 2011; Sajatovic *et al*[162], 2011a; Scott *et al*[140], 2012; Sharma *et al*[94], 2012; Col *et al*[141], 2014	Sajatovic *et al*[72], 2009a; Sajatovic *et al*[86], 2011b

BD: Bipolar disorder.

Table 6 Studies of clinical correlates of medication non-adherence in bipolar disorder

Clinical correlates	Studies with positive associations	Studies without positive associations	Others
Early age of onset	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Drotar *et al*[133], 2007 Perlis *et al*[82], 2010; Barraco *et al*[88], 2012	Colom *et al*[51], 2000; Scott and Pope[127], 2002a; Sajatovic *et al*[59], 2006a; Gonzalez-Pinto *et al*[132], 2006; González-Pinto *et al*[78], 2010; Murru *et al*[90], 2012; Levin *et al*[106], 2015; Azadforouz *et al*[108], 2016	Later onset - Col *et al*[141], 2014 Hajda *et al*[104], 2015
Short durations of illness	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; González-Pinto *et al*[78], 2010; Belzeaux *et al*[95], 2013; Azadforouz *et al*[108], 2016	Danion *et al*[111], 1987; Aagaard and Vestergaard[118], 1990; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Scott and Pope[127], 2002a; Jose *et al*[161], 2003; Gonzalez-Pinto *et al*[132], 2006; Taj *et al*[69], 2008; Sajatovic *et al*[72], 2009a; Hou *et al*[79], 2010; Savaş *et al*[85], 2011; Murru *et al*[90], 2012; Sharma *et al*[94], 2012; Montes *et al*[150], 2013; Col *et al*[141], 2014	Longer durations - Coletti *et al*[57], 2005; Belzeaux *et al*[95], 2013
Greater number of hospitalizations	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Aagaard and Vestergaard[118], 1990; Colom *et al*[51], 2000; Svarstad *et al*[52], 2001; Scott[126], 2002; Scott and Pope[128], 2002b; Gonzalez-Pinto *et al*[132], 2006; Baldessarini *et al*[138], 2008b; Gianfrancesco *et al*[168], 2008; Hassan and Lage[145], 2009; Lage and Hassan[146], 2009; Martinez-Aran *et al*[74],2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Hong *et al*[84], 2011; Lang *et al*[147], 2011; Savaş *et al*[85], 2011; Scott *et al*[140], 2012; Kutzelnigg *et al*[151], 2014	Johnson and McFarland[169], 1996; Keck *et al*[47], 1996a; Schumann *et al*[123], 1999; Jose *et al*[161], 2003; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[40], 2008; Clatworthy *et al*[71], 2009; Sharifi *et al*[73], 2009; Bauer *et al*[44], 2010; González-Pinto *et al*[78], 2010; Hou *et al*[79], 2010; Murru *et al*[90], 2012; Sharma *et al*[94], 2012; Montes *et al*[150], 2013; Hajda *et al*[104], 2015; Azadforouz *et al*[108], 2016	Fewer hospitalizations - Sajatovic *et al*[137], 2007a; Col *et al*[141], 2014
Higher total number of episodes	Danion *et al*[111], 1987; Gonzalez-Pinto *et al*[132], 2006; Vega *et al*[139], 2009; Gutiérrez-Rojas *et al*[81], 2010; Murru *et al*[100], 2013	Lenzi *et al*[116], 1989; Keck *et al*[47], 1996a; Jose *et al*[161], 2003; Martinez-Aran *et al*[74], 2009; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Col *et al*[141], 2014	Fewer episodes - Colom *et al*[51], 2000
Higher number of manic episodes	Gonzalez-Pinto *et al*[132], 2006; Vega *et al*[139], 2009; Murru *et al*[100], 2013	Johnson *et al*[61], 2007; Zeber *et al*[68], 2008; Martinez-Aran *et al*[74], 2009; Bates *et al*[76], 2010; Gutiérrez-Rojas *et al*[81], 2010; Murru *et al*[90], 2012; Col *et al*[141], 2014	Fewer hypomanic episodes - Colom *et al*[51], 2000
Higher number of depressive episodes	Danion *et al*[111], 1987; Gutiérrez-Rojas *et al*[81], 2010; Col *et al*[141], 2014	Gonzalez-Pinto *et al*[132], 2006; Johnson *et al*[61], 2007; Martinez-Aran *et al*[74], 2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; Murru *et al*[90], 2012	Fewer depressive episodes - Colom *et al*[51], 2000
Higher number of mixed episodes/ rapid cycling	Calabrese *et al*[56], 2005; Perlis *et al*[82], 2010	Maarbjerg *et al*[113], 1988; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[40], 2008; Martinez-Aran *et al*[74], 2009; Murru *et al*[90], 2012; Murru *et al*[100], 2013	
BD *vs* UP disorders	Arvilommi *et al*[101], 2014; Mert *et al*[107], 2015	Connelly *et al*[109], 1982; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Aagaard and Vestergaard[118], 1990; Schumann *et al*[123], 1999; McCleod and Sharp[37], 2001; Scott and Pope[127], 2002a; Taj *et al*[69], 2008; Ghaffari-Nejad *et al*[103], 2015	
BP Ⅰ *vs* BP Ⅱ	Martinez-Aran *et al*[74], 2009; Mazza *et al*[75], 2009	Jamison *et al*[9], 1979; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bauer *et al*[44], 2010; Perlis *et al*[82], 2010; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014	Higher in BP Ⅱ - Murru *et al*[100], 2013
Polarity of episodes	Gutiérrez-Rojas *et al*[81], 2010; Montes *et al*[150], 2013	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Sajatovic *et al*[59], 2006a; Col *et al*[141], 2014	
Overall severity of illness	Baldessarini *et al*[66], 2008a; Sajatovic *et al*[72], 2009a; Sajatovic *et al*[40], 2008; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Kutzelnigg *et al*[151], 2014; Hajda *et al*[104], 2015	Danion *et al*[111], 1987; Nilsson and Axelsson[117], 1989; Sajatovic *et al*[63], 2007 c; Sajatovic *et al*[72], 2009a; Mazza *et al*[75], 2009; Hong *et al*[84], 2011; Sajatovic *et al*[86], 2011b; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	
Manic symptoms	Van Putten[20], 1975; Connelly *et al*[109], 1982; Keck *et al*[47], 1996a; Keck *et al*[142], 1996b; Lenzi *et al*[116], 1989; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Bowden *et al*[130], 2005; Gonzalez-Pinto *et al*[132], 2006; Gaudiano and Miller[173], 2006; Baldessarini *et al*[66], 2008a; Copeland *et al*[67], 2008; Bauer *et al*[44], 2010; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010; Hong *et al*[84], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014; Levin *et al*[106], 2015	Colom *et al*[51], 2000; Rosa *et al*[136], 2007; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[63], 2007 c; Sajatovic *et al*[40], 2008; Clatworthy *et al*[71], 2009; Mazza *et al*[75],2009; Martinez-Aran *et al*[74], 2009; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Ghaffari-Nejad *et al*[103], 2015; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	

Depressive symptoms	Bowden *et al*[130], 2005; Gaudiano and Miller[173], 2006; Johnson *et al*[61], 2007; Martinez-Aran *et al*[74], 2009; Bates *et al*[76], 2010; Bauer *et al*[44], 2010; Perlis *et al*[82], 2010; Hong *et al*[84], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Arvilommi *et al*[101], 2014; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Murru *et al*[100], 2013; Gibson *et al*[97], 2013; Levin *et al*[106], 2015; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	Colom *et al*[51], 2000; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[63], 2007c; Rosa *et al*[136], 2007; Sajatovic *et al*[40], 2008; Sajatovic *et al*[72], 2009a; Clatworthy *et al*[71], 2009; González-Pinto *et al*[78], 2010; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Hibdye *et al*[98], 2013; Sylvia *et al*[42], 2014; Ghaffari-Nejad *et al*[103], 2015	Better adherence with depression - Lenzi *et al*[116], 1989
Mixed symptoms	Bowden *et al*[130], 2005; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010	Licht *et al*[125], 2001; Azorin *et al*[70], 2009; Hibdye *et al*[98], 2013; Ghaffari-Nejad *et al*[103], 2015	
Psychotic symptoms	Miklowitz *et al*[174], 1992; Maj *et al*[122], 1998; Yen *et al*[157], 2005; Martinez-Aran *et al*[74], 2009; González-Pinto *et al*[78], 2010; Murru *et al*[90], 2012; Murru *et al*[100], 2013; Levin *et al*[106], 2015; Sajatovic *et al*[152], 2016	Danion *et al*[111], 1987; Aagaard and Vestergaard[118], 1990; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Sajatovic *et al*[72], 2009a; Perlis *et al*[82], 2010; Belzeaux *et al*[95], 2013; Azadforouz *et al*[108], 2016	
Cognitive impairment	Danion *et al*[111], 1987; Jose *et al*[161], 2003; Baldessarini *et al*[66], 2008a; Depp *et al*[175], 2008; Martinez-Aran *et al*[74], 2009; Eker and Harkin[89], 2012	Maarbjerg *et al*[113], 1988; Jónsdóttir *et al*[99], 2013	
Familial psychiatric disorder	Drotar *et al*[133], 2007	Colom *et al*[51], 2000; Gonzalez-Pinto *et al*[132], 2006; Martinez-Aran *et al*[74], 2009; Savas *et al*[85], 2011; Murru *et al*[90], 2012; Col *et al*[141], 2014; Hajda *et al*[104], 2015	
Poor insight	Schumann *et al*[123], 1999; Greenhouse *et al*[54], 2000; Jose *et al*[161], 2003; Fleck *et al*[58], 2005; Yen *et al*[157], 2005; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Copeland *et al*[67], 2008; Sajatovic *et al*[72], 2009a; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Sajatovic *et al*[86], 2011b; Savaş *et al*[85], 2011; Vieta *et al*[93], 2012; Kutzelnigg *et al*[151], 2014; Mert *et al*[107], 2015; Novick *et al*[176], 2015	Wong *et al*[124], 1999; Jonsdottir *et al*[99], 2013	
Comorbid SUD	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Weiss *et al*[50], 1998; Aagaard and Vestergaard[118], 1990; Keck *et al*[121], 1997; Keck *et al*[48], 1998; Strakowski *et al*[49], 1998; Licht *et al*[125], 2001; Fleck *et al*[58], 2005; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; DelBello *et al*[60], 2007; Manwani *et al*[135], 2007; Baldessarini *et al*[138], 2008b; Copeland *et al*[67], 2008; Darling *et al*[177], 2008; Zeber *et al*[68], 2008; Sajatovic *et al*[72], 2009a; van Rossum *et al*[178], 2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010; Cely *et al*[83], 2011; Hong *et al*[84], 2011; Lang *et al*[147], 2011; Sajatovic *et al*[162], 2011a; Teter *et al*[179], 2011; Barraco *et al*[88], 2012; Vieta *et al*[93], 2012; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Montes *et al*[150], 2013; Arvilommi *et al*[101], 2014	Nilsson and Axelsson[117],1989; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Sajatovic *et al*[63], 2007c; Sajatovic *et al*[40], 2008; Mazza *et al*[75], 2009; Sharifi *et al*[73],2009; Rascati *et al*[148], 2011; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Sharma *et al*[94], 2012 Murru *et al*[100], 2013; Col *et al*[141], 2014; Kutzelnigg *et al*[151], 2014; Sylvia *et al*[42], 2014; Mert *et al*[107], 2015; Ghaffari-Nejad *et al*[103], 2015	
Comorbid personality disorders	Danion *et al*[111], 1987; Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Colom *et al*[51], 2000; Murru *et al*[100], 2013; Arvilommi *et al*[101], 2014	Aagaard and Vestergaard[118], 1990; Schumann *et al*[123],1999; Kliendienst and Griel[156], 2004; Mazza *et al*[75], 2009; Murru *et al*[90], 2012; Kutzelnigg *et al*[151], 2014	
Comorbid anxiety disorders or ADHD	DelBello *et al*[60], 2007; Baldessarini *et al*[66], 2008a; Taj *et al*[69], 2008; Perlis *et al*[82], 2010; Arvilommi *et al*[101], 2014	Sajatovic *et al*[59], 2006a; Sajatovic *et al*[144], 2007b; Drotar *et al*[133], 2007; Sajatovic *et al*[40], 2008; Cely *et al*[83], 2011; Rascati *et al*[148], 2011; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Kutzelnigg *et al*[151], 2014; Sylvia *et al*[42], 2014	Better adherence with comorbid anxiety disorder - Baldessarini *et al*[138], 2008b

ADHD: Attention deficit hyperactivity disorder; BD: Bipolar disorder; SUD: Substance use disorders; UP: Unipolar disorder.

(6 studies with positive associations and 2 without) with non-adherence in BD. Finally, a clear association with medication non-adherence was evident only in the case of two clinical parameters, that is comorbid SUD and lack of insight, where the number of studies with positive associations far outnumbered the studies without such associations.

Treatment-related correlates of medication non-adherence in BD

Reviews: Several studies have examined the effects of different classes of medications, the duration of treatment with medications, intensity of treatment, *i.e.*, the number of medications and their doses, and the complexity of medication regimens on medication non-adherence in BD. Reviews of literature have found occasional differences in adherence between some of the second-generation antipsychotics (SGAs), but rates of non-adherence with mood stabilizers and antipsychotics have been largely similar[2]. No differences have been found between older and newer medications; indeed rates of non-adherence in BD

appear to have remained unchanged over the years despite the availability of newer medications[4,6,15,17,19]. The influence of duration of treatment has been uncertain with non-adherence occurring both in the early as well as late phases of treatment[4,15,17,22]. The number of medications, higher doses and more complicated medication regimes are all expected to increase the risk of non-adherence, but even this has not been reported consistently[4,10,15,17,18]. The bulk of studies, however, have been about side effects of treatment. Reviews of non-adherence in BD have found a link with side effects among certain studies[3,12,21,23], both for side effects associated with mood stabilizers and antipsychotics[16,181-184]. However, many others have concluded that side effects are often not among the major reasons for non-adherence[2,4,6,14,17]. The latter reviews also agree in finding that it is the fear or concern about side effects that frequently leads to non-adherence, rather than the actual presence of side effects. Inadequate efficacy of medication-treatment has also been proposed as a risk factor for non-adherence in BD, with efficacy in reducing depressive symptoms being particularly important from the patient's perspective[3,12,23].

Studies: Similar to the results of studies examining demographic and illness related correlates of non-adherence in BD, studies examining medication-related variables have also yielded few unequivocal associations. Thus, drug classes, the duration of treatment, greater number or higher doses of medications and more complex medication regimens were associated with non-adherence only in a few studies, while the number of studies without such associations were either equal in number or far greater. A positive association with the presence of side effects was reported in 35 studies; more than a-third of these involved lithium. However, 26 studies did not find a positive association and 17 studies found that fear of side effects than their actual presence had a greater impact on non-adherence. Efficacy of treatment had a positive association with non-adherence, but only among 12 studies. These results are depicted in Table 7.

DISCUSSION

Given its chronic, relapsing and remitting nature as well as attendant disability, comorbidity and frequent negative therapeutic outcomes, BD is expected to be characterized by high rates of treatment non-adherence. The existing reviews on medication non-adherence in BD (included in Table 1) support this notion by finding that about 40% to 50% of the patients with BD do not take their medications properly. However most of these reviews are several years old and have included about 25 studies or less in most instances. The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. It also used somewhat broader selection criteria in an effort to include data from as many studies as possible. This resulted in a much larger list of close to 200 reviews and studies on the subject; 132 of these studies were used derive rates of medication non-adherence in BD. The obvious disadvantage of casting such a broad net was the substantial difference in methodologies across the studies that formed a part of this review. Though this significant heterogeneity did not allow a meta-analysis of the data, the results probably reflected a truer and a more up to date picture of medication non-adherence in BD than some of the existing reviews, simply because of the large number of studies included and the longer period covered by this review.

The results of the review yielded some notable findings about the rate of medication non-adherence in BD. To start with there was a wide variation in rates of non-adherence ranging from 0%-96%, which was more a result of the methodological disparities across studies. Nevertheless, the entire group of studies yielded an average rate of 41.5% and a median rate of 40% for medication non-adherence. When the rates were computed excluding outliers with very high or low rates, the mean rate of non-adherence rose to 43% and the median rate to 41%. These rates were remarkably similar to those found in the majority of previously published reviews (Table 1), which have found rates of non-adherence in BD to vary from 8% to 68% with a mean rate of about 40% and a median rate of 41%-42%. Rates of non-adherence were the highest for studies of patients on treatment with antipsychotics (mean 48%-51%; median 47%-48%) followed by studies of patients on all three classes of medications (mean 45%; median 41%-43.5%). Surprisingly, the rates were significantly lower in studies of patients being treated with mood stabilizers (mean 34%-38%; median 31.5%-34%). It was not exactly clear why this was so, particularly since other studies and reviews have not found rates to differ among different classes of medications[2,5,6,21,22].

However, studies of mood stabilizers mainly included lithium; a significant proportion of them (41%) had been conducted in the 1970s to 1990s; and, the number of studies with very low rates was higher than the other two groups. In direct contrast, studies of patients on antipsychotics were conducted more recently and were based mostly on claims data, which also meant that the sample sizes were very large in many of these studies.

Thus, the overall conclusion from the group of studies included in this review is that between a third to about half of the patients with BD are medication non-adherent. However, there is reason to treat these rates with caution because of the considerable divergence in study designs. Differences in rates of non-adherence across studies usually arise principally from the definition of adherence used, the nature and size of the patient sample included, the setting in which the study is conducted, the duration of assessment and

Table 7 Studies of treatment correlates of medication non-adherence in bipolar disorder

Treatment correlates	Studies with positive associations	Studies without positive associations	Others
Differences between mood stabilizers	Weiss *et al*[50], 1998; Revicki *et al*[155], 2005; Baldessarini *et al*[138], 2008b; Sajatovic *et al*[137], 2007a	Baldessarini *et al*[66], 2008a; Darling *et al*[177], 2008; Bauer *et al*[45], 2013a; Col *et al*[141], 2014	
Differences between antipsychotics	Gianfrancesco *et al*[184], 2005; Gianfrancesco *et al*[185], 2006; Hassan *et al*[186], 2007; Sajatovic *et al*[144], 2007b; Rascati *et al*[148], 2011; Ibrahim *et al*[105], 2015	Patel *et al*[131], 2005; Sajatovic *et al*[143], 2006b; Baldessarini *et al*[66], 2008a	
Differences between mood stabilizers and antipsychotics or antidepressants	González-Pinto *et al*[78], 2010; Lang *et al*[147], 2011; Murru *et al*[100], 2013; Arvilommi *et al*[101], 2014; Ibrahim *et al*[105], 2015	Danion *et al*[111], 1987; Keck *et al*[48], 1998; Colom *et al*[51], 2000; Patel *et al*[131], 2005; Sajatovic *et al*[143], 2006b; Baldessarini *et al*[66], 2008a; Azorin *et al*[70], 2009; Clatworthy *et al*[71], 2009; Gianfrancesco *et al*[187], 2009; Martinez-Aran *et al*[74], 2009; Mazza *et al*[75], 2009; Bates *et al*[76], 2010; Cely *et al*[83], 2011; Savaş *et al*[85], 2011; Murru *et al*[90], 2012; Bauer *et al*[153], 2013b; Hibdye *et al*[98], 2013; Arvilommi *et al*[101], 2014; Hajda *et al*[104], 2015	
Shorter duration of treatment	Johnson and McFarland[169], 1996; Colom *et al*[51], 2000; Lang *et al*[147], 2011; Azadforouz *et al*[108], 2016	Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Darling *et al*[177], 2008; Sharma *et al*[94], 2012; Hibdye *et al*[98], 2013; Col *et al*[141], 2014	Longer durations - Jamison *et al*[9], 1979; Scott and Pope[127], 2002a Kessing *et al*[134], 2007 Sharifi *et al*[73], 2009; Short and long durations - Kutzelnigg *et al*[151], 2014
Greater number of medications	Keck *et al*[47], 1996a; Revicki *et al*[155], 2005; Baldessarini *et al*[138], 2008b; Gianfrancesco *et al*[187], 2009; Bates *et al*[76], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Cruz *et al*[35], 2011; Rascati *et al*[148], 2011; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Ibrahim *et al*[105], 2015	Colom *et al*[51], 2000; Licht *et al*[125], 2001; Rosa *et al*[136], 2007; Baldessarini *et al*[66], 2008a; Darling *et al*[177], 2008; Depp *et al*[175], 2008; Taj *et al*[69], 2008; Martinez-Aran *et al*[74], 2009; Bauer *et al*[44], 2010; Sajatovic *et al*[86], 2011b; Savaş *et al*[85],2011; Miasso *et al*[91], 2012; Sharma *et al*[94], 2012; Col *et al*[141], 2014; Ghaffari-Nejad *et al*[103], 2015	Less intensive treatment - Johnson and McFarland[169], 1996; Keck *et al*[121], 1997; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[40], 2008
Higher doses of medications	McCleod and Sharp[37], 2001; Gianfrancesco *et al*[185], 2006	Baldessarini *et al*[66], 2008a; Col *et al*[141], 2014; Hajda *et al*[104], 2015	Lower doses of medications - Mazza *et al*[75], 2009; Bauer *et al*[44], 2010
Complex medication regimens	Baldessarini *et al*[138], 2008b; Sajatovic *et al*[72], 2009a; Hibdye *et al*[98], 2013; Ibrahim *et al*[105], 2015	Keck *et al*[48], 1998; Baldessarini *et al*[66], 2008a; Miasso *et al*[91], 2012; Col *et al*[141], 2014	
Side effects	Bech *et al*[30], 1976; Vestergaard and Amdisen[188], 1983; Maarbjerg *et al*[113], 1988; Gitlin *et al*[189], 1989; Nilsson and Axelsson[117], 1989; Aagaard and Vestergaard[118], 1990; Maj *et al*[122], 1998; Weiss *et al*[50], 1998; Licht *et al*[125], 2001; Kliendienst and Griel[156], 2004; Lewis[190], 2005; Bowden *et al*[130], 2005; Calabrese *et al*[56], 2005; Fleck *et al*[58], 2005; Revicki *et al*[155], 2005; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bates *et al*[76], 2010; Mączka *et al*[191], 2010; Wang and Henning[192], 2010; Cely *et al*[83], 2011; Cruz *et al*[35], 2011; Miasso *et al*[193], 2011; Sajatovic *et al*[162], 2011a; Teter *et al*[1179], 2011; Eker and Harkin[89], 2012; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Gibson *et al*[97], 2013; Arvilommi *et al*[101], 2014; Sylvia *et al*[42], 2014; Ibrahim *et al*[105], 2015; Mert *et al*[107], 2015 Ghaffari-Nejad *et al*[103], 2015	Van Putten[20], 1975; Jamison *et al*[9], 1979; Connelly *et al*[109], 1982; Danion *et al*[111], 1987; Lenzi *et al*[116], 1989; Johnson and McFarland[169], 1996; Schuman *et al*[123], 1999; Scott[196], 2000; Scott[126], 2002; Scott and Pope[127], 2002a; Morselli *et al*[194], 2003; Morselli *et al*[195], 2004; Pope and Scott[129], 2003; Roy *et al*[33], 2005; Sajatovic *et al*[143], 2006b; Drotar *et al*[133],2007; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Perlis *et al*[82], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Vieta *et al*[93], 2012; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Kutzelnigg *et al*[151], 2014; Col *et al*[141], 2014	Fear of side effects - Cochran *et al*[31], 1984; Schumann *et al*[123], 1999; Scott[196], 2000; Scott[126], 2002; Scott and Pope[127], 2002a; Scott and Tacchi[197], 2002; Morselli *et al*[194], 2003; Morselli *et al*[195], 2004; Fleck *et al*[58], 2005; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Clatworthy *et al*[36], 2007; Clatworthy *et al*[71], 2009; Sajatovic *et al*[198], 2009c; Kriegshauser *et al*[199], 2010; Cruz *et al*[35], 2011; Sajatovic *et al*[162], 2011a
Efficacy	Bech *et al*[30], 1976; Jamison *et al*[9], 1979; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Lewis[190], 2005; Fleck *et al*[58], 2005; Patel *et al*[131], 2005; Gaudiano and Miller[173], 2006; Drotar *et al*[133], 2007; Johnson *et al*[61], 2007; Sajatovic *et al*[198], 2009c; Cely *et al*[83], 2011		

BD: Bipolar disorder. References in Tables 2-4 and text (No. 155-199).

the way non-adherence is estimated[4,15,18,80]. Larger studies with more representative samples and longer durations may be more likely to yield more accurate rates of non-adherence. In this review, about half of

the studies had less than 100 patients (48%) while studies with 100-500 patients formed a significant proportion of the total number of studies (39%) Studies with large and more representative samples (naturalistic studies with > 500 patients) were fewer (14%) but the mean rate of 49% obtained from them was higher than the mean rate of 41.5%-43% obtained for the entire group. Studies with longer durations (> 1-10 years) formed 25% of the sample. However, the mean rate of non-adherence (36%) among studies with longer durations was lower than the average rate of 41.5%-43% of the entire group. This was possibly due to fact that the bulk of studies with long durations involved mood stabilizers, a group in which mean rates of non-adherence (34%-38%) were lower than that for other medication classes. Different types of subjective and objective methods are often used to estimate adherence. In the absence of a "gold standard" the use of more than one method is recommended as the next best alternative[2,6,12,14,27]. In this review the majority of studies (54%) had used either self-reports or clinical interviews to estimate adherence; a smaller proportion (11%) used claims data. The low proportion of studies using multiple measures of adherence (29%) could thus cast some doubts on the rates of non-adherence obtained in this review.

A major problem of research in the area of determinants of non-adherence in BD has been the exclusive focus on demographic, illness and treatment related predictors of non-adherence[3,6,13,15,127]. This has been largely driven by the traditional medical model and compliance-based approaches to the problem of non-adherence in BD. As demonstrated in this review, studies examining demographic, illness and treatment related variables (numbering close to 160) far exceeded those that focused on patient-related factors such as attitudes and beliefs about medications, relationship with the clinician, knowledge about the illness and the influence of the wider socio-cultural environment on medication taking in BD. Social and cultural factors are of potential importance and likely to play a major role in determining treatment-adherence in BD[154]. However, despite the large number of studies and the long list of variables examined, the search to identify demographic, illness and treatment related factors associated with non-adherence in BD has yielded little of note. This review found that none of the demographic attributes of patients such as age, gender, marital status, education, employment, income or social disadvantage were consistently linked to medication non-adherence in BD. Among clinical characteristics the presence of comorbid SUD and the absence of insight were the only two factors consisted associated with non-adherence with BD. The severity of manic symptoms appeared to show some association with non-adherence among studies of BD included in this review, as did cognitive impairment in a few studies. Given that about half or more of the patients with BD might have a comorbid SUD, the usefulness of this determinant has been questioned[8]. Lack of insight is expected to adversely affect adherence more so among patients in acute symptomatic phases of mania. However, the role of insight is less certain in other phases such as depression or in the inter-episodic period. Moreover, lack of insight is only one among several influences on non-adherence in BD; therefore, the presence of adequate insight by itself may not be enough to ensure adherence. In accordance with several previous reviews[2,4,6,10,15] medication-related variables such as the types of medications, duration of treatment, greater number of medications, higher doses and complexity of treatment regimens did not demonstrate consistent associations with non-adherence among studies of BD included in this review. Earlier reviews of non-adherence in BD have found a link with side effects of medications[3,12,21,23]. A positive association with the presence of side effects was reported in 35 studies of this review; more than a-third of these involved lithium. At the same time almost an equal number of studies did not find a positive association and many found that fear of side effects than their actual presence had a greater impact on non-adherence. This indicates that side effects are often not among the major reasons for non-adherence in BD and that fear or concern about side effects (an attitudinal variable) may be the more important determinant[2,4,6,17,167].

There could be several reasons for the unequivocal findings regarding clinical and socio-demographic determinants of non-adherence in BD. The simplified and dichotomous approach to examining the association between these parameters and non-adherence in BD has usually ignored the complex relationship between several such variables. For example, the link with manic symptoms could well be related to the lack of insight or cognitive impairment during episodes rather than the severity of symptoms. Moreover, the pathways through which demographic and illness or medication related variables influence could include subjective factors such as attitudes, knowledge or other socio-environmental influences. Therefore, though some of these factors such as comorbid SUD or lack of insight may identify patient groups at higher risk for non-adherence, they cannot identify which of the patients from these high risk groups will go on to develop non-adherence.

Despite being based on a comprehensive search and a much larger number of studies than earlier reviews, the findings of this review were not without their limitations. Many reviews on the management of BD, which mention the problem of non-adherence in passing have not been included. In all likelihood the number of studies on medication non-adherence in BD is larger than the current list of studies, because some studies especially those publications not in English were probably missed. The relative lack of studies from non-Western countries was also a handicap. However, the principal shortcoming was the difficulty of drawing reliable conclusions from studies with such widely disparate methodologies. Nevertheless, it was quite evident that the rate of medication non-

adherence in BD was quite high and no different from other chronic psychiatric or medical disorders. The failure of demographic, illness and treatment related factors to predict non-adherence was also not entirely unexpected. However, this emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Research over the last two decades or so has consistently endorsed the significance of several such factors including patients' attitudes and beliefs about medications, their treatment alliance with the health-care provider, their knowledge and causal beliefs about the illness, the influence of the family, and the role of stigma and treatment-access in determining non-adherence in BD[200]. A patient-centred approach to non-adherence in BD is also in consonance with the current theoretical perspectives on medication-taking behaviour and the emphasis on combining pharmacological and psychosocial strategies to enhance adherence in BD[201]. Therefore, future research which combines some of more consistent clinical and demographic correlates with patient-centred determinants is likely to predict non-adherence in BD with a greater degree of accuracy. Such an approach may also lead to a better understanding of this complex phenomenon and suggest more effective ways to deal with the continuing challenge of medication non-adherence in BD.

COMMENTS

Background

Previously published reviews on medication non-adherence in bipolar disorder (BD) have estimated rates to vary from around 8% to 68%, with mean rates ranging from 25% to 40% and median rates from 40% to 42%. However, these most of these reviews are based on a relatively small number of studies, are somewhat dated and have not comprehensively searched the existing literature. Given these drawbacks, the present review aimed to conduct a more comprehensive and systematic search for all studies estimating rates of medication non-adherence in BD and/or providing information on demographic, illness and medication related determinants of non-adherence.

Research frontiers

Treatment non-adherence in BD has attracted a lot of research attention lately because not only is it common in BD, but it also has a number of negative effects on outcome, and enhancing adherence has proved to be challenging.

Innovations and breakthroughs

The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. This resulted in a much larger list of close to 200 reviews and studies on the subject. Nevertheless, the results endorsed the consensus in existing literature that medication non-adherence is present in a third to about half of the patients with BD. There is also little consensus among earlier reviews regarding the association of clinical, demographic and treatment-related variables with medication non-adherence in BD. The present review clearly demonstrated that demographic and medication-related factors have little influence on medication non-adherence in BD, while among clinical factors only comorbid substance use disorder and absence of insight were clearly linked to non-adherence in BD.

Applications

The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Therefore, future research should also focus on patient-centred determinants of medication non-adherence in BD and adherence interventions should emphasize the role of these factors.

Terminology

Adherence has been defined as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".

Peer-review

The manuscript is well organized and written, the used methodology is rigorous and the conclusions are coherent with the main findings.

REFERENCES

1 **Sabate E**. Adherence to long term therapies: evidence for action. Geneva: World Health Organization, 2003
2 **Berk L**, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, Berk M. Enhancing medication adherence in patients with bipolar disorder. *Hum Psychopharmacol* 2010; **25**: 1-16 [PMID: 20041478 DOI: 10.1002/hup.1081]
3 **Busby KK**, Sajatovic M. REVIEW: Patient, treatment, and systems-level factors in bipolar disorder nonadherence: A summary of the literature. *CNS Neurosci Ther* 2010; **16**: 308-315 [PMID: 21050421 DOI: 10.1111/j.1755-5949.2010.00191.x]
4 **Colom F**, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. *Bipolar Disord* 2005; **7** Suppl 5: 24-31 [PMID: 16225557 DOI: 10.1111/j.1399-5618.2005.00248]
5 **Cochran SD**. Compliance with lithium regimens in the outpatient treatment of bipolar affective disorders. *J Compliance Health Care* 1986; **1**: 153-170
6 **Lingam R**, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand* 2002; **105**: 164-172 [PMID: 11939969 DOI: 10.1034/j.1600-0447.2002.1r084]
7 **Perlick DA**, Rosenheck RA, Kaczynski R, Kozma L. Medication non-adherence in bipolar disorder: a patient-centered review of research findings. *Clin Approaches Bipolar Disord* 2004; **3**: 56-64
8 **Basco MR**, Smith J. Faulty decision-making: impact on treatment adherence in bipolar disorder. *Primary Psychiatry* 2009; **16**: 53-58
9 **Jamison KR**, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium: relationship to compliance. *Arch Gen Psychiatry* 1979; **36**: 866-869 [PMID: 454105 DOI: 10.1001/archpsyc.1979.01780080040011]
10 **Pompili M**, Serafini G, Del Casale A, Rigucci S, Innamorati M, Girardi P, Tatarelli R, Lester D. Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Rev Neurother* 2009; **9**: 985-1004 [PMID: 19589049 DOI: 10.1586/ern.09.62]
11 **Rakofsky JJ**, Levy ST, Dunlop BW. Conceptualizing Treatment Nonadherence in Patients with Bipolar Disorder and PTSD. *CNS Spectr* 2011; **16**: 11-20 [PMID: 24725297 DOI: 10.1017/S1092852912000119]
12 **Leclerc E**, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. *J Affect Disord* 2013; **149**: 247-252 [PMID: 23489403 DOI: 10.1016/j.jad.2013.01.036]
13 **Scott J**. Cognitive and behavioural approaches to medication adherence. *Adv Psychiatr Treat* 1999; **5**: 338-345 [DOI: 10.1192/apt.5.5.338]
14 **Depp CA**, Moore DJ, Patterson TL, Lebowitz BD, Jeste DV. Psychosocial interventions and medication adherence in bipolar disorder. *Dialogues Clin Neurosci* 2008; **10**: 239-250 [PMID: 18689293]
15 **Crowe M**, Wilson L, Inder M. Patients' reports of the factors influencing medication adherence in bipolar disorder - an integrative review of the literature. *Int J Nurs Stud* 2011; **48**: 894-903 [PMID: 21481391 DOI: 10.1016/j.ijnurstu.2011.03.008]
16 **García S**, Martínez-Cengotitabengoa M, López-Zurbano S, Zorrilla I, López P, Vieta E, González-Pinto A. Adherence to Antipsychotic

Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review. *J Clin Psychopharmacol* 2016; **36**: 355-371 [PMID: 27307187 DOI: 10.1097/JCP.0000000000000523]
17 **Berk M**, Berk L, Castle D. A collaborative approach to the treatment alliance in bipolar disorder. *Bipolar Disord* 2004; **6**: 504-518 [PMID: 15541066 DOI: 10.1111/j.1399-5618.2004.00154]
18 **Gaudiano BA**, Weinstock LM, Miller IW. Improving treatment adherence in bipolar disorder: a review of current psychosocial treatment efficacy and recommendations for future treatment development. *Behav Modif* 2008; **32**: 267-301 [PMID: 18391049 DOI: 10.1177/0145445507309023]
19 **Schou M**. The combat of non-compliance during prophylactic lithium treatment. *Acta Psychiatr Scand* 1997; **95**: 361-363 [PMID: 9197898 DOI: 10.1111/j.1600-0447.1997.tb09646]
20 **Van Putten T**. Why do patients with manic-depressive illness stop their lithium? *Compr Psychiatry* 1975; **16**: 179-183 [PMID: 1120419 DOI: 10.1016/0010-440X(75)90064-4]
21 **Jamison KR**, Akiskal HS. Medication compliance in patients with bipolar disorder. *Psychiatr Clin North Am* 1983; **6**: 175-192 [PMID: 6889171]
22 **Goodwin F**, Jamison JK. Manic depressive illness. New York: Oxford University Press, 1990
23 **Foster A**, Sheehan L, Johns L. Promoting treatment adherence in patients with bipolar disorder. *Current Psychiatry* 2011: **10**: 45-52
24 **Schou M**. No help from lithium? About patients who might have been but were not helped by prophylactic lithium treatment. *Compr Psychiatry* 1988; **29**: 83-90 [PMID: 3370972 DOI: 10.1016/0010-440X(88)90001-6]
25 **Guscott R**, Taylor L. Lithium prophylaxis in recurrent affective illness. Efficacy, effectiveness and efficiency. *Br J Psychiatry* 1994; **164**: 741-746 [PMID: 7952980 DOI: 10.1192/bjp.164.6.741]
26 **Scott J**. Psychotherapy for bipolar disorder. *Br J Psychiatry* 1995; **167**: 581-588 [PMID: 8564312 DOI: 10.1192/bjp.167.5.581]
27 **Sajatovic M**, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disorder. *Psychiatr Serv* 2004; **55**: 264-269 [PMID: 15001726 DOI: 10.1176/appi.ps.55.3.264]
28 **Byrne N**, Regan C, Livingston G. Adherence to treatment in mood disorders. *Curr Opin Psychiatry* 2006; **19**: 44-49 [PMID: 16612178 DOI: 10.1097/01.yco.0000191501.54034.7c]
29 **Depp CA**, Lebowitz BD. Enhancing medication adherence: in older adults with bipolar disorder. *Psychiatry* (Edgmont) 2007; **4**: 22-32 [PMID: 20711333]
30 **Bech P**, Vendsborg PB, Rafaelsen OJ. Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine. *Acta Psychiatr Scand* 1976; **53**: 70-81 [PMID: 1251757 DOI: 10.1111/j.1600-0447.1976.tb00060.x]
31 **Cochran SD**. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *J Consult Clin Psychol* 1984; **52**: 873-878 [PMID: 6501672 DOI: 10.1037/0022-006X.52.5.873]
32 **Mousavi MEZ**, Mohammadkhani P, Pourshahbaz A, Samiei, M, Rigi Kooteh R. Nonadherence: effective factors in bipolar disorder with previous rehospitalization. *JPCP* 2016; **4**: 255-262 [DOI: 10.18869/acadpub.jpcp.4.4.255]
33 **Roy R**, Jahan M, Kumari S, Chakraborty PK. Reasons for drug non-compliance of psychiatric patients: a centre based study. *JIAAP* 2005; **31**: 24-28
34 **Berger A**, Edelsberg J, Sanders KN, Alvir JM, Mychaskiw MA, Oster G. Medication adherence and utilization in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: a retrospective cohort study. *BMC Psychiatry* 2012; **12**: 99 [PMID: 22856540 DOI: 10.1186/1471-244X-12-99]
35 **Cruz LP**, Miranda PM, Vedana KG, Miasso AI. Medication therapy: adherence, knowledge and difficulties of elderly people from bipolar disorder. *Rev Lat Am Enfermagem* 2011; **19**: 944-952 [PMID: 21876947]
36 **Clatworthy J**, Bowskill R, Rank T, Parham R, Horne R. Adherence to medication in bipolar disorder: a qualitative study exploring the role of patients' beliefs about the condition and its treatment. *Bipolar Disord* 2007; **9**: 656-664 [PMID: 17845282 DOI: 10.1111/j.1399-5618.2007.00434]
37 **McCleod MS**, Sharp DM. Precursors of compliance with lithium treatment in affective disorders. *Psychiatr Bull* 2001; **25**: 183-186 [DOI: 10.1192/pb.25.5.183]
38 **Courtney ME**, Acomb JA, Lovatt V. A pharmacy-controlled lithium clinic. *Psychiatr Bull* 1995; **19**: 15-17 [DOI: 10.1192/pb.19.1.15]
39 **Sajatovic M**, Davies MA, Ganocy SJ, Bauer MS, Cassidy KA, Hays RW, Safavi R, Blow FC, Calabrese JR. A comparison of the life goals program and treatment as usual for individuals with bipolar disorder. *Psychiatr Serv* 2009; **60**: 1182-1189 [PMID: 19723732 DOI: 10.1176/ps.2009.60.9.1182]
40 **Sajatovic M**, Biswas K, Kilbourne AK, Fenn H, Williford W, Bauer MS. Factors associated with prospective long-term treatment adherence among individuals with bipolar disorder. *Psychiatr Serv* 2008; **59**: 753-759 [PMID: 18586992 DOI: 10.1176/appi.ps.59.7.753]
41 **Salloum IM**, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry* 2005; **62**: 37-45 [PMID: 15630071 DOI: 10.1001/archpsyc.62.1.37]
42 **Sylvia LG**, Reilly-Harrington NA, Leon AC, Kansky CI, Calabrese JR, Bowden CL, Ketter TA, Friedman ES, Iosifescu DV, Thase ME, Ostacher MJ, Keyes M, Rabideau D, Nierenberg AA. Medication adherence in a comparative effectiveness trial for bipolar disorder. *Acta Psychiatr Scand* 2014; **129**: 359-365 [PMID: 24117232 DOI: 10.1111/acps.12202]
43 **Dharmendra MS**, Eagles JM. Factors associated with patients' knowledge of and attitudes towards treatment with lithium. *J Affect Disord* 2003; **75**: 29-33 [PMID: 12781347 DOI: 10.1016/S0165-0327(02)00027-7]
44 **Bauer M**, Glenn T, Grof P, Marsh W, Sagduyu K, Alda M, Murray G, Lewitzka U, Schmid R, Haack S, Whybrow PC. The association between concurrent psychotropic medications and self-reported adherence with taking a mood stabilizer in bipolar disorder. *Hum Psychopharmacol* 2010; **25**: 47-54 [PMID: 20033908 DOI: 10.1002/hup.1077]
45 **Bauer M**, Glenn T, Alda M, Sagduyu K, Marsh W, Grof P, Munoz R, Baethge C, Lewitzka U, Pilhatsch M, Bauer R, Whybrow PC. Regularity in daily mood stabilizer dosage taken by patients with bipolar disorder. *Pharmacopsychiatry* 2013; **46**: 163-168 [PMID: 23797414 DOI: 10.1055/s-0033-1343398]
46 **Sajatovic M**, Davies M, Bauer MS, McBride L, Hays RW, Safavi R, Jenkins J. Attitudes regarding the collaborative practice model and treatment adherence among individuals with bipolar disorder. *Compr Psychiatry* 2005; **46**: 272-277 [PMID: 16175758 DOI: 10.1016/j.comppsych.2004.10.007]
47 **Keck PE Jr**, McElroy SL, Strakowski SM, Stanton SP, Kizer DL, Balistreri TM, Bennett JA, Tugrul KC, West SA. Factors associated with pharmacologic noncompliance in patients with mania. *J Clin Psychiatry* 1996; **57**: 292-297 [PMID: 8666570]
48 **Keck PE Jr**, McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, Bourne ML, Haggard P. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry* 1998; **155**: 646-652 [PMID: 9585716 DOI: 10.1176/ajp.155.5.646]
49 **Strakowski SM**, Keck PE Jr, McElroy SL, West SA, Sax KW, Hawkins JM, Kmetz GF, Upadhyaya VH, Tugrul KC, Bourne ML. Twelve-month outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiatry* 1998; **55**: 49-55 [PMID: 9435760 DOI: 10.1001/archpsyc.55.1.49]
50 **Weiss RD**, Greenfield SF, Najavits LM, Soto JA, Wyner D, Tohen M, Griffin ML. Medication compliance among patients with bipolar disorder and substance use disorder. *J Clin Psychiatry* 1998; **59**: 172-174 [PMID: 9590667 DOI: 10.4088/JCP.v59n0405]
51 **Colom F**, Vieta E, Martínez-Arán A, Reinares M, Benabarre A, Gastó C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry* 2000; **61**: 549-555 [PMID: 10982196 DOI: 10.4088/JCP.v61n0802]
52 **Svarstad BL**, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatr Serv* 2001; **52**: 805-811 [PMID: 11376229 DOI: 10.1176/appi.ps.52.6.805]
53 **Calabrese JR**, Suppes T, Bowden CL, Sachs GS, Swann AC,

McElroy SL, Kusumakar V, Ascher JA, Earl NL, Greene PL, Monaghan ET. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry* 2000; **61**: 841-850 [PMID: 11105737 DOI: 10.4088/JCP.v61n1106]

54 **Greenhouse WJ**, Meyer B, Johnson SL. Coping and medication adherence in bipolar disorder. *J Affect Disord* 2000; **59**: 237-241 [PMID: 10854641 DOI: 10.1016/S0165-0327(99)00152-4]

55 **Lam DH**, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Arch Gen Psychiatry* 2003; **60**: 145-152 [PMID: 12578431 DOI: 10.1001/archpsyc.60.2.145]

56 **Calabrese JR**, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 2005; **162**: 2152-2161 [PMID: 16263857 DOI: 10.1176/appi.ajp.162.11.2152]

57 **Coletti DJ**, Leigh E, Gallelli KA, Kafantaris V. Patterns of adherence to treatment in adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 2005; **15**: 913-917 [PMID: 16379511 DOI: 10.1089/cap.2005.15.913]

58 **Fleck DE**, Keck PE Jr, Corey KB, Strakowski SM. Factors associated with medication adherence in African American and white patients with bipolar disorder. *J Clin Psychiatry* 2005; **66**: 646-652 [PMID: 15889954 DOI: 10.4088/JCP.v66n0517]

59 **Sajatovic M**, Bauer MS, Kilbourne AM, Vertrees JE, Williford W. Self-reported medication treatment adherence among veterans with bipolar disorder. *Psychiatr Serv* 2006; **57**: 56-62 [PMID: 16399963 DOI: 10.1176/appi.ps.57.1.56]

60 **DelBello MP**, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry* 2007; **164**: 582-590 [PMID: 17403971 DOI: 10.1176/ajp.2007.164.4.582]

61 **Johnson FR**, Ozdemir S, Manjunath R, Hauber AB, Burch SP, Thompson TR. Factors that affect adherence to bipolar disorder treatments: a stated-preference approach. *Med Care* 2007; **45**: 545-552 [PMID: 17515782 DOI: 10.1097/MLR.0b013e318040ad90]

62 **Montoya A**, Pérez Sánchez Toledo J, Gilaberte I, González-Pinto A, Haro JM, Vieta E, Tohen M. Patterns of drug treatment for manic episode in the clinical practice. Outcomes of the Spanish sample in the EMBLEM Study. *Actas Esp Psiquiatr* 2007; **35**: 315-322 [PMID: 17885823]

63 **Sajatovic M**, Elhaj O, Youngstrom EA, Bilali SR, Rapport DJ, Ganocy SJ, Calabrese JR. Treatment adherence in individuals with rapid cycling bipolar disorder: results from a clinical-trial setting. *J Clin Psychopharmacol* 2007; **27**: 412-414 [PMID: 17632236 DOI: 10.1097/01.jcp.0000280310.50871.ff]

64 **Shabani A**, Eftekhar M. Non-compliance after first episode of manic or mixed mood state: a 17-months follow-up. *IJPBS* 2007; **1**: 46-49

65 **Strakowski SM**, Tsai SY, Delbello MP, Chen CC, Fleck DE, Adler CM, Arndt S, Amicone J. Outcome following a first manic episode: cross-national US and Taiwan comparison. *Bipolar Disord* 2007; **9**: 820-827 [PMID: 18076531 DOI: 10.1111/j.1399-5618.2007.00411.x]

66 **Baldessarini RJ**, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. *Hum Psychopharmacol* 2008; **23**: 95-105 [PMID: 18058849 DOI: 10.1002/hup.908]

67 **Copeland LA**, Zeber JE, Salloum IM, Pincus HA, Fine MJ, Kilbourne AM. Treatment adherence and illness insight in veterans with bipolar disorder. *J Nerv Ment Dis* 2008; **196**: 16-21 [PMID: 18195637 DOI: 10.1097/NMD.0b013e318160ea00]

68 **Zeber JE**, Copeland LA, Good CB, Fine MJ, Bauer MS, Kilbourne AM. Therapeutic alliance perceptions and medication adherence in patients with bipolar disorder. *J Affect Disord* 2008; **107**: 53-62 [PMID: 17822779 DOI: 10.1016/j.jad.2007.07.026]

69 **Taj F**, Tanwir M, Aly Z, Khowajah AA, Tariq A, Syed FK, Waqar F, Shahzada K. Factors associated with non-adherence among psychiatric patients at a tertiary care hospital, Karachi, Pakistan: a questionnaire based cross-sectional study. *J Pak Med Assoc* 2008; **58**: 432-436 [PMID: 18822640]

70 **Azorin JM**, Aubrun E, Bertsch J, Reed C, Gerard S, Lukasiewicz M. Mixed states vs. pure mania in the French sample of the EMBLEM study: results at baseline and 24 months--European mania in bipolar longitudinal evaluation of medication. *BMC Psychiatry* 2009; **9**: 33 [PMID: 19500417 DOI: 10.1186/1471-244X-9-33]

71 **Clatworthy J**, Bowskill R, Parham R, Rank T, Scott J, Horne R. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. *J Affect Disord* 2009; **116**: 51-55 [PMID: 19101038 DOI: 10.1016/j.jad.2008.11.004]

72 **Sajatovic M**, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, Blow FC. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. *Compr Psychiatry* 2009; **50**: 100-107 [PMID: 19216885 DOI: 10.1016/j.comppsych.2008.06.008]

73 **Sharifi A**, Shabani A, Ahmadzad-Asl M. The pattern of adherence in patients with bipolar I disorder an eight weeks study. *IJPBS* 2009; **3**: 39-43

74 **Martinez-Aran A**, Scott J, Colom F, Torrent C, Tabares-Seisdedos R, Daban C, Leboyer M, Henry C, Goodwin GM, Gonzalez-Pinto A, Cruz N, Sanchez-Moreno J, Vieta E. Treatment nonadherence and neurocognitive impairment in bipolar disorder. *J Clin Psychiatry* 2009; **70**: 1017-1023 [PMID: 19497247 DOI: 10.4088/JCP.08m04408]

75 **Mazza M**, Mandelli L, Di Nicola M, Harnic D, Catalano V, Tedeschi D, Martinotti G, Colombo R, Bria P, Serretti A, Janiri L. Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. *J Affect Disord* 2009; **115**: 27-35 [PMID: 18845344 DOI: 10.1016/j.jad.2008.08.019]

76 **Bates JA**, Whitehead R, Bolge SC, Kim E. Correlates of medication adherence among patients with bipolar disorder: results of the bipolar evaluation of satisfaction and tolerability (BEST) study: a nationwide cross-sectional survey. *Prim Care Companion J Clin Psychiatry* 2010; **12**: [PMID: 21274363 DOI: 10.4088/PCC.09m00883yel]

77 **Devulapalli KK**, Ignacio RV, Weiden P, Cassidy KA, Williams TD, Safavi R, Blow FC, Sajatovic M. Why do persons with bipolar disorder stop their medication? *Psychopharmacol Bull* 2010; **43**: 5-14 [PMID: 21150842]

78 **González-Pinto A**, Reed C, Novick D, Bertsch J, Haro JM. Assessment of medication adherence in a cohort of patients with bipolar disorder. *Pharmacopsychiatry* 2010; **43**: 263-270 [PMID: 20842617 DOI: 10.1055/s-0030-1263169]

79 **Hou R**, Cleak V, Peveler R. Do treatment and illness beliefs influence adherence to medication in patients with bipolar affective disorder? A preliminary cross-sectional study. *Eur Psychiatry* 2010; **25**: 216-219 [PMID: 20005683 DOI: 10.1016/j.eurpsy.2009.09.003]

80 **Jónsdóttir H**, Opjordsmoen S, Birkenaes AB, Engh JA, Ringen PA, Vaskinn A, Aamo TO, Friis S, Andreassen OA. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. *J Clin Psychopharmacol* 2010; **30**: 169-175 [PMID: 20520290 DOI: 10.1097/JCP.0b013e3181d2191e]

81 **Gutiérrez-Rojas L**, Jurado D, Martínez-Ortega JM, Gurpegui M. Poor adherence to treatment associated with a high recurrence in a bipolar disorder outpatient sample. *J Affect Disord* 2010; **127**: 77-83 [PMID: 20576292 DOI: 10.1016/j.jad.2010.05.021]

82 **Perlis RH**, Ostacher MJ, Miklowitz DJ, Hay A, Nierenberg AA, Thase ME, Sachs GS. Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. *J Clin Psychiatry* 2010; **71**: 296-303 [PMID: 20331931 DOI: 10.4088/JCP.09m05514yel]

83 **Cely EEP**, Fierro M, Pinilla MI. Prevalence and factors associated with non-adherence in drug maintenance treatment in adults with bipolar affective disorder. *Rev Colomb Psiquiatr* 2011; **40**: 85-98 [DOI: 10.1016/S0034-7450(14)601062]

84 **Hong J**, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. *Psychiatry Res* 2011; **190**: 110-114 [PMID: 21571375 DOI: 10.1016/j.psychres.2011.04.016]

85 **Savaş HA**, UnalA,Vırıt O. Treatment adherence in bipolar disorder.

JMOOD 2011; **1**: 95-102 [DOI: 10.5455/jmood.20110827015615]

86 **Sajatovic M**, Micula-Gondek W, Tatsuoka C, Bialko C. The relationship of gender and gender identity to treatment adherence among individuals with bipolar disorder. *Gend Med* 2011; **8**: 261-268 [PMID: 21763217 DOI: 10.1016/j.genm.2011.06.002]

87 **Mahmood KT**, Akram SK, Razzaq UA, Haq IU, Minaa T. Mangement of bipolar disorder (BD) through medication at public sector hospital in Lahore. *J Pharm Sci Res* 2011; **3**: 1491-1498

88 **Barraco A**, Rossi A, Nicolò G; EPHAR Study Group. Description of study population and analysis of factors influencing adherence in the observational Italian study "Evaluation of Pharmacotherapy Adherence in Bipolar Disorder" (EPHAR). *CNS Neurosci Ther* 2012; **18**: 110-118 [PMID: 21199448 DOI: 10.1111/j.1755-5949.2010.00225.x]

89 **Eker F**, Harkın S. Effectiveness of six-week psychoeducation program on adherence of patients with bipolar affective disorder. *J Affect Disord* 2012; **138**: 409-416 [PMID: 22316565 DOI: 10.1016/j.jad.2012.01.004]

90 **Murru A**, Pacchiarotti I, Nivoli AM, Bonnin CM, Patrizi B, Amann B, Vieta E, Colom F. Rates and clinical correlates of treatment non-adherence in schizoaffective bipolar patients. *Acta Psychiatr Scand* 2012; **125**: 412-418 [PMID: 22321052 DOI: 10.1111/j.1600-0447.2012.01837.x]

91 **Miasso AI**, do Carmo BP, Tirapelli CR. [Bipolar affective disorder: pharmacotherapeutic profile and adherence to medication]. *Rev Esc Enferm USP* 2012; **46**: 689-695 [PMID: 22773491 DOI: 10.1590/S0080-62342012000300022]

92 **Sajatovic M**, Levin J, Tatsuoka C, Micula-Gondek W, Fuentes-Casiano E, Bialko CS, Cassidy KA. Six-month outcomes of customized adherence enhancement (CAE) therapy in bipolar disorder. *Bipolar Disord* 2012; **14**: 291-300 [PMID: 22548902 DOI: 10.1111/j.1399-5618.2012.01010.x]

93 **Vieta E**, Azorin JM, Bauer M, Frangou S, Perugi G, Martinez G, Schreiner A. Psychiatrists' perceptions of potential reasons for non- and partial adherence to medication: results of a survey in bipolar disorder from eight European countries. *J Affect Disord* 2012; **143**: 125-130 [PMID: 22840608 DOI: 10.1016/j.jad.2012.05.041]

94 **Sharma S**, Kumar N, Chakraborti S, Sinha S, Kumari S, Gajendragad JM. Prevalence and factors associated with medication compliance in Indian patients suffering from mental disorders. *Trop Doct* 2012; **42**: 28-31 [PMID: 22037517]

95 **Belzeaux R**, Correard N, Boyer L, Etain B, Loftus J, Bellivier F, Bougerol T, Courtet P, Gard S, Kahn JP, Passerieux C, Leboyer M, Henry C, Azorin JM; Fondamental Academic Centers of Expertise for Bipolar Disorders (FACE-BD) collaborators. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: results from the FACE-BD cohort. *J Affect Disord* 2013; **151**: 1009-1015 [PMID: 24051101 DOI: 10.1016/j.jad.2013.08.028]

96 **de Souza C**, Vedana KG, Mercedes BP, Miasso AI. Bipolar disorder and medication: adherence, patients' knowledge and serum monitoring of lithium carbonate. *Rev Lat Am Enfermagem* 2013; **21**: 624-631 [PMID: 23797558 DOI: 10.1590/S0104-11692013000200021]

97 **Gibson S**, Brand SL, Burt S, Boden ZV, Benson O. Understanding treatment non-adherence in schizophrenia and bipolar disorder: a survey of what service users do and why. *BMC Psychiatry* 2013; **13**: 153 [PMID: 23714262 DOI: 10.1186/1471-244X-13-153]

98 **Hibdye G**, Dessalegne Y, Debero N, Bekan L, Sintayehu M. Prevalence of drug non adherence and associated factors among patients with bipolar disorder at outpatient unit of Amanuel Hospital, Addis Ababa, Ethiopia, 2013. *J Psychiatry* 2015; **S1**: 003 [DOI: 10.4172/2378-5756.S1-003]

99 **Jónsdóttir H**, Opjordsmoen S, Birkenaes AB, Simonsen C, Engh JA, Ringen PA, Vaskinn A, Friis S, Sundet K, Andreassen OA. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. *Acta Psychiatr Scand* 2013; **127**: 23-33 [PMID: 22900964 DOI: 10.1111/j.1600-0447.2012.01911]

100 **Murru A**, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F. Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. *J Affect Disord* 2013; **151**: 1003-1008 [PMID: 24099884 DOI: 10.1016/j.jad.2013.08.026]

101 **Arvilommi P**, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä E. Predictors of adherence to psychopharmacological and psychosocial treatment in bipolar I or II disorders - an 18-month prospective study. *J Affect Disord* 2014; **155**: 110-117 [PMID: 24262639 DOI: 10.1016/j.jad.2013.10.032]

102 **Kassis IT**, Ghuloum S, Mousa H, Bener A. Treatment non-compliance of psychiatric patients and associated factors: are patients satisfied from their psychiatrist? *Br J Med Med Res* 2014; **4**: 785-796 [DOI: 10.9734/BJMMR/2014/6127]

103 **Ghaffari-Nejad A**, Mashayekhi A, Mazhari S, Ghayoumi A. Factors associated with drug non-adherence after discharge among patients with mood disorders hospitalized in Shahid Beheshti Hospital in Kerman: a prospective study. *Zahedan J Res Med Sci* 2015; **17**: e968 [DOI: 10.5812/zjrms.17(4)2015.968]

104 **Hajda M**, Kamaradova D, Latalova K, Prasko J, Ociskova M, Mainerova B. Self-stigma, treatment adherence, and medication discontinuation in patients with bipolar disorders in remission - a cross sectional study. *Act Nerv Super Rediviva* 2015; **57**: 6-11

105 **Ibrahim AW**, Pindar SK, Yerima MM, Rabbebe IB, Shehu S, Garkuwa HA, Bashir IY, Wakil MA, Yahya SJ. Medication-related factors of non adherence among patients with schizophrenia and bipolar disorder: Outcome of a cross-sectional survey in Maiduguri, North-eastern Nigeria. *Journal of Neuroscience and Behavioral Health* 2015; **7**: 31-39 [DOI: 10.5897/JNBH2015.0128]

106 **Levin JB**, Tatsuoka C, Cassidy KA, Aebi ME, Sajatovic M. Trajectories of medication attitudes and adherence behavior change in non-adherent bipolar patients. *Compr Psychiatry* 2015; **58**: 29-36 [PMID: 25617964 DOI: 10.1016/j.comppsych.2014.11.023]

107 **Mert DG**, Turgut NH, Kelleci M, Semiz M. Perspectives on reasons of medication nonadherence in psychiatric patients. *Patient Prefer Adherence* 2015; **9**: 87-93 [PMID: 25609930 DOI: 10.2147/PPA.S75013]

108 **Azadforouz S**, Shabani A, Nohesara S, Ahmadzad-Asl M. Non-Compliance and Related Factors in Patients With Bipolar I Disorder: A Six Month Follow-Up Study. *Iran J Psychiatry Behav Sci* 2016; **10**: e2448 [PMID: 27803718 DOI: 10.17795/ijpbs-2448]

109 **Connelly CE**, Davenport YB, Nurnberger JI Jr. Adherence to treatment regimen in a lithium carbonate clinic. *Arch Gen Psychiatry* 1982; **39**: 585-588 [PMID: 6807256 DOI: 10.1001/archpsyc.1982.04290050057011]

110 **Connelly CE**. Compliance with outpatient lithium therapy. *Perspect Psychiatr Care* 1984; **22**: 44-50 [PMID: 6570862 DOI: 10.1111/j.1744-6163.1984.tb00203.x]

111 **Danion JM**, Neunreuther C, Krieger-Finance F, Imbs JL, Singer L. Compliance with long-term lithium treatment in major affective disorders. *Pharmacopsychiatry* 1987; **20**: 230-231 [PMID: 3671494 DOI: 10.1055/s-2007-1017111]

112 **Aagaard J**, Vestergaard P, Maarbjerg K. Adherence to lithium prophylaxis: II. Multivariate analysis of clinical, social, and psychosocial predictors of nonadherence. *Pharmacopsychiatry* 1988; **21**: 166-170 [PMID: 3205885 DOI: 10.1055/s-2007-1014670]

113 **Maarbjerg K**, Aagaard J, Vestergaard P. Adherence to lithium prophylaxis: I. Clinical predictors and patient's reasons for nonadherence. *Pharmacopsychiatry* 1988; **21**: 121-125 [PMID: 3406049 DOI: 10.1055/s-2007-1014662]

114 **Cochran SD**, Gitlin MJ. Attitudinal correlates of lithium compliance in bipolar affective disorders. *J Nerv Ment Dis* 1988; **176**: 457-464 [PMID: 3404137 DOI: 10.1097/00005053-198808000-00001]

115 **Vestergaard P**, Schou M. Prospective studies on a lithium cohort. 1. General features. *Acta Psychiatr Scand* 1988; **78**: 421-426 [PMID: 3227961 DOI: 10.1111/j.1600-0447.1988.tb06361.x]

116 **Lenzi A**, Lazzerini F, Placidi GF, Cassano GB, Akiskal HS. Predictors of compliance with lithium and carbamazepine regimens in the long-term treatment of recurrent mood and related psychotic disorders. *Pharmacopsychiatry* 1989; **22**: 34-37 [PMID: 2652160 DOI: 10.1055/s-2007-1014574]

117 **Nilsson A**, Axelsson R. Factors associated with discontinuation of long-term lithium treatment. *Acta Psychiatr Scand* 1989; **80**: 221-230 [PMID: 2510458 DOI: 10.1111/j.1600-0447.1989]

118 **Aagaard J**, Vestergaard P. Predictors of outcome in prophylactic lithium treatment: a 2-year prospective study. *J Affect Disord* 1990; **18**:

259-266 [PMID: 2140378 DOI: 10.1016/0165-0327(90)90077-L]
119 **Lee S**, Wing YK, Wong KC. Knowledge and compliance towards lithium therapy among Chinese psychiatric patients in Hong Kong. *Aust N Z J Psychiatry* 1992; **26**: 444-449 [PMID: 1417630 DOI: 10.3109/00048679209072068]
120 **Berghöfer A**, Kossmann B, Müller-Oerlinghausen B. Course of illness and pattern of recurrences in patients with affective disorders during long-term lithium prophylaxis: a retrospective analysis over 15 years. *Acta Psychiatr Scand* 1996; **93**: 349-354 [PMID: 8792904 DOI: 10.1111/j.1600-0447.1996.tb10659.x]
121 **Keck PE Jr**, McElroy SL, Strakowski SM, Bourne ML, West SA. Compliance with maintenance treatment in bipolar disorder. *Psychopharmacol Bull* 1997; **33**: 87-91 [PMID: 9133756]
122 **Maj M**, Pirozzi R, Magliano L, Bartoli L. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. *Am J Psychiatry* 1998; **155**: 30-35 [PMID: 9433335 DOI: 10.1176/ajp.155.1.30]
123 **Schumann C**, Lenz G, Berghöfer A, Müller-Oerlinghausen B. Non-adherence with long-term prophylaxis: a 6-year naturalistic follow-up study of affectively ill patients. *Psychiatry Res* 1999; **89**: 247-257 [PMID: 10708271 DOI: 10.1016/S0165-1781(99)00108-0]
124 **Wong SS**, Lee S, Wat KH. A preliminary communication of an insight scale in the assessment of lithium non-adherence among Chinese patients in Hong Kong. *J Affect Disord* 1999; **55**: 241-244 [PMID: 10628895 DOI: 10.1016/S0165-0327(99)00003-8]
125 **Licht RW**, Vestergaard P, Rasmussen NA, Jepsen K, Brodersen A, Hansen PE. A lithium clinic for bipolar patients: 2-year outcome of the first 148 patients. *Acta Psychiatr Scand* 2001; **104**: 387-390 [PMID: 11722321 DOI: 10.1111/j.1600-0447.2001.00389.x]
126 **Scott J**. Using Health Belief Models to understand the efficacy-effectiveness gap for mood stabilizer treatments. *Neuropsychobiology* 2002; **46** Suppl 1: 13-15 [PMID: 12571427 DOI: 10.1159/000068022]
127 **Scott J**, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. *J Clin Psychiatry* 2002; **63**: 384-390 [PMID: 12019661 DOI: 10.4088/JCP.v63n0502]
128 **Scott J**, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. *Am J Psychiatry* 2002; **159**: 1927-1929 [PMID: 12411230 DOI: 10.1176/appi.ajp.159.11.1927]
129 **Pope M**, Scott J. Do clinicians understand why individuals stop taking lithium? *J Affect Disord* 2003; **74**: 287-291 [PMID: 12738048 DOI: 10.1016/S0165-0327(02)00341-5]
130 **Bowden CL**, Collins MA, McElroy SL, Calabrese JR, Swann AC, Weisler RH, Wozniak PJ. Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. *Neuropsychopharmacology* 2005; **30**: 1932-1939 [PMID: 15956987 DOI: 10.1038/sj.npp.1300788]
131 **Patel NC**, DelBello MP, Keck PE Jr, Strakowski SM. Ethnic differences in maintenance antipsychotic prescription among adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 2005; **15**: 938-946 [PMID: 16379514 DOI: 10.1089/cap.2005.15.938]
132 **Gonzalez-Pinto A**, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, Baldessarini RJ. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord* 2006; **8**: 618-624 [PMID: 17042834 DOI: 10.1111/j.1399-5618.2006.00368.x]
133 **Drotar D**, Greenley RN, Demeter CA, McNamara NK, Stansbrey RJ, Calabrese JR, Stange J, Vijay P, Findling RL. Adherence to pharmacological treatment for juvenile bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 831-839 [PMID: 17581447 DOI: 10.1097/chi.0b013e31805c7421]
134 **Kessing LV**, Søndergård L, Kvist K, Andersen PK. Adherence to lithium in naturalistic settings: results from a nationwide pharmacoepidemiological study. *Bipolar Disord* 2007; **9**: 730-736 [PMID: 17988363 DOI: 10.1111/j.1399-5618.2007.00405.x]
135 **Manwani SG**, Szilagyi KA, Zablotsky B, Hennen J, Griffin ML, Weiss RD. Adherence to pharmacotherapy in bipolar disorder patients with and without co-occurring substance use disorders. *J Clin Psychiatry* 2007; **68**: 1172-1176 [PMID: 17854240 DOI: 10.4088/JCP.v68n0802]
136 **Rosa AR**, Marco M, Fachel JM, Kapczinski F, Stein AT, Barros HM. Correlation between drug treatment adherence and lithium treatment attitudes and knowledge by bipolar patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 217-224 [PMID: 16982121 DOI: 10.1016/j.pnpbp.2006.08.007]
137 **Sajatovic M**, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. *Psychiatr Serv* 2007; **58**: 855-863 [PMID: 17535948 DOI: 10.1176/ps.2007.58.6.855]
138 **Baldessarini R**, Henk H, Sklar A, Chang J, Leahy L. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv* 2008; **59**: 1175-1183 [PMID: 18832504 DOI: 10.1176/appi.ps.59.10.1175]
139 **Vega P**, Alonso M, Alberich S, Barbeito S, de Azúa SR, Ugarte A. Why do bipolar men not comply with treatment? The Spanish CIBERSAM data. *Eur J Psychiatr* 2009; **23** (Suppl): 63-69
140 **Scott J**, Colom F, Pope M, Reinares M, Vieta E. The prognostic role of perceived criticism, medication adherence and family knowledge in bipolar disorders. *J Affect Disord* 2012; **142**: 72-76 [PMID: 22944191 DOI: 10.1016/j.jad.2012.04.005]
141 **Col SE**, Caykoylu A, Karakas Ugurlu G, Ugurlu M. Factors affecting treatment compliance in patients with bipolar I disorder during prophylaxis: a study from Turkey. *Gen Hosp Psychiatry* 2014; **36**: 208-213 [PMID: 24359677 DOI: 10.1016/j.genhosppsych.2013.11.006]
142 **Keck PE**, McElroy SL, Strakowski SM, Balistreri TM, Kizer DI, West SA. Factors associated with maintenance antipsychotic treatment of patients with bipolar disorder. *J Clin Psychiatry* 1996; **57**: 147-151 [PMID: 8601549]
143 **Sajatovic M**, Valenstein M, Blow FC, Ganoczy D, Ignacio RV. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord* 2006; **8**: 232-241 [PMID: 16696824 DOI: 10.1111/j.1399-5618.2006.00314.x]
144 **Sajatovic M**, Blow FC, Kales HC, Valenstein M, Ganoczy D, Ignacio RV. Age comparison of treatment adherence with antipsychotic medications among individuals with bipolar disorder. *Int J Geriatr Psychiatry* 2007; **22**: 992-998 [PMID: 17323327 DOI: 10.1002/gps.1777]
145 **Hassan M**, Lage MJ. Risk of rehospitalization among bipolar disorder patients who are nonadherent to antipsychotic therapy after hospital discharge. *Am J Health Syst Pharm* 2009; **66**: 358-365 [PMID: 19202045 DOI: 10.2146/ajhp080374]
146 **Lage MJ**, Hassan MK. The relationship between antipsychotic medication adherence and patient outcomes among individuals diagnosed with bipolar disorder: a retrospective study. *Ann Gen Psychiatry* 2009; **8**: 7 [PMID: 19226463 DOI: 10.1186/1744-859X-8-7]
147 **Lang K**, Korn J, Muser E, Choi JC, Abouzaid S, Menzin J. Predictors of medication nonadherence and hospitalization in Medicaid patients with bipolar I disorder given long-acting or oral antipsychotics. *J Med Econ* 2011; **14**: 217-226 [PMID: 21370989 DOI: 10.3111/13696998.2011.562265]
148 **Rascati KL**, Richards KM, Ott CA, Goddard AW, Stafkey-Mailey D, Alvir J, Sanders KN, Mychaskiw M. Adherence, persistence of use, and costs associated with second-generation antipsychotics for bipolar disorder. *Psychiatr Serv* 2011; **62**: 1032-1040 [PMID: 21885581 DOI: 10.1176/appi.ps.62.9.1032]
149 **Stephenson JJ**, Tunceli O, Gu T, Eisenberg D, Panish J, Crivera C, Dirani R. Adherence to oral second-generation antipsychotic medications in patients with schizophrenia and bipolar disorder: physicians' perceptions of adherence vs. pharmacy claims. *Int J Clin Pract* 2012; **66**: 565-573 [PMID: 22574724 DOI: 10.1111/j.1742-1241.2012.02918.x]
150 **Montes JM**, Maurino J, de Dios C, Medina E. Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning. *Patient Prefer Adherence* 2013; **7**: 89-94 [PMID: 23378745 DOI: 10.2147/PPA.S39290]
151 **Kutzelnigg A**, Kopeinig M, Chen CK, Fábián A, Pujol-Luna MG, Shin YC, Treuer T, D'yachkova Y, Deix C, Kasper S, Doby D. Compliance as a stable function in the treatment course of bipolar disorder in patients stabilized on olanzapine: results from a 24-month observational study. *Int J Bipolar Disord* 2014; **2**: 13 [PMID: 25360398 DOI: 10.1186/s40345-014-0013-x]

152 **Sajatovic M**, Ng-Mak D, Solem CT, Lin FJ, Rajagopalan K, Loebel A. Dosing patterns and medication adherence in bipolar disorder patients treated with lurasidone: a US retrospective claims database analysis. *Ther Adv Psychopharmacol* 2016; **6**: 355-368 [PMID: 28008349 DOI: 10.1177/2045125316672135]

153 **Bauer R**, Glenn T, Alda M, Sagduyu K, Marsh W, Grof P, Munoz R, Murray G, Ritter P, Lewitzka U, Severus E, Whybrow PC, Bauer M. Antidepressant dosage taken by patients with bipolar disorder: factors associated with irregularity. *Int J Bipolar Disord* 2013; **1**: 26 [PMID: 25505689 DOI: 10.1186/2194-7511-1-26]

154 **Ragesh G**, Ameer Hamza A, Santosh K. Chaturvedi SK. Sociocultural determinants of treatment adherence in bipolar disorders: a review of recent trends. *Int J Ment Health* 2016; **9**: 285-292 [DOI: 10.1080/1754 2863.2016.1196716]

155 **Revicki DA**, Hanlon J, Martin S, Gyulai L, Nassir Ghaemi S, Lynch F, Mannix S, Kleinman L. Patient-based utilities for bipolar disorder-related health states. *J Affect Disord* 2005; **87**: 203-210 [PMID: 16005983 DOI: 10.1016/j.jad.2005.03.017]

156 **Kleindienst N**, Greil W. Are illness concepts a powerful predictor of adherence to prophylactic treatment in bipolar disorder? *J Clin Psychiatry* 2004; **65**: 966-974 [PMID: 15291686]

157 **Yen CF**, Chen CS, Ko CH, Yeh ML, Yang SJ, Yen JY, Huang CF, Wu CC. Relationships between insight and medication adherence in outpatients with schizophrenia and bipolar disorder: prospective study. *Psychiatry Clin Neurosci* 2005; **59**: 403-409 [PMID: 16048445 DOI: 10.1111/j.1440-1819.2005.01392.x]

158 **Frank E**, Prien RF, Kupfer DJ, Alberts L. Implications of noncompliance on research in affective disorders. *Psychopharmacol Bull* 1985; **21**: 37-42 [PMID: 3983336]

159 **Lehmann SW**, Rabins PV. Factors related to hospitalization in elderly manic patients with early and late-onset bipolar disorder. *Int J Geriatr Psychiatry* 2006; **21**: 1060-1064 [PMID: 16955445 DOI: 10.1002/gps.1607]

160 **Rosa AR**, Andreazza AC, Sanchez-Moreno J, Gazalle FK, Santin, A, Stein A. Validation of the Portuguese version of the Lithium Attitudes Questionnaire (LAQ) in bipolar patients treated with lithium: cross-over study. *Clin Pract Epidemiol Ment Health* 2006; **2**: 32 [DOI: 10.1186/1745-0179-2-32]

161 **Jose TT**, Bhaduri A, Mathew B. A study of the factors associated with compliance or non- compliance to lithium therapy among the patients with bipolar affective disorder. *Nurs J India* 2003; **91**: 9-11

162 **Sajatovic M**, Levin J, Fuentes-Casiano E, Cassidy KA, Tatsuoka C, Jenkins JH. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. *Compr Psychiatry* 2011; **52**: 280-287 [PMID: 21497222 DOI: 10.1016/j.comppsych.2010.07.002]

163 **Salloum IM**, Thase ME. Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar Disord* 2000; **2**: 269-280 [PMID: 11249805 DOI: 10.1034/j.1399-5618.2000.20308.x]

164 **Sherwood Brown E**, Suppes T, Adinoff B, Rajan Thomas N. Drug abuse and bipolar disorder: comorbidity or misdiagnosis? *J Affect Disord* 2001; **65**: 105-115 [PMID: 11356233 DOI: 10.1016/S0165-0327(00)00169-5]

165 **Cerullo MA**, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst Abuse Treat Prev Policy* 2007; **2**: 29 [PMID: 17908301 DOI: 10.1186/1747-597X-2-29]

166 **Peselow ED**. Adherence with respect to medication management. *Primary Psychiatry* 2007. Available from: URL: http://primarypsychiatry.com/adherence-with-respect-to-medication-management/

167 **Prasko J**, Ociskova M, Kamaradova D, Sedlackova Z, Cerna M, Mainerova B, Sandoval A. Bipolar affective disorder and psychoeducation. *Neuro Endocrinol Lett* 2013; **34**: 83-96 [PMID: 23645303]

168 **Gianfrancesco FD**, Sajatovic M, Rajagopalan K, Wang RH. The association between treatment adherence and antipsychotic dose among individuals with bipolar disorder. *Int Clin Psychopharmacol* 2008; **23**: 305-316 [PMID: 18854718 DOI: 10.1097/YIC.0b013e32830b0f88]

169 **Johnson RE**, McFarland BH. Lithium use and discontinuation in a health maintenance organization. *Am J Psychiatry* 1996; **153**: 993-1000 [PMID: 8678195 DOI: 10.1176/ajp.153.8.993]

170 **Sajatovic M**, Levin JB, Sams J, Cassidy KA, Akagi K, Aebi ME, Ramirez LF, Safren SA, Tatsuoka C. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. *Bipolar Disord* 2015; **17**: 653-661 [PMID: 26529124 DOI: 10.1111/bdi.12326]

171 **Miklowitz DJ**, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, Suddath R. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biol Psychiatry* 2000; **48**: 582-592 [PMID: 11018229 DOI: 10.1016/S0006-3223(00)00931-8]

172 **Miklowitz DJ**, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch Gen Psychiatry* 2003; **60**: 904-912 [PMID: 12963672 DOI: 10.1001/archpsyc.60.9.904]

173 **Gaudiano BA**, Miller IW. Patients' expectancies, the alliance in pharmacotherapy, and treatment outcomes in bipolar disorder. *J Consult Clin Psychol* 2006; **74**: 671-676 [PMID: 16881774 DOI: 10.1037/0022-006X.74.4.671]

174 **Miklowitz DJ**. Longitudinal outcome and medication noncompliance among manic patients with and without mood-incongruent psychotic features. *J Nerv Ment Dis* 1992; **180**: 703-711 [PMID: 1359003 DOI: 10.1097/00005053-199211000-00004]

175 **Depp CA**, Cain AE, Palmer BW, Moore DJ, Eyler LT, Lebowitz BD, Patterson TL, Jeste DV. Assessment of medication management ability in middle-aged and older adults with bipolar disorder. *J Clin Psychopharmacol* 2008; **28**: 225-229 [PMID: 18344736 DOI: 10.1097/JCP.0b013e318166dfed]

176 **Novick D**, Montgomery W, Treuer T, Aguado J, Kraemer S, Haro JM. Relationship of insight with medication adherence and the impact on outcomes in patients with schizophrenia and bipolar disorder: results from a 1-year European outpatient observational study. *BMC Psychiatry* 2015; **15**: 189 [PMID: 26239486 DOI: 10.1186/s12888-015-0560-4]

177 **Darling CA**, Olmstead SB, Lund VE, Fairclough JF. Bipolar disorder: medication adherence and life contentment. *Arch Psychiatr Nurs* 2008; **22**: 113-126 [PMID: 18505693 DOI: 10.1016/j.apnu.2008.02.004]

178 **van Rossum I**, Boomsma M, Tenback D, Reed C, van Os J; EMBLEM Advisory Board. Does cannabis use affect treatment outcome in bipolar disorder? A longitudinal analysis. *J Nerv Ment Dis* 2009; **197**: 35-40 [PMID: 19155808 DOI: 10.1097/NMD.0b013e31819292a6]

179 **Teter CJ**, Falone AE, Bakaian AM, Tu C, Ongür D, Weiss RD. Medication adherence and attitudes in patients with bipolar disorder and current versus past substance use disorder. *Psychiatry Res* 2011; **190**: 253-258 [PMID: 21696830 DOI: 10.1016/j.psychres.2011.05.042]

180 **Zarate CA Jr**. Antipsychotic drug side effect issues in bipolar manic patients. *J Clin Psychiatry* 2000; **61** Suppl 8: 52-61; discussion 62-3 [PMID: 10811244]

181 **Berk M**, Berk L. Mood stabilizers and treatment adherence in bipolar disorder: addressing adverse events. *Ann Clin Psychiatry* 2003; **15**: 217-224 [PMID: 14971867 DOI: 10.1023/B:]

182 **Mago R**, Borra D, Mahajan R. Adverse effects and nonadherence with mood stabilizers. *Journal of Mood Disorders* 2013; **3** (Suppl. 1): S4-S6

183 **Mago R**, Borra D, Mahajan R. Role of adverse effects in medication nonadherence in bipolar disorder. *Harv Rev Psychiatry* 2014; **22**: 363-366 [PMID: 25377611 DOI: 10.1097/HRP.0000000000000017]

184 **Gianfrancesco F**, Pesa J, Wang RH. Comparison of mental health resources used by patients with bipolar disorder treated with risperidone, olanzapine, or quetiapine. *J Manag Care Pharm* 2005; **11**: 220-230 [PMID: 15804206 DOI: 10.18553/jmcp.2005.11.3.220]

185 **Gianfrancesco FD**, Rajagopalan K, Sajatovic M, Wang RH. Treatment adherence among patients with bipolar or manic disorder taking atypical and typical antipsychotics. *J Clin Psychiatry* 2006; **67**: 222-232 [PMID: 16566617 DOI: 10.4088/JCP.v67n0208]

186 **Hassan M**, Madhavan SS, Kalsekar ID, Makela EH, Rajagopalan K, Islam S, Kavookjian J, Miller LA. Comparing adherence to and

persistence with antipsychotic therapy among patients with bipolar disorder. *Ann Pharmacother* 2007; **41**: 1812-1818 [PMID: 17925501 DOI: 10.1345/aph.1K205]

187 **Gianfrancesco FD**, Sajatovic M, Tafesse E, Wang RH. Association between antipsychotic combination therapy and treatment adherence among individuals with bipolar disorder. *Ann Clin Psychiatry* 2009; **21**: 3-16 [PMID: 19239828]

188 **Vestergaard P**, Amdisen A. Patient attitudes towards lithium. *Acta Psychiatr Scand* 1983; **67**: 8-12 [PMID: 6846037 DOI: 10.1111/j.1600-0447.1983.tb00325.x]

189 **Gitlin MJ**, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. *J Clin Psychiatry* 1989; **50**: 127-131 [PMID: 2925600]

190 **Lewis L.** Patient perspectives on the diagnosis, treatment, and management of bipolar disorder. *Bipolar Disord* 2005; **7** (Suppl 1): 33-37 [DOI: 10.1111/j.1399-5618.2005.00192.x]

191 **Mączka G**, Siwek M, Skalski M, Grabski B, Dudek D. Patients' and doctors' attitudes towards bipolar disorder - do we share our beliefs? *Arch Psychiatr Psychother* 2010; **2**: 43-50

192 **Wang Y**, Henning M. Bipolar disorder and medical adherence: A Chinese perspective. *Asian J Psychiatr* 2010; **3**: 7-11 [PMID: 23051130 DOI: 10.1016/j.ajp.2009.11.003]

193 **Miasso AI**, Cassiani SH, Pedrão LJ. [Affective bipolar disorder and ambivalence in relation to the drug treatment: analyzing the causal conditions]. *Rev Esc Enferm USP* 2011; **45**: 433-441 [PMID: 21655795 DOI: 10.1590/S0080-62342011000200019]

194 **Morselli PL**, Elgie R; GAMIAN-Europe. GAMIAN-Europe/BEAM survey I--global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. *Bipolar Disord* 2003; **5**: 265-278 [PMID: 12895204 DOI: 10.1034/j.1399-5618.2003.00037.x]

195 **Morselli PL**, Elgie R, Cesana BM. GAMIAN-Europe/BEAM survey II: cross-national analysis of unemployment, family history, treatment satisfaction and impact of the bipolar disorder on life style. *Bipolar Disord* 2004; **6**: 487-497 [PMID: 15541064 DOI: 10.1111/j.1399-5618.2004.00160.x]

196 **Scott J**. Predicting medication non-adherence in severe affective disorders. *Acta Neuropsychiatr* 2000; **12**: 128-130 [PMID: 26975270 DOI: 10.1017/S0924270800035584]

197 **Scott J**, Tacchi MJ. A pilot study of concordance therapy for individuals with bipolar disorders who are non-adherent with lithium prophylaxis. *Bipolar Disord* 2002; **4**: 386-392 [PMID: 12519098 DOI: 10.1034/j.1399-5618.2002.02242.x]

198 **Sajatovic M**, Jenkins JH, Cassidy KA, Muzina DJ. Medication treatment perceptions, concerns and expectations among depressed individuals with Type I Bipolar Disorder. *J Affect Disord* 2009; **115**: 360-366 [PMID: 18996600 DOI: 10.1016/j.jad.2008.10.002]

199 **Kriegshauser K**, Sajatovic M, Jenkins JH, Cassidy KA, Muzina D, Fattal O, Smith D, Singer B. Gender differences in subjective experience and treatment of bipolar disorder. *J Nerv Ment Dis* 2010; **198**: 370-372 [PMID: 20458200 DOI: 10.1097/NMD.0b013e3181da8ef7]

200 **Chakrabarti S**. Treatment-adherence in bipolar disorder: A patient-centred approach. *World J Psychiatry* 2016; **6**: 399-409 [PMID: 28078204 DOI: 10.5498/wjp.v6.i4.399]

201 **MacDonald L**, Chapman S, Syrett M, Bowskill R, Horne R. Improving medication adherence in bipolar disorder: A systematic review and meta-analysis of 30 years of intervention trials. *J Affect Disord* 2016; **194**: 202-221 [PMID: 26851552 DOI: 10.1016/j.jad.2016.01.002]

P- Reviewer: Specchia ML, Tang Y **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com