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EMDR therapy vs. Supportive Therapy as adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial.

--Manuscript Draft--

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Corresponding Author:	Alicia Valiente, Ph.D Hospital del Mar Medical Research Institute Barcelona, BARCELONA SPAIN
First Author:	Bridget Hogg
Order of Authors:	Bridget Hogg
	Joaquim Radua
	Itxaso Gardoki-Souto, PhD
	Marta Fontana-McNally
	Walter Lupo
	María Reinares
	Esther Jiménez
	Mercè Madre
	Laura Blanco-Presas
	Romina Cortizo
	Anna Massó-Rodríguez
	Juan Castaño
	Isabel Argila
	Jose Ignacio Castro-Rodriguez
	Mercè Comes
	Cristina Macias
	Roberto Sánchez-González
	Estanislao Mur
	Patricia Novo
	Adriane R Rosa
	Eduard Vieta
	Frank Padberg
	Víctor Pérez-Solà
	Alicia Valiente
	Ana Moreno-Alcázar
	Benedikt L Amann
Abstract:	Introduction. Patients with Bipolar Disorder (BD) are frequently exposed to traumatic events which worsen disease course, but this study is the first multicentre randomised controlled trial to test the efficacy of a trauma-focused adjunctive psychotherapy in reducing BD affective relapse rates.

	Materials and Methods. This multicentre randomised controlled trial included 77 patients with BD and current trauma-related symptoms. Participants were randomised to either 20 sessions of trauma-focused Eye Movement Desensitization and Reprocessing (EMDR) therapy for BD, or 20 sessions of supportive therapy (ST). The primary outcome was relapse rates over 24-months, and secondary outcomes were improvements in affective and trauma symptoms, general functioning, and cognitive impairment, assessed at baseline, post-treatment, and at 12- and 24-month follow-up. The trial was registered prior to starting enrolment in clinical trials (NCT02634372) and carried out in accordance with CONSORT guidelines. Results. There was no significant difference between treatment conditions in terms of relapse rates either with or without hospitalization. EMDR was significantly superior to ST at the 12-month follow up in terms of reducing depressive symptoms (p=0.0006, d=0.969), manic symptoms (p=0.027, d=0.513), and improving functioning (p=0.038, d=0.486). There was no significant difference in dropout between treatment arms. Conclusions. Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR was superior to ST in reducing of affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment. Both EMDR and ST reduced trauma symptoms as compared to baseline, possibly due to a shared benefit of psychotherapy. Importantly, focusing on traumatic events did not increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.
Suggested Reviewers:	Caterina del Mar Bonnín, PhD Hospital of the Holy Cross and Saint Paul mar.bonnin@gmail.com Dr. Mar Bonnin is a specialist in Bipolar Disorder and in psychosocial adjunctive treatments to improve functioning and quality of life.
	Rafael Tabares Seisdedos, PhD Prof, University of Valencia rafael.tabares@uv.es Prof Tabarés is a psychiatrist and expert on Bipolar Disorder.
	Gustavo Vázquez, PhD Queen's University g.vazquez@queensu.ca Prof Vazquez is an expert on bipolar disorder and its treatment.
	Fu-Chun Zhou, PhD Capital Medical University frankchow@ccmu.edu.cn Dr. Zhou is an expert in Bipolar Disorder and other severe mental disorders.
	Vicente Balanza, Phd Prof, University of Valencia vicente.balanza@uv.es Prof Balanza is a psychiatrist expert in Bipolar Disorder.
Opposed Reviewers:	
Response to Reviewers:	Many thanks for the time in reviewing the manuscript and for the opportunity to address this valuable feedback and improve our manuscript. Please find below a point by point response to each of the suggestions and comments related to the article. [editor's comments: Many thanks for submitting this RCT - lots of work and efforts on it and nice idea. The results are interesting, but a bit puzzle by the comparator choice (ST) and its effect. What was the rationale behind choosing this comparator? could that be developed in the text? I am uncertain whether both intervention and comparator are effective on reducing relapses or none of them are. It would be helpful having your views on it. Additionally, it would also be helpful to put a bit of economic context: how much is the estimated cost of the intervention (and the comparator?). Please see also the comments by the reviewers below. Thanks and kind regards Emilio Response to editor: Many thanks for your consideration of our article and time in reviewing our paper and the helpful comments. We have given more detail on our reasons for choosing

supportive therapy as the comparator in the introduction:
Supportive therapy was chosen as the comparator because, firstly, it can be applied with the same frequency and duration as EMDR but has no trauma component. As research shows that trauma can have a negative impact on relapse rate in BD, comparing EMDR with a non-trauma focused therapy allows for the analysis of the specific impact of the EMDR technique focused on trauma, controlling for more general effects of Furthermore, ST has previously been used as a comparator in studies regarding BD 25,26 and PTSD.27
Furthermore, we have commented more on our views on whether both ST and EMDR are effective or neither of them in the discussion, firstly regarding relapses and then regarding trauma symptoms. We make a cautious interpretation that both are effective but this would need to be tested in the future against a control condition with no therapeutic component:
Regarding relapses: A previous study comparing cognitive behavioural therapy with ST in reducing relapses in BD similarly found no significant difference between treatment arms,26 which was attributed to shared therapeutic components, which suggests that both therapies may have been helpful in reducing relapses, but this would need to be tested in the future against a wait-list control group.
Regarding trauma: It is therefore in our view probable that both treatments were effective in reducing trauma symptoms as compared to baseline, but this would need to be tested against a third group which is a wait-list control. Satisfaction with treatment was very high in both groups with no significant difference between them (p=0.887), with qualitative responses frequently referencing how helpful it was to have the opportunity to receive regular therapy sessions, regardless of treatment arm. However, the impact of ST on trauma symptoms was unexpected.
Thank you also for your comment regarding the cost, which is an important factor. We have included some further information about this in the discussion:
In terms of treatment cost, both treatment arms had the same cost (968 euros/per patient). Although we cannot demonstrate cost-effectiveness of an EMDR intervention in terms of significantly reducing hospital admissions and related medical costs, the improvement in functioning may reduce indirect costs, and future studies can focus on identifying the cost-effectiveness of trauma-focused adjunctive psychotherapy in EMDR.

Reviewer #1: In this article, the authors investigated the efficacy of a trauma-focused adjunctive psychotherapy for bipolar disorder, which is a significant research question, as there is a paucity of previous research on this topic. The article is meticulously written and provides a clear description of the EMDR Bipolar protocol employed.

However, some clarifications are needed to improve the reader's comprehension.
1- Clarification is needed regarding the definition of "affective episodes" and whether hypomania was included as an episode.
Response to reviewer 1: Many thanks for the time taken to review the article and the valuable comments. Regarding the first point, this is an important point to clarify. We have added this phrase to make it clear:
Affective episodes were defined as episodes meeting DSM-5 criteria for a hypomanic, manic, or depressive episode.

2- In a similar way, further explanation is required about how "relapses" were defined and identified.
Response: Thank you for this comment. We have provided more detail about this in the methods section:
Relapses were defined as the participant meeting DSM-5 criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study.

3- Patients were euthymic, but it is not specified if changes in treatments were allowed in the pre-enrolment and study phases.
Response: thank you for this. We have specified this:
Where necessary, changes in pharmacological treatment at any point throughout the study period were permitted, due to the clinical manifestations of bipolar disorder often changing over time, requiring a different pharmacological approach.
Further to this, we included an analysis to verify if there were any significant differences between groups in medication changes, which could have influenced the results, finding that there were no significant difference in pharmacological changes at any time point in the study:
The analysis in Table 1 shows no significant differences between EMDR and ST groups in pharmacological treatment at baseline. There were no significant between-group differences in terms of changes to pharmacological between baseline and post-treatment (X2 =0.188, p=0.885), between post-treatment and 12-month follow-up (X2 =1.245, p=0.448), nor between 12-month and 24-month follow-up (X2 =4.408, p=0.119).
4- Given the small sample size and the number of variables, particularly with multiple groups (e.g., 9 groups for work status), clarification is needed on whether corrections, such as Fisher's test, were applied when using the chi-square test for group comparison (the test may not be accurate if more than 20% of the cells have expected frequencies below five).
Response: Thanks for this. Yates' continuity correction was applied to all the Chi Square calculations. Where there were variables with multiple groups, we have redone these analyses combining groups with small values (e.g. widowed has been combined with separated/divorced) - these changes can be seen in Table 1.

5- While the study mentions the inclusion of both bipolar type 1 and type 2 groups as a strength, it omits a comparative analysis between them. Could the authors provide an analysis of the differences between these two diagnostic groups? Furthermore, the assertion that "EMDR appears promising for male and female BD-I and BD-II patients with trauma symptoms" appears to lack precision, as the efficacy could potentially be attributed to a sole diagnostic group, possibly as a sum effect (given that only sex was factored into the statistical models).
Response: Thank you for this comment. We agree that it is interesting to factor BD type into the analysis, and that with the current analysis we cannot justify the assertion in the text. We have included three supplementary analyses: one regarding risk of relapse according to BD type, another regarding differences between BD type at each time point, and a final analysis to understand differences between BD-I and BD-II in terms of treatment response to each treatment arms. This has been added into the text as follows:
There was no significant difference between BD-I and BD-II in terms of risk of relapse (z=-0.26, p=0.80 for a relapse of any type; z=-0.34, p=0.74 for a relapse with hospital admission).
Furthermore, there was no significant difference in BD results for BD-II as compared to BD-I at any time point, except for a possibly significant result for the SCIP at 12 months (unadjusted p=0.015), where BD-II participants scored on average higher than BD-I (see Supplementary Table 4). An analysis of differences between BD-I and BD-II in response to the different treatment arms revealed no significant differences in any variable (please see Supplementary Table 5).

6- Were there any observed differences between depressive and manic relapses that could provide further insights?
Thank you for this comment. Unfortunately we did not collect the data to make this analysis possible, but this is a very interesting point which we will keep in mind for future studies.

7- Despite the therapies' efficacy (as their safety and acceptability), a high dropout rate is noted. Could the authors offer an explanation for this trend?
Thank you for this comment. We have discussed this further in the discussion:
Dropout rates in BD studies at 12 months have been estimated at 34 and between 25% and 50% in outpatient psychiatric care, whereas in our study at 12 months the dropout rate was 56%. This may be due to the long illness duration and high number of previous affective episodes in our study population, which can negatively impact dropout. Furthermore, it was a highly traumatised sample, and dropout rates in PTSD

interventions are considered high as systematic reviews in the treatment of PTSD in combat veterans show, with an overall pooled dropout rate between 24% and 36%. Furthermore, the SARS-COV-2 pandemic may have had a negative impact in drop-out rates, particularly for the 12-month and 24-month follow-ups

8- The transition to internet-based interventions due to the COVID-19 pandemic is intriguing. It might be beneficial for the authors to briefly share their perspective on the feasibility of this approach as a potential standard procedure compared to in-person therapy.

Response: Many thanks. Given that we applied this approach with a very small number of patients in exceptional circumstances, we have not commented more extensively in this paper, but in more recent studies we have continued to offer EMDR online where it is more appropriate (for example, where patients have difficulties in coming to the hospital for treatment) and anecdotal evidence is that the results are similar (Faretta et al, 2022 10.3389/fpsyg.2022.964407). We have added in this sentence;
Future research can determine whether online delivery can be considered as a possible intervention delivery mode.

Reviewer #2: 1. Abstract: "This multicentre RCT included 77 patients with BD and current trauma-related Symptoms."
It is important that when utilizing the acronym 'RCT,' its expansion as 'Randomized Controlled Trial' is provided for elucidation. This practice is particularly significant within the abstract section and during the initial instance of employing this terminology.

Response: Many thanks for your time in reviewing the article and your helpful comments. Thank you for pointing this out, we have removed the acronym.

Abstract: What were the conclusions for supportive therapy? What were the conclusions for EMDR versus ST?
Response: Thank you, we have added some more detail in the abstract to make this clearer:
Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR was superior to ST in reducing of affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment. Both EMDR and ST reduced trauma symptoms as compared to baseline, possibly due to a shared benefit of psychotherapy. Importantly, focusing on traumatic events did not increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.

2. Introduction: " BD has a strong genetic components…."
Please provide more in-depth explanation regarding the genetic components.
Response: Thank you, we have included more information explaining the genetic components:
It is considered one of the most heritable mental illnesses, and recent genome-wide association studies have shown that, while variations of the gene CACNA1C are the most widely studied and replicated,11 there are 64 genes implicated in BD.12 However, environmental factors as well as gene x environment interactions can best explain its aetiology.1

3. Introduction: "Eye Movement Desensitization and Reprocessing (EMDR) therapy….."
Please provide a more in-depth explanation regarding what eye movement desensitization and reprocessing therapy is.
Response: Thank you, we have provided more information on this:
Eye Movement Desensitisation and Reprocessing (EMDR) therapy23 is recommended, a, alongside cognitive behavioural therapy, as one of the first line treatments for PTSD according to reviews and treatment guidelines from the American Psychiatric Association, American Psychological Association, World Health Organisation, and International Society for Traumatic Stress Studies, among others24,25 EMDR therapy comprises a structured eight-phase protocol to help patients heal from traumatic events. Each traumatic memory is processed by the client focusing on its visual, emotional, and somatic components, while the therapist applies sets of bilateral stimulation, most commonly in the form of side-to-side eye movements.

	Through this process, the person becomes desensitised to the traumatic memory (i.e. they can think about it without any negative emotional, cognitive, or somatic reaction), and the therapist then works with the client to install a positive reinterpretation of the traumatic event, thus helping the patient to heal from each traumatic event. Following processing of past traumatic memories, the same protocol is applied to current stressors and potential future stressors. 4. Randomization: "Evaluators provided the study coordinator (AM-A)….., who sent theses to JR….." Please clarify the acronyms 'AM-A' and 'JR' Response: apologies this was not clear. These are the initials of the authors involved in the process – Ana Moreno-Alcázar and Joaquim Radua. We have included “the author” to help make this clearer. 5. Results and Discussion Please review the format and ensure to replace 'affective relapse' with the specific context of your study, and verify that the values and interpretations accurately reflect your research findings. Response: thank you. We have provided a more exact definition of both affective episode and relapse in the methods section to make this clearer: Affective episodes were defined as episodes meeting DSM-V criteria for a hypomanic, manic, or depressive episode. Relapses were defined as the participant meeting DSM-5criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study. We have reviewed carefully the values and interpretations and have verified that they are accurate. We spotted a small error with the calculation of the effects sizes and these have been changed in the text. 6. Discussion It is important to enhance the organization of the content and concentrate more on bipolar patients. Some redundant comments should be removed, as there is no need to repeat the same point multiple times. Many thanks for this comment. We have reviewed the discussion in detail and attempted to ensure the organization is coherent and focused on bipolar patients, and to remove redundancies, while also amplifying other points in accordance with the requested revisions. 7. There are numerous acronyms present; it is advisable to reduce their usage to improve the readability and understanding of the text. Thank you, we have removed the acronyms which were not present many times in the text. 8. The majority of the bibliography is more than 4 years old. A minimum of 50% should be no older than 4 years. Response: thank you. We have added in some new references. Leaving to one side the references for the scales, which are numerous as there are all the Spanish validations in addition to the English versions, and these are generally older than four years, we have now improved the bibliography so that 50% are within the last four years. 9. Keyword: Why is the term "supportive therapy" not present? Response: thank you, this was an oversight. We have now added this. 10.Every time new terminology is introduced, it should be accompanied by an explanation to elucidate the purpose of its incorporation. In this context, it is crucial to

	clarify the rationale behind utilizing such terminology, ensuring that the readers comprehend its significance within the research context. In the manuscript, some terms like ANOVA (among other examples) are used; however, they did not provide an explanation for their usage. To enhance the clarity and comprehensibility of the manuscript, it is recommended to provide concise explanations for the introduction of new terminologies. Many thanks, we have included a definition of ANOVA; and have reviewed the text for other acronyms and have removed them where they are not helpful, and ensured the definition is next to it.

Title page (authors names, affiliations and corresponding author)

EMDR therapy vs. Supportive Therapy as adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial.

Bridget Hogg[a-d], Joaquim Radua[d-g], Itxaso Gardoki-Souto[a,c], Marta Fontana-McNally[a,b], Walter Lupo[a], María Reinares[d,h-k], Esther Jiménez[d,h-j], Mercè Madre[l-n], Laura Blanco-Presas[m-o], Romina Cortizo[p,q], Anna Massó-Rodriguez[r], Juan Castaño[q], Isabel Argila[m,n], José Ignacio Castro-Rodriguez[q], Mercè Comes[i], Cristina Macias[a,q,s], Roberto Sánchez-González[b,d,q,t], Estanislao Mur[b,q], Patricia Novo[r,u], Adriane R Rosa[v-x], Eduard Vieta[d,h-j], Frank Padberg[y], Victor Pérez-Solà[b,d,q,t], Alicia Valiente-Gómez[a,b,d], Ana Moreno-Alcázar[a,b,d+] and Benedikt L. Amann [a,b,d,t,y+]

[a] Centre Fòrum Research Unit, Hospital del Mar Research Institute, Barcelona, Spain
[b] Mental Health Institute, Hospital del Mar Barcelona, Barcelona, Spain
[c] PhD Programme, Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto Carlos III, Madrid, Spain
[e] Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain
[f] Department of Clinical Neuroscience, Karolinska Institutet (KI), Sweden
[g] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom
[h] Departament de Medicina, Facultat de Medicina i Ciencias de la Salut, Universitat de Barcelona (UB), Barcelona, Spain
[i] Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain
[j] Institute of Neurosciences (UBNeuro), Universitat de Barcelona, Barcelona, Spain
[k] Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU)
[l] Addictive Behaviours Unit, Psychiatry Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[m] Hospital Benito Menni-CASM, Sant Boi de Llobregat, Barcelona, Spain.
[n] FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain.
[o] Programa TEPT-AGRESX, Instituto de Neurociencias (ICN), Hospital Clinic, Barcelona, Spain
[p] Centro Salud Mental Adultos Ciutat Vella, Parc Sanitari Sant Joan de Déu, Barcelona, Spain
[q] Centro Salud Mental Adultos, Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain
[r] Centro Salud Mental Infanto-Juvenil, Parc de Salut Mar, Barcelona, Spain
[s] Centre Emili Mira, Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain
[t] Universitat Pompeu Fabra, Barcelona, Spain
[u] Day Hospital, Centro de Psicoterapia de Barcelona (CPB), Barcelona, Spain
[v] Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil
[w] Departamento de Farmacologia, Instituto de Ciéncias Básicas de Saúde, Universidade Federal do Rio Grande do Sul, Brazil
[x] Postgraduate Program in Psychiatry and Behavioral Sciences, Federal University of Rio Grande doSul

(UFRGS), Porto Alegre, RS, Brazil.
[y] Department of Psychiatry and Psychotherapy, LMU University Hospital, Munich, Germany

Corresponding Author:

Dr. Alicia Valiente-Gómez

avalientego@gmail.com

Statements

Acknowledgement

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Declaration of Interest

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. BLA served as head of the EMDR Europe Research Committee from 2016 to 2021 and has been invited as speaker in national or international EMDR conferences. The rest of the authors have no conflicts of interest to declare.

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Brain and Behavior Research Foundation (Number: 24397). The funders had no role in the study design, collection, analysis, and interpretation of data, or writing of the report.

Author Contributions

BLA conceived the idea for the study and led the study. BLA and WL (with others) developed the EMDR Bipolar protocol. AMA coordinated the study. BH, AV, IG, WL, EJ, MM, LB, MR, RC, RSG, AMR, and JC were involved in the recruitment and evaluation of patients and data collection. BH, IGS, MF and AMA prepared the data for analysis. JR carried out the statistical analysis. BH worked on the first draft of the paper with BLA, AMA, and JR. All authors contributed to the interpretation of results and the final draft and approved the final draft.

Statement of Ethics

This study was carried out in accordance the World Medical Association Declaration of Helsinki (World Medical Association, 2013).

Study approval statement: Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/I). Informed consent was signed by all participants prior to enrolment in the study.

Consent to participate statement: The study was explained to all participants and written informed consent prior to enrolment in the study was obtained.

Data Availability Statement

The data that support the findings of this study are openly available in Figshare at https://figshare.com/articles/dataset/Bipolar_data_EMDR_vs_Supportive_Psychotherapy/21688448

Abstract

Introduction. Patients with Bipolar Disorder (BD) are frequently exposed to traumatic events which worsen disease course, but this study is the first multicentre randomised controlled trial to test the efficacy of a trauma-focused adjunctive psychotherapy in reducing BD affective relapse rates.

Materials and Methods. This multicentre ~~RCT~~ randomised controlled trial included 77 patients with BD and current trauma-related symptoms. Participants were randomised to either 20 sessions of trauma-focused Eye Movement Desensitization and Reprocessing (EMDR) therapy for BD, or 20 sessions of supportive therapy (ST). The primary outcome was relapse rates over 24-months, and secondary outcomes were improvements in affective and trauma symptoms, general functioning, and cognitive impairment, assessed at baseline, post-treatment, and at 12- and 24-month follow-up. The trial was registered prior to starting enrolment in clinical trials (NCT02634372) and carried out in accordance with CONSORT guidelines.

Results. There was no significant difference between treatment conditions in terms of relapse rates either with or without hospitalization. EMDR was significantly superior to ST at the 12-month follow up in terms of reducing depressive symptoms (p=0.0006, d=0.969), manic symptoms (p=0.027, d=0.513), and improving functioning (p=0.038, d=0.486). There was no significant difference in dropout between treatment arms.

Conclusions. Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR was superior to ST in reducing of ~~led to the reduction of~~ affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment. Both EMDR and ST reduced trauma symptoms as compared to baseline, possibly due to a shared benefit of psychotherapy. Importantly, focusing on traumatic events did not increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.

Keywords: Bipolar Disorder, EMDR, PTSD, psychological trauma, relapse prevention, ~~supportive therapy.~~ supportive therapy.

Introduction

Bipolar disorder (BD) is characterised by episodes of elevated mood and depression, affects >1% of the population worldwide, and is associated with increased mortality.[1,2] It can be severely disabling, and lead to cognitive and functional impairment.[3]

BD presents challenges for both diagnosis and treatment.[1,4] Pharmacological interventions include antipsychotic drugs, mood stabilisers, antidepressants and some anticonvulsants.[5] Adjunctive BD-specific psychosocial interventions are recommended,[4] based on research showing they consistently provide better results than pharmacological treatment alone.[6,7] Family therapy, cognitive behavioural therapy, and psychoeducational therapy are all associated with a reduction in BD affective relapses when compared to treatment as usual,[8] but full functional recovery in BD patients is difficult to achieve, meaning novel approaches are needed.[9]

BD has a strong genetic component.[10] It is considered one of the most heritable mental illnesses, and recent genome-wide association studies have shown that, while variations of the gene CACNA1C are the most widely studied and replicated,[11] there are 64 genes implicated in BD.[12] However, ~~and~~ environmental factors as well as gene x environment interactions can best explain its aetiology.[1] A genetic interaction with childhood trauma can result in an increased risk for developing BD and an earlier age of onset.[13–15] A meta-analysis shows that childhood adversity is associated with a 2.63 greater risk of having BD.[16] Furthermore, childhood trauma impacts BD prognosis in terms of a greater number of mood episodes and hospital admissions, a lower age of onset, increased suicidality, more rapid cycling[17–19] and poor response to treatment.[20]

Given the association between trauma and BD, it is unsurprising that post-traumatic stress disorder (PTSD) is a frequent comorbidity in BD, estimated in 4-40% of patients,[21] as compared to 1.3% to 8.8% in the general population.[22] The high rates of trauma and PTSD in BD, and its negative impact on disease course, have important implications for treatment.[16] However, there is a dearth of investigation into the safety and acceptability of employing trauma-focused interventions in a BD population, and into whether alleviating trauma symptoms can have a positive impact on the course of BD itself.

Eye Movement Desensitisation and Reprocessing (EMDR) therapy[23] is, alongside cognitive behavioural therapy, one of the first line treatments for PTSD according to reviews and treatment guidelines from the American Psychiatric Association, American Psychological Association, World Health Organisation, and International Society for Traumatic Stress Studies, among others.[24,25] EMDR therapy comprises a structured eight-phase protocol to help patients heal from traumatic events. Each traumatic memory is processed by the client focusing on its visual, emotional, and somatic components, while the therapist applies sets of bilateral stimulation, most commonly in the form of side-to-side eye movements. Through this process, the person becomes desensitised to the traumatic memory (i.e. they can think about it without any negative emotional, cognitive, or somatic reaction), and the therapist then works with the client to install a positive reinterpretation of the traumatic event, thus helping the patient to heal from each traumatic event. Following processing of past traumatic memories, the same protocol is applied to current stressors and potential future stressors. ~~is recommended as a first line treatment for PTSD, and comprises a structured eight-phase protocol which includes bilateral stimulation to help patients heal from traumatic events. is~~ EMDR was piloted

in BD patients with comorbid trauma and showed positive results in reducing depression, hypomania and trauma symptoms.[26] Following these positive preliminary results, the current multicentre, randomised controlled trial was developed to compare the efficacy of an EMDR protocol for BD, developed specifically for this study, with supportive therapy (ST), a control condition used previously in BD adjunctive psychotherapy studies.[27,28] Supportive therapy was chosen as the comparator because, firstly, it can be applied with the same frequency and duration as EMDR but has no trauma component. As research shows that trauma can have a negative impact on relapse rate in BD,[29] comparing EMDR with a non-trauma focused therapy allows for the analysis of the specific impact of the EMDR technique focused on trauma, controlling for more general effects of psychotherapy. Furthermore, ST has previously been used as a comparator in studies regarding BD [27,28]and PTSD.[30]

The primary objective of this study was to investigate whether the EMDR Bipolar protocol could reduce affective relapses, as compared to ST. Secondary objectives were to investigate the effect of EMDR therapy on affective and trauma-related symptoms, and on cognition and on psychosocial functioning, as compared to ST.

Material and Methods

This study is a single-blind RCT comparing EMDR therapy with ST in bipolar patients with a history of psychological trauma. The trial was registered in clinical trials (www.clinicaltrials.gov; NCT02634372), carried out according to CONSORT guidelines,[31] and the protocol was published.[32]

This multicentre study recruited participants from three large medical centres in the Barcelona area of Catalonia, Spain (Hospital del Mar Barcelona, Hospital Benito Menni, and Hospital Clínic). Potential participants were referred by their psychiatrist to the study coordinator (AM-A) for enrolment. Inclusion criteria were: 1) age 18 to 65; 2) between two and six affective episodes in the previous 12 months; 3) current euthymic or subyndromal symptoms: i.e. scores <15 on the Bipolar Depression Rating Scale (BDRS)[33] and <13 points on the Young Mania Rating Scale (YMRS)[34]; 4) at least one traumatic event according to the Clinician-Administered PTSD Scale (CAPS)[35] with current trauma symptoms (score >0 on the Impact of Event Scale-Revised (IES-R).[36] Affective episodes were defined as episodes meeting DSM-5 criteria[37] for a hypomanic, manic, or depressive episode. Exclusion criteria were: 1) current substance abuse or dependency not in remission (i.e., within previous three months), except nicotine; 2) history of brain trauma and/or neurological disease; 3) acute suicidal ideation at enrolment; 4) having received any type of trauma-focused psychotherapy in the previous 24 months; and 5) planning to receive any type of concurrent psychotherapy during the study (both active and follow-up). Where necessary, changes in pharmacological treatment at any point throughout the study period were permitted, due to the clinical manifestations of bipolar disorder often changing over time, requiring a different pharmacological approach.[5]

Sample size calculation

The sample size was calculated based on a survival analysis, with risk of relapse after treatment as the dependent variable, using the statistical software "powerSurvEpi" for R (http://www.r-project.org). To be able to detect a hazard ratio of two in a Cox regression with a statistical power of 80%, and an alpha set at 0.005 to allow for multiple comparisons, 36 people in each intervention arm are needed.

Allowing for dropouts, 41 patients should be recruited for each study arm. This sample size is sufficient to show clinically relevant differences.[38]

Randomisation

Evaluators provided the study coordinator (author AM-A) with the age, sex, illness duration and number of affective episodes over the previous year of each new participant, who sent these to the author JR at Hospital Clínic for randomisation using the following procedure: participants were assigned to either the EMDR or ST condition according to the covariate-adaptive allocation procedure.[38] In this procedure, the first two patients are randomly assigned to one of the two intervention arms at p=0.5. Next, if one treatment arm includes two or more patients more than the other group, the participant is assigned to the smaller group with p=0.8. Otherwise, the participant was assigned to the treatment arm (p=0.8) which led to the lowest simulated between-group square standardised differences in terms of age, sex, illness duration, and number of affective episodes in the past year, to ensure groups that were balanced in terms of these variables. AM-A then contacted each participant to explain the randomisation outcome and organise the psychotherapy. Randomisation was not stratified by centre, but this was adjusted for in the analysis.

Ethical approval

Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/I). Informed consent was signed by all participants prior to enrolment in the study.

Interventions

Both study arms provided 20 x 1-hour weekly therapy sessions. Participants were randomly assigned to either EMDR or ST, and attended sessions either in the medical facility for their area or the assigned therapist's office. During the first COVID-19-related lockdown, this was altered to permit online sessions, which affected two participants from the EMDR group and two from the ST group. All EMDR therapists were fully accredited by the Spanish EMDR Association, and received specific training and supervisions throughout with the EMDR consultant involved in elaborating the EMDR Bipolar protocol (WL). All ST therapists were accredited with the Official College of Psychology in Catalonia (COPC) and received training regarding the study.

<u>EMDR</u>

In the EMDR arm, the EMDR Bipolar protocol was used,[26] which first employs five optional BD sub-protocols, applied according to each participant's clinical needs: 1) mood stabilisation, 2) treatment adherence, 3) illness awareness, 4) detection of prodromal symptoms, and 5) de-idealisation of manic symptoms. A detailed description is in the study protocol.[32] Following stabilisation of BD symptoms, trauma symptoms were treated with the standard EMDR eight-phase protocol:[23] 1) patient history, 2) preparation with emotional regulation resources, 3) assessment of the target memory, 4) desensitisation, 5) installation of a positive belief, 6) body scan, 7) closure, and 8) re-evaluation of the target memory. In the study, 20 EMDR sessions were provided. Typically, each BD sub-protocol (applied only if the patient requires it) and phase one and two of the standard protocol (applied in all

cases) require one session each, although patients with difficulties in emotional regulation may require further sessions of phase 2 before processing trauma. Phases three to eight are completed for each target memory with phases three to seven usually requiring one session per memory, or two if processing is not completed within the session. Phase eight is a short reappraisal applied at the beginning of the following session to ensure the memory is fully desensitised before proceeding with the next memory. If the memory is not fully desensitised, phases three to seven are repeated.

Supportive Psychotherapy

In ST, patients were given the opportunity to evaluate and express the impact BD is having on their lives, with the therapist providing emotional support, active listening, general information about BD without the use of structured material, support in recognising and managing moods, relaxation exercises and training in problem-solving. This control condition provides the same level of support, but without any structured material related to BD or trauma-focused component.

Outcome variables

Data were collected through a specific Case Report Form (CRF) and validated scales at baseline, six-months (post-treatment), 12- and 24-months (follow-up). Additionally, data regarding affective symptoms was collected at two weeks and three months to evaluate clinical symptoms and possible relapses. The CRF gathered sociodemographic data and clinical history through patient interview and a review of medical history at baseline, and gathered information on relapses at each timepoint. Relapses were defined as the participant meeting DSM-5 criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study.

Evaluators were blind to the treatment arm; patients could not be blind to their treatment condition due to the distinctive bilateral stimulation techniques in EMDR therapy.

Clinical Variables

Bipolar Depression Rating Scale (BDRS),[33] Spanish validation:[39] This 22-item scale measures depressive and mixed symptoms in BD during the previous week, with a higher score denoting a greater degree of clinical severity.

Young Mania Rating Scale (YMRS),[34] Spanish validation:[40] This 11-item scale measures symptoms of mania in patients over the previous two days, with a higher score indicating a greater degree of clinical severity.

Trauma presence and symptoms

Clinician-Administered PTSD Scale (CAPS),[35] Spanish validation:[41] this is the gold standard diagnostic test used to determine the presence of a current or lifetime PTSD diagnosis, according to DSM-IV criteria.

Impact of Events Scale-Revised (IES-R),[36] Spanish validation:[42] this scale evaluates trauma symptoms (intrusion, avoidance, and hyperarousal) over the previous week: higher scores indicate greater affectation.

Dissociative Experiences Scale (DES),[43] Spanish validation:[44] this scale measures the presence of dissociative symptoms, with higher scores denoting more symptoms. This scale was included after the initial protocol was developed but before enrolment began to provide a more complete assessment of trauma symptoms.

Functioning and cognition

Functioning Assessment Short Test (FAST),[45] developed originally in Spanish: this scale measures psychosocial functioning in BD patients, with higher scores indicating poorer functioning.

Screen for Cognitive Impairment in Psychiatry (SCIP-S),[46] Spanish Validation:[47] this scale was designed to detect cognitive impairment in psychiatric patients. Lower scores indicate poorer cognitive function.

Furthermore, the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BD),[48] Spanish version[49] and the Meyer-Salovey-Caruso Emotional Intelligence Test (MSCEIT),[50] Spanish version[51] were in the protocol but data were not analysed due to, respectively, discrepancies between centres in measuring changes on the CGI-BD compared to baseline, and reported difficulties from participants in answering the Spanish version of the MSCEIT.[51] Finally, the social readjustment rating scale,[52] Spanish version[53] was used to measure stressful life events over the previous year: this scale was applied at baseline only, as per the protocol, and analysed in a previous paper.[54]

Comparison of the risk of relapse and hospitalisation

We fitted a mixed-effects Cox proportional hazards model to analyze whether the risk of relapse (or hospitalisation) differed between groups. The dependent variable was the time to relapse (or the time to last completed evaluation in case of no relapse) and the relapse status. The primary independent variable was the group. The covariates were sex, age, illness duration, number of affective episodes in the previous year, and centre (as a random factor). We conducted this analysis twice: once for relapses (with or without hospitalisation) and once for hospitalisation. The statistician was blind to the treatment condition. The mixed effects Cox proportional hazards model was then repeated adding BD type as an additional independent variable.

Comparison of affective/trauma-related symptoms and cognitive/psychosocial functioning

To conduct an intention-to-treat analysis, we performed multiple imputations of the missing scores. Specifically, we imputed the missing scores of the second time point based on the scores of the first time point. Next, we imputed the missing scores of the third time point based on the (observed or imputed) scores of the second time point, and so on.

To impute the missing values, we fitted a mixed-effects linear model. The dependent variable was the difference in the score between the current and the previous time point. The independent variables and covariates were the group, sex, age, illness duration, number of affective episodes during the last year, and centre (as a random factor). We used this model to predict the missing values, added a random residual of the model to preserve the variance, and limited the imputed score to the range of the scale (e.g., between 0 and 60 for BDRS). We conducted the imputations 50 times, resulting in 50 datasets.

We compared the symptoms and functioning between groups at 6, 12, and 24 months using mixed-effects repeated-measures analysis of variances (ANOVAs). The dependent variable was the score (at baseline and at the follow-up time point). The primary independent variables were the group, time, and their interaction. The covariates of interest were sex, age, illness duration, number of affective episodes in the previous year, centre (as a random factor), and individual (as a random factor nested within the centre). We conducted these ANOVAs separately for each imputed dataset and then combined the results using Rubin's rules. The mixed-effects repeated measures ANOVA was then repeated adding BD type as an additional independent variable. Where there were no significant between-group differences, a paired samples t-test was applied to compare the baseline and post results, and baseline and 12-month results, of the variable across the whole sample. A chi-squared test was used to analyse between-group differences in changes to pharmacological treatment at baseline, between baseline and post-treatment, between post-treatment and 12-month follow-up, and between 12-month follow-up and 24-month follow-up and Yates' continuity correction was applied.

Comparison of the dropout rates

We calculated the proportion of patients lost to follow-up at 6, 12, and 24 months separately for the two groups and compared the proportions using chi-square tests.

We used the "survival" and "coxme" packages for R to fit the mixed-effects Cox proportional hazards models and the "lme4" and "lmertTest" packages for R to fit the mixed-effects repeated-measures ANOVAs. The analyst was blind to which group was EMDR.

Results

Recruitment took place between 19th May, 2016 and 13th February, 2020; 102 patients were screened for the study and 82 invited to a baseline evaluation (see Fig. 1). Three patients later withdrew informed consent, and two did not meet inclusion criteria during the baseline visit due to acute symptoms, meaning 77 patients were randomised to the two treatment conditions (39 to EMDR, and 38 to ST). Of these, 24 of the EMDR group and 26 of the ST group completed the intervention; 17 of the EMDR group and 17 of the ST group completed the 12-month follow-up; and 9 of the EMDR group and 11 of the ST group completed the 24-month follow-up.

An overview of sociodemographic and clinical variables of the overall sample at baseline, and the trauma profile of the participants, has previously been reported.[54] A comparison of each group in terms of clinical and sociodemographic variables can be seen in Table 1. There was no significant difference between groups on any variable except illness duration, where the mean average illness duration in the ST group was 19.3 years compared to 15.0 years in the EMDR group (t[-2.0654], df=73.46, p=0.042); this was adjusted for in the subsequent analyses. The analysis in Table 1 shows no significant

differences between EMDR and ST groups in terms of pharmacological treatment at baseline. There were no significant between-group differences in terms of changes to pharmacological between baseline and post-treatment (X^2 =0.188, p=0.885), between post-treatment and 12-month follow-up (X^2 =1.245, p=0.448), nor between 12-month and 24-month follow-up (X^2 =4.408, p=0.119).

Primary outcomes: Relapse rates

For the primary outcome, all 77 participants were included in the analysis. Overall, 35.1% (n=27) of the sample had a relapse of a mood episode of any type, and 15.6% of the sample (n=12) had a relapse of a mood episode resulting in hospitalisation during the course of the study. The average time to hospitalisation in the sample was 45.0 weeks, while the average time to any affective relapse of any type was 27.3 weeks. There was no significant difference between groups in terms of risk of affective relapse (z(-0.04), p=0.97) or hospitalization (z(-1.50, p=0.13); see figures 2 and 3.

Secondary outcomes: Affective and trauma-related symptoms

Due to the high dropout rate for our primary outcome at 24-month (74%), available data were not representative for the whole sample, and therefore not reported in the main results but can be seen in Supplementary Table 1, along with the statistics for all time points for all affective and trauma-related variables.

In terms of affective symptoms, EMDR was significantly more effective in reducing depressive symptoms (t=4.252, p=0.00006, Cohen's d=0.969059905) and manic symptoms (t=2.248, p=0.027, Cohen's d=0.444513) than ST at the 12-month follow-up; there were no significant differences at 6 months. The results for BDRS remained significant following the application of multiple corrections. These results can be seen in Supplementary Figures 1 and 2.

In terms of trauma related symptoms, there was a significant reduction across the whole sample as measured by the IES-R between baseline and post (t=5.139, df=44, p=<0.001), maintained at 12-months (t=4.911, df=30, p=<0.001), but no significant between-group differences at either 6- or 12-month time points. In addition, there were no significant between-group differences in the DES at either comparison.

Secondary outcomes: Functioning and cognitive impairment

Regarding functioning, scores improved at all time points as compared to baseline in both groups, but the only significant between-group difference was found at 12 months, where significantly improved FAST scores were observed in the EMDR group compared to the ST group (t=2.118, p=0.038, Cohen's *d*=0.43286).

There were no significant between-group differences in cognitive impairment according to the SCIP at any time point, although there was a significant improvement between baseline and 6-months (t=-2.615, df=42, p=0.006), which was maintained at 12 months (t=-2.723, df=25, p=0.006) across the sample.

Dropout

Dropout rates were similarly high in both groups (38.5% at 6 months, 56.4% at 12 months and 76.9% at 24 months in the EMDR group, and 31.2% at 6 months, 55.3% at 12 months and 71.1% at 24 months in the ST group) without statistically significant differences between the two groups (see Supplementary Table 2 and Supplementary Figure 3).

A univariate analysis was carried out which found no significant association between clinical and sociodemographic variables at baseline and risk of dropout (see Supplementary Table 3).

Results by BD-Type

There was no significant difference between BD-I and BD-II in terms of risk of relapse (z=-0.26, p=0.80 for a relapse of any type; z=-0.34, p=0.74 for a relapse with hospital admission).

Furthermore, there was no significant difference in BD results for BD-II as compared to BD-I at any time point, except for a possibly significant result for the SCIP at 12 months (unadjusted p=0.015), where BD-II participants scored on average higher than BD-I (see Supplementary Table 4). An analysis of differences between BD-I and BD-II in response to the different treatment arms revealed no significant differences in any variable (please see Supplementary Table 5).

Discussion

To our knowledge, these are the results of the first multicentre randomised controlled trial ~~RCT~~ investigating the efficacy of a trauma-focused therapy in reducing affective relapses in BD. Although there was no significant difference between EMDR and ST in terms of this primary outcome, EMDR was significantly more effective than ST in the secondary outcomes of improving symptoms of depression, mania, and psychosocial functioning at the 12-month time point. Surprisingly, trauma symptoms reduced significantly in both the EMDR and ST groups.

The majority of previous studies aiming at a reduction of BD relapses have compared the intervention with a waitlist control group,[7,8] whereas we compared EMDR with ST, an active control condition which is often as effective as the therapies it is compared with in non-BD populations.[55] In a previous study aimed at reducing relapses in BD, where ST was the comparator for cognitive behavioural therapy, no significant difference between treatment arms was found.[28] ~~A previous study comparing CBT with ST in reducing relapses in BD similarly found no significant difference between treatment arms, which~~ This was attributed to shared therapeutic components, which suggests that both therapies may have been helpful in reducing relapses, but this would need to be tested in the future against a wait-list control group.~~.~~ In our study, shared characteristics between EMDR and ST include psychoeducation and emotional support and alliance. BD patients tend to have low levels of social support,[56] so the therapeutic alliance may be especially beneficial. Future research could include the presence of a third group receiving pharmacological treatment only to clarify non-specific therapeutic benefits.

~~Preventing relapses in BD remains a challenge, with a~~A recent meta-analysis estimated the risk of relapse at 44% in the first year following a BD mood episode, and at 70% within five years.[57] It is difficult to put the relapse rates from our study into context, due to the inclusion criteria of current trauma symptoms, which impact negatively on BD's clinical course,[19] and a minimum of two affective episodes in the previous year, which is important as a high number of previous episodes and shorter intervals

between affective episodes are both associated with a higher risk of relapse.[58] Also of note is that we applied a strict intention-to-treat rule in our analysis, meaning dropouts who abandoned the study early for reasons other than relapse were included in the analysis, contributing to shorter relapse rates. The lack of hospitalisation prevention in the EMDR group contradicted our main hypothesis, but resembled findings from other studies in severe mental disorder.[59]

Furthermore, previous meta-analysis indicated that non-euthymic patients with 13 or more lifetime affective episodes respond poorly to adjunctive psychotherapy for BD~~A meta-analysis into the efficacy of adjunctive psychotherapy for reducing BD relapses indicates that non-euthymic patients with 13 or more lifetime affective episodes respond poorly to adjunctive psychotherapy~~.[60] The participants in our study had subsyndromal depression (BDRS = 9.1), and the mean number of previous episodes was 14.75 (SD 17.2), and thus may have been prone to a reduced treatment response. However, at the 12-month time point, EMDR was significantly superior to ST for reducing symptoms of depression (p=0.0006) and mania (p=0.027), which means that positive effects of EMDR appear to have been maintained for at least six months following the end of therapy. A much larger effect size was observed for the effects of EMDR on depression severity than on mania scores (d=0.969 compared to 0.513). This may partly be due to the 'ceiling effect' of the low hypomania scores at the baseline in our study.

The significant improvement in subsyndromal depressive symptoms is especially encouraging, given not only the high burden of illness and the increased risk of suicide associated with these symptoms, but also the important clinical challenge of successfully treating depressive episodes in BD.[61,62] Untreated (subsyndromal) depressive symptoms can have an important negative impact on quality of life, psychosocial functioning, and cognition,[63–65] and the improvement in these symptoms may partially explain the significant improvement in our study in psychosocial functioning at 12 months in the EMDR group (p=0.038). Psychosocial functioning tends to deteriorate in BD patients following multiple affective episodes,[66] and subsyndromal depressive symptoms should be targeted early in the disease course to improve functional outcomes,[67] so the improvement in the EMDR treatment condition in a sample of patients with a long history of affective episodes and subsyndromal depressive symptoms is promising. Poor psychosocial functioning is also associated with cognitive impairment[68] related to a worse disease course.[69] In our study, cognitive impairment scores improved significantly across conditions (t=2.615, df=42, p=0.006), although there were no between-group differences.

As this was the first multicentre randomised controlled trial~~RCT~~ on trauma-focused psychotherapy, an important aim was to investigate the safety and tolerability of EMDR. Trauma-focused treatments are safe in patients with PTSD with no comorbid psychiatric disorder,[70] but patients with severe mental disorder are usually excluded from PTSD trials, and a major concern of addressing trauma in BD patients is that it may destabilise affective symptoms.[71] Our findings of comparable relapse and dropout rates for EMDR and ST support EMDR as a safe and acceptable adjunctive psychotherapy for BD with sequelae from psychological trauma, and support the results of our pilot trial.[26] As trauma symptoms and diagnosis of PTSD are associated with a poorer prognosis in BD,[19] it may be counter-productive to leave these unaddressed for fear of destabilising the patient.

Interestingly, there was a significant reduction in trauma symptoms in both EMDR and ST conditions. This was unexpected in the ST condition, and unlikely to be due to spontaneous remission as the average interval between the traumatic event and study enrolment in our sample was 22.4 years. It is

therefore in our view probable that both treatments were effective in reducing trauma symptoms as compared to baseline, but this would need to be tested against a third group which is a wait-list control. Satisfaction with treatment was very high in both groups with no significant difference between them (p=0.887), with qualitative responses frequently referencing how helpful it was to have the opportunity to receive regular therapy sessions, regardless of treatment arm. However, the impact of ST on trauma symptoms was unexpected. In non-BD populations, EMDR and trauma-focused cognitive behavioural therapy~~CBT~~ are more effective treatments for PTSD than supportive and present-centred therapies.[25] However, ST can be superior to a waitlist condition[72] and can be as effective as cognitive behavioural therapy~~CBT~~ in chronic PTSD among those who complete all the sessions.[27] Thus, ST may include elements which alleviate trauma symptoms despite not directly focusing on traumatic events. Again, the social support factor may contribute to the efficacy of EMDR and ST, as social support has been shown to moderate PTSD symptoms.[73] Similarly, difficulties in emotion regulation, often experienced in PTSD,[74] may be ameliorated by ST. Furthermore, the evaluation and reappraisal of prior traumatic events during study assessments is likely to have impacted trauma-related symptoms, as re-telling trauma narratives can have therapeutic effects.[75] Finally, it is of note that traumatic memories were only processed once the appropriate subprotocols for clinical needs related to BD were applied, and once the patient had sufficient emotional regulation resources. Our study comprised a real-world sample of patients with a generally severe clinical profile, and a high number of previous episodes. Given this, many only began to process traumatic memories in the final therapy sessions. This, therefore, may explain the positive results with affective symptoms, and future trials may wish to extend the number of sessions to provide more opportunity for more clinically severe patients to be able to process trauma.

BD carries a high economic burden in terms of direct medical costs and indirect costs such as unemployment and reduced productivity of patients and caregivers.[76] In terms of treatment cost, both treatment arms had the same cost (968 euros). Although we cannot demonstrate cost-effectiveness of an EMDR intervention in terms of significantly reducing hospital admissions and related medical costs, the improvement in functioning may reduce indirect costs, and future studies can focus on identifying the cost-effectiveness of trauma-focused adjunctive psychotherapy in EMDR.

This study's strengths include, firstly, being the first multicentre randomised controlled trial~~RCT~~ investigating a trauma-focused psychotherapy in comparison with an active control condition (i.e. ST) in trauma exposed BD patients. Secondly, the EMDR intervention followed a strict protocol facilitating replication of the study interventions in future research as well as its implementation in clinical practice. Third, our study included both BD-I and BD-II patients which allows us to generalize findings to the bipolar spectrum. In this respect, EMDR appears to be promising for male and female BD-I and BD-II patients with trauma symptoms, who are either in a euthymic state or show subsyndromal affective symptoms.

However, there are also several limitations: firstly, our primary endpoint (relapse rates over 24 months) may have been too ambitiously chosen, not considering the putative high dropout rate in a potentially severe mental health condition as BD. Dropout rates in BD studies at 12 months have been estimated at 34%[77] and between 25% and 50% in outpatient psychiatric care,[78] whereas in our study at 12 months the dropout rate was 56%. This may be due to the long illness duration and high number of previous affective episodes in our study population, which can negatively impact dropout.

Furthermore, it was a highly traumatised sample, and dropout rates in PTSD interventions are considered high as systematic reviews in the treatment of PTSD in combat veterans show, with an overall pooled dropout rate between 24%[79] and 36%.[80] Furthermore, the SARS-COV-2 pandemic may have had a negative impact in drop-out rates, particularly for the 12-month and 24-month follow-ups. Secondly, as a limitation, the final stages of the trial coincided with the first wave of the COVID-19 pandemic, meaning four subjects received part of the treatment online. We could not find any research comparing online and face-to-face psychotherapy in BD patients, but EMDR has been shown to be effective delivered online,[81] and the pandemic affected both treatment arms equally. Future research can determine whether online delivery can be considered as a possible intervention delivery mode. A third limitation is the concomitant pharmacotherapy which may have had confounding effects, although there were no significant between-group differences in pharmacological treatment. Moreover, although raters were blind to treatment allocation, patients were not blind to treatment modality because of the nature of the interventions. We were also unable to include a sensitivity analysis for gender due to the low number of males in our sample. Finally, comorbid psychiatric disorders were not diagnosed by standardized interviews, but rather assessed by reviewing the medical history together with the patient. Furthermore, at the time the study was planned and initiated, complex post-traumatic stress disorder was not yet a recognised diagnosis in the ICD-11,[82] and the standard tool for measuring it, the International Trauma Questionnaire,[83] was not yet developed. However, complex post-traumatic stress disorder~~CPTSD~~ has been shown to be a frequent comorbidity in patients with severe mental disorder[84] and future studies would benefit from assessing this comorbidity.

Conclusions

In summary, the specific EMDR protocol for BD shows promise in treating affective symptoms, but was not superior to ST in reducing relapses of mood episodes or hospitalisations. This study provides valuable data supporting the safety and tolerability of trauma-focused EMDR in trauma-exposed patients with BD. Future trials ~~RCTs~~ should focus on exploring the therapeutic effects of EMDR on affective symptoms observed in this study. These findings pave the way for future research in treating comorbid trauma in BD, which is often associated with less favorable outcomes and chronicity.

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Abstract

Introduction. Patients with Bipolar Disorder (BD) are frequently exposed to traumatic events which worsen disease course, but this study is the first multicentre randomised controlled trial to test the efficacy of a trauma-focused adjunctive psychotherapy in reducing BD affective relapse rates.

Materials and Methods. This multicentre randomised controlled trial included 77 patients with BD and current trauma-related symptoms. Participants were randomised to either 20 sessions of trauma-focused Eye Movement Desensitization and Reprocessing (EMDR) therapy for BD, or 20 sessions of supportive therapy (ST). The primary outcome was relapse rates over 24-months, and secondary outcomes were improvements in affective and trauma symptoms, general functioning, and cognitive impairment, assessed at baseline, post-treatment, and at 12- and 24-month follow-up. The trial was registered prior to starting enrolment in clinical trials (NCT02634372) and carried out in accordance with CONSORT guidelines.

Results. There was no significant difference between treatment conditions in terms of relapse rates either with or without hospitalization. EMDR was significantly superior to ST at the 12-month follow up in terms of reducing depressive symptoms (p=0.0006, d=0.969), manic symptoms (p=0.027, d=0.513), and improving functioning (p=0.038, d=0.486). There was no significant difference in dropout between treatment arms.

Conclusions. Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR was superior to ST in reducing of affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment. Both EMDR and ST reduced trauma symptoms as compared to baseline, possibly due to a shared benefit of psychotherapy. Importantly, focusing on traumatic events did not increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.

Keywords: Bipolar Disorder, EMDR, PTSD, psychological trauma, relapse prevention, supportive therapy.

Introduction

Bipolar disorder (BD) is characterised by episodes of elevated mood and depression, affects >1% of the population worldwide, and is associated with increased mortality.[1,2] It can be severely disabling, and lead to cognitive and functional impairment.[3]

BD presents challenges for both diagnosis and treatment.[1,4] Pharmacological interventions include antipsychotic drugs, mood stabilisers, antidepressants and some anticonvulsants.[5] Adjunctive BD-specific psychosocial interventions are recommended,[4] based on research showing they consistently provide better results than pharmacological treatment alone.[6,7] Family therapy, cognitive behavioural therapy, and psychoeducational therapy are all associated with a reduction in BD affective relapses when compared to treatment as usual,[8] but full functional recovery in BD patients is difficult to achieve, meaning novel approaches are needed.[9]

BD has a strong genetic component.[10] It is considered one of the most heritable mental illnesses, and recent genome-wide association studies have shown that, while variations of the gene CACNA1C are the most widely studied and replicated,[11] there are 64 genes implicated in BD.[12] However, environmental factors as well as gene x environment interactions can best explain its aetiology.[1] A genetic interaction with childhood trauma can result in an increased risk for developing BD and an earlier age of onset.[13–15] A meta-analysis shows that childhood adversity is associated with a 2.63 greater risk of having BD.[16] Furthermore, childhood trauma impacts BD prognosis in terms of a greater number of mood episodes and hospital admissions, a lower age of onset, increased suicidality, more rapid cycling[17–19] and poor response to treatment.[20]

Given the association between trauma and BD, it is unsurprising that post-traumatic stress disorder (PTSD) is a frequent comorbidity in BD, estimated in 4-40% of patients,[21] as compared to 1.3% to 8.8% in the general population.[22] The high rates of trauma and PTSD in BD, and its negative impact on disease course, have important implications for treatment.[16] However, there is a dearth of investigation into the safety and acceptability of employing trauma-focused interventions in a BD population, and into whether alleviating trauma symptoms can have a positive impact on the course of BD itself.

Eye Movement Desensitisation and Reprocessing (EMDR) therapy[23] is, alongside cognitive behavioural therapy, one of the first line treatments for PTSD according to reviews and treatment guidelines from the American Psychiatric Association, American Psychological Association, World Health Organisation, and International Society for Traumatic Stress Studies, among others.[24,25] EMDR therapy comprises a structured eight-phase protocol to help patients heal from traumatic events. Each traumatic memory is processed by the client focusing on its visual, emotional, and somatic components, while the therapist applies sets of bilateral stimulation, most commonly in the form of side-to-side eye movements. Through this process, the person becomes desensitised to the traumatic memory (i.e. they can think about it without any negative emotional, cognitive, or somatic reaction), and the therapist then works with the client to install a positive reinterpretation of the traumatic event, thus helping the patient to heal from each traumatic event. Following processing of past traumatic memories, the same protocol is applied to current stressors and potential future stressors. EMDR was piloted in BD patients with comorbid trauma and showed positive results in reducing depression, hypomania and trauma symptoms.[26] Following these positive preliminary results, the current

multicentre, randomised controlled trial was developed to compare the efficacy of an EMDR protocol for BD, developed specifically for this study, with supportive therapy (ST), a control condition used previously in BD adjunctive psychotherapy studies.[27,28] Supportive therapy was chosen as the comparator because, firstly, it can be applied with the same frequency and duration as EMDR but has no trauma component. As research shows that trauma can have a negative impact on relapse rate in BD,[29] comparing EMDR with a non-trauma focused therapy allows for the analysis of the specific impact of the EMDR technique focused on trauma, controlling for more general effects of psychotherapy. Furthermore, ST has previously been used as a comparator in studies regarding BD [27,28]and PTSD.[30]

The primary objective of this study was to investigate whether the EMDR Bipolar protocol could reduce affective relapses, as compared to ST. Secondary objectives were to investigate the effect of EMDR therapy on affective and trauma-related symptoms, and on cognition and on psychosocial functioning, as compared to ST.

Material and Methods

This study is a single-blind RCT comparing EMDR therapy with ST in bipolar patients with a history of psychological trauma. The trial was registered in clinical trials (www.clinicaltrials.gov; NCT02634372), carried out according to CONSORT guidelines,[31] and the protocol was published.[32]

This multicentre study recruited participants from three large medical centres in the Barcelona area of Catalonia, Spain (Hospital del Mar Barcelona, Hospital Benito Menni, and Hospital Clínic). Potential participants were referred by their psychiatrist to the study coordinator (AM-A) for enrolment. Inclusion criteria were: 1) age 18 to 65; 2) between two and six affective episodes in the previous 12 months; 3) current euthymic or subyndromal symptoms: i.e. scores <15 on the Bipolar Depression Rating Scale (BDRS)[33] and <13 points on the Young Mania Rating Scale (YMRS)[34]; 4) at least one traumatic event according to the Clinician-Administered PTSD Scale (CAPS)[35] with current trauma symptoms (score >0 on the Impact of Event Scale-Revised (IES-R).[36] Affective episodes were defined as episodes meeting DSM-5 criteria[37] for a hypomanic, manic, or depressive episode. Exclusion criteria were: 1) current substance abuse or dependency not in remission (i.e., within previous three months), except nicotine; 2) history of brain trauma and/or neurological disease; 3) acute suicidal ideation at enrolment; 4) having received any type of trauma-focused psychotherapy in the previous 24 months; and 5) planning to receive any type of concurrent psychotherapy during the study (both active and follow-up). Where necessary, changes in pharmacological treatment at any point throughout the study period were permitted, due to the clinical manifestations of bipolar disorder often changing over time, requiring a different pharmacological approach.[5]

Sample size calculation

The sample size was calculated based on a survival analysis, with risk of relapse after treatment as the dependent variable, using the statistical software "powerSurvEpi" for R (http://www.r-project.org). To be able to detect a hazard ratio of two in a Cox regression with a statistical power of 80%, and an alpha set at 0.005 to allow for multiple comparisons, 36 people in each intervention arm are needed. Allowing for dropouts, 41 patients should be recruited for each study arm. This sample size is sufficient to show clinically relevant differences.[38]

Randomisation

Evaluators provided the study coordinator (author AM-A) with the age, sex, illness duration and number of affective episodes over the previous year of each new participant, who sent these to the author JR at Hospital Clínic for randomisation using the following procedure: participants were assigned to either the EMDR or ST condition according to the covariate-adaptive allocation procedure.[38] In this procedure, the first two patients are randomly assigned to one of the two intervention arms at p=0.5. Next, if one treatment arm includes two or more patients more than the other group, the participant is assigned to the smaller group with p=0.8. Otherwise, the participant was assigned to the treatment arm (p=0.8) which led to the lowest simulated between-group square standardised differences in terms of age, sex, illness duration, and number of affective episodes in the past year, to ensure groups that were balanced in terms of these variables. AM-A then contacted each participant to explain the randomisation outcome and organise the psychotherapy. Randomisation was not stratified by centre, but this was adjusted for in the analysis.

Ethical approval

Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/I). Informed consent was signed by all participants prior to enrolment in the study.

Interventions

Both study arms provided 20 x 1-hour weekly therapy sessions. Participants were randomly assigned to either EMDR or ST, and attended sessions either in the medical facility for their area or the assigned therapist's office. During the first COVID-19-related lockdown, this was altered to permit online sessions, which affected two participants from the EMDR group and two from the ST group. All EMDR therapists were fully accredited by the Spanish EMDR Association, and received specific training and supervisions throughout with the EMDR consultant involved in elaborating the EMDR Bipolar protocol (WL). All ST therapists were accredited with the Official College of Psychology in Catalonia (COPC) and received training regarding the study.

<u>EMDR</u>

In the EMDR arm, the EMDR Bipolar protocol was used,[26] which first employs five optional BD sub-protocols, applied according to each participant's clinical needs: 1) mood stabilisation, 2) treatment adherence, 3) illness awareness, 4) detection of prodromal symptoms, and 5) de-idealisation of manic symptoms. A detailed description is in the study protocol.[32] Following stabilisation of BD symptoms, trauma symptoms were treated with the standard EMDR eight-phase protocol:[23] 1) patient history, 2) preparation with emotional regulation resources, 3) assessment of the target memory, 4) desensitisation, 5) installation of a positive belief, 6) body scan, 7) closure, and 8) re-evaluation of the target memory. In the study, 20 EMDR sessions were provided. Typically, each BD sub-protocol (applied only if the patient requires it) and phase one and two of the standard protocol (applied in all cases) require one session each, although patients with difficulties in emotional regulation may require further sessions of phase 2 before processing trauma. Phases three to eight are completed for each target memory with phases three to seven usually requiring one session per memory, or two if processing is not completed within the session. Phase eight is a short reappraisal applied at the

beginning of the following session to ensure the memory is fully desensitised before proceeding with the next memory. If the memory is not fully desensitised, phases three to seven are repeated.

Supportive Psychotherapy

In ST, patients were given the opportunity to evaluate and express the impact BD is having on their lives, with the therapist providing emotional support, active listening, general information about BD without the use of structured material, support in recognising and managing moods, relaxation exercises and training in problem-solving. This control condition provides the same level of support, but without any structured material related to BD or trauma-focused component.

Outcome variables

Data were collected through a specific Case Report Form (CRF) and validated scales at baseline, six-months (post-treatment), 12- and 24-months (follow-up). Additionally, data regarding affective symptoms was collected at two weeks and three months to evaluate clinical symptoms and possible relapses. The CRF gathered sociodemographic data and clinical history through patient interview and a review of medical history at baseline, and gathered information on relapses at each timepoint. Relapses were defined as the participant meeting DSM-5 criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study.

Evaluators were blind to the treatment arm; patients could not be blind to their treatment condition due to the distinctive bilateral stimulation techniques in EMDR therapy.

Clinical Variables

Bipolar Depression Rating Scale (BDRS),[33] Spanish validation:[39] This 22-item scale measures depressive and mixed symptoms in BD during the previous week, with a higher score denoting a greater degree of clinical severity.

Young Mania Rating Scale (YMRS),[34] Spanish validation:[40] This 11-item scale measures symptoms of mania in patients over the previous two days, with a higher score indicating a greater degree of clinical severity.

Trauma presence and symptoms

Clinician-Administered PTSD Scale (CAPS),[35] Spanish validation:[41] this is the gold standard diagnostic test used to determine the presence of a current or lifetime PTSD diagnosis, according to DSM-IV criteria.

Impact of Events Scale-Revised (IES-R),[36] Spanish validation:[42] this scale evaluates trauma symptoms (intrusion, avoidance, and hyperarousal) over the previous week: higher scores indicate greater affectation.

Dissociative Experiences Scale (DES),[43] Spanish validation:[44] this scale measures the presence of dissociative symptoms, with higher scores denoting more symptoms. This scale was included after the initial protocol was developed but before enrolment began to provide a more complete assessment of trauma symptoms.

Functioning and cognition

Functioning Assessment Short Test (FAST),[45] developed originally in Spanish: this scale measures psychosocial functioning in BD patients, with higher scores indicating poorer functioning.

Screen for Cognitive Impairment in Psychiatry (SCIP-S),[46] Spanish Validation:[47] this scale was designed to detect cognitive impairment in psychiatric patients. Lower scores indicate poorer cognitive function.

Furthermore, the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BD),[48] Spanish version[49] and the Meyer-Salovey-Caruso Emotional Intelligence Test (MSCEIT),[50] Spanish version[51] were in the protocol but data were not analysed due to, respectively, discrepancies between centres in measuring changes on the CGI-BD compared to baseline, and reported difficulties from participants in answering the Spanish version of the MSCEIT.[51] Finally, the social readjustment rating scale,[52] Spanish version[53] was used to measure stressful life events over the previous year: this scale was applied at baseline only, as per the protocol, and analysed in a previous paper.[54]

Comparison of the risk of relapse and hospitalisation

We fitted a mixed-effects Cox proportional hazards model to analyze whether the risk of relapse (or hospitalisation) differed between groups. The dependent variable was the time to relapse (or the time to last completed evaluation in case of no relapse) and the relapse status. The primary independent variable was the group. The covariates were sex, age, illness duration, number of affective episodes in the previous year, and centre (as a random factor). We conducted this analysis twice: once for relapses (with or without hospitalisation) and once for hospitalisation. The statistician was blind to the treatment condition. The mixed effects Cox proportional hazards model was then repeated adding BD type as an additional independent variable.

Comparison of affective/trauma-related symptoms and cognitive/psychosocial functioning

To conduct an intention-to-treat analysis, we performed multiple imputations of the missing scores. Specifically, we imputed the missing scores of the second time point based on the scores of the first time point. Next, we imputed the missing scores of the third time point based on the (observed or imputed) scores of the second time point, and so on.

To impute the missing values, we fitted a mixed-effects linear model. The dependent variable was the difference in the score between the current and the previous time point. The independent variables and covariates were the group, sex, age, illness duration, number of affective episodes during the last year, and centre (as a random factor). We used this model to predict the missing values, added a random residual of the model to preserve the variance, and limited the imputed score to the range of the scale (e.g., between 0 and 60 for BDRS). We conducted the imputations 50 times, resulting in 50 datasets.

We compared the symptoms and functioning between groups at 6, 12, and 24 months using mixed-effects repeated-measures analysis of variances (ANOVAs). The dependent variable was the score (at baseline and at the follow-up time point). The primary independent variables were the group, time, and their interaction. The covariates of interest were sex, age, illness duration, number of affective episodes in the previous year, centre (as a random factor), and individual (as a random factor nested within the centre). We conducted these ANOVAs separately for each imputed dataset and then combined the results using Rubin's rules. The mixed-effects repeated measures ANOVA was then repeated adding BD type as an additional independent variable. Where there were no significant between-group differences, a paired samples t-test was applied to compare the baseline and post results, and baseline and 12-month results, of the variable across the whole sample. A chi-squared test was used to analyse between-group differences in changes to pharmacological treatment at baseline, between baseline and post-treatment, between post-treatment and 12-month follow-up, and between 12-month follow-up and 24-month follow-up and Yates' continuity correction was applied.

Comparison of the dropout rates

We calculated the proportion of patients lost to follow-up at 6, 12, and 24 months separately for the two groups and compared the proportions using chi-square tests.

We used the "survival" and "coxme" packages for R to fit the mixed-effects Cox proportional hazards models and the "lme4" and "lmertTest" packages for R to fit the mixed-effects repeated-measures ANOVAs. The analyst was blind to which group was EMDR.

Results

Recruitment took place between 19th May, 2016 and 13th February, 2020; 102 patients were screened for the study and 82 invited to a baseline evaluation (see Fig. 1). Three patients later withdrew informed consent, and two did not meet inclusion criteria during the baseline visit due to acute symptoms, meaning 77 patients were randomised to the two treatment conditions (39 to EMDR, and 38 to ST). Of these, 24 of the EMDR group and 26 of the ST group completed the intervention; 17 of the EMDR group and 17 of the ST group completed the 12-month follow-up; and 9 of the EMDR group and 11 of the ST group completed the 24-month follow-up.

An overview of sociodemographic and clinical variables of the overall sample at baseline, and the trauma profile of the participants, has previously been reported.[54] A comparison of each group in terms of clinical and sociodemographic variables can be seen in Table 1. There was no significant difference between groups on any variable except illness duration, where the mean average illness duration in the ST group was 19.3 years compared to 15.0 years in the EMDR group (t[-2.0654], df=73.46, p=0.042); this was adjusted for in the subsequent analyses. The analysis in Table 1 shows no significant differences between EMDR and ST groups in terms of pharmacological treatment at baseline. There were no significant between-group differences in terms of changes to pharmacological between baseline and post-treatment (X^2 =0.188, p=0.885), between post-treatment and 12-month follow-up (X^2 =1.245, p=0.448), nor between 12-month and 24-month follow-up (X^2 =4.408, p=0.119).

Primary outcomes: Relapse rates

For the primary outcome, all 77 participants were included in the analysis. Overall, 35.1% (n=27) of the sample had a relapse of a mood episode of any type, and 15.6% of the sample (n=12) had a relapse of a mood episode resulting in hospitalisation during the course of the study. The average time to hospitalisation in the sample was 45.0 weeks, while the average time to any affective relapse of any type was 27.3 weeks. There was no significant difference between groups in terms of risk of affective relapse (z(-0.04), p=0.97) or hospitalization (z(-1.50, p=0.13); see figures 2 and 3.

Secondary outcomes: Affective and trauma-related symptoms

Due to the high dropout rate for our primary outcome at 24-month (74%), available data were not representative for the whole sample, and therefore not reported in the main results but can be seen in Supplementary Table 1, along with the statistics for all time points for all affective and trauma-related variables.

In terms of affective symptoms, EMDR was significantly more effective in reducing depressive symptoms (t=4.252, p=0.00006, Cohen's d=0.905) and manic symptoms (t=2.248, p=0.027, Cohen's d=0.444) than ST at the 12-month follow-up; there were no significant differences at 6 months. The results for BDRS remained significant following the application of multiple corrections. These results can be seen in Supplementary Figures 1 and 2.

In terms of trauma related symptoms, there was a significant reduction across the whole sample as measured by the IES-R between baseline and post (t=5.139, df=44, p=<0.001), maintained at 12-months (t=4.911, df=30, p=<0.001), but no significant between-group differences at either 6- or 12-month time points. In addition, there were no significant between-group differences in the DES at either comparison.

Secondary outcomes: Functioning and cognitive impairment

Regarding functioning, scores improved at all time points as compared to baseline in both groups, but the only significant between-group difference was found at 12 months, where significantly improved FAST scores were observed in the EMDR group compared to the ST group (t=2.118, p=0.038, Cohen's *d*=0.432).

There were no significant between-group differences in cognitive impairment according to the SCIP at any time point, although there was a significant improvement between baseline and 6-months (t=-2.615, df=42, p=0.006), which was maintained at 12 months (t=-2.723, df=25, p=0.006) across the sample.

Dropout

Dropout rates were similarly high in both groups (38.5% at 6 months, 56.4% at 12 months and 76.9% at 24 months in the EMDR group, and 31.2% at 6 months, 55.3% at 12 months and 71.1% at 24 months in the ST group) without statistically significant differences between the two groups (see Supplementary Table 2 and Supplementary Figure 3).

A univariate analysis was carried out which found no significant association between clinical and sociodemographic variables at baseline and risk of dropout (see Supplementary Table 3).

Results by BD-Type

There was no significant difference between BD-I and BD-II in terms of risk of relapse (z=-0.26, p=0.80 for a relapse of any type; z=-0.34, p=0.74 for a relapse with hospital admission).

Furthermore, there was no significant difference in BD results for BD-II as compared to BD-I at any time point, except for a possibly significant result for the SCIP at 12 months (unadjusted p=0.015), where BD-II participants scored on average higher than BD-I (see Supplementary Table 4). An analysis of differences between BD-I and BD-II in response to the different treatment arms revealed no significant differences in any variable (please see Supplementary Table 5).

Discussion

To our knowledge, these are the results of the first multicentre randomised controlled trial investigating the efficacy of a trauma-focused therapy in reducing affective relapses in BD. Although there was no significant difference between EMDR and ST in terms of this primary outcome, EMDR was significantly more effective than ST in the secondary outcomes of improving symptoms of depression, mania, and psychosocial functioning at the 12-month time point. Surprisingly, trauma symptoms reduced significantly in both the EMDR and ST groups.

The majority of previous studies aiming at a reduction of BD relapses have compared the intervention with a waitlist control group,[7,8] whereas we compared EMDR with ST, an active control condition which is often as effective as the therapies it is compared with in non-BD populations.[55] In a previous study aimed at reducing relapses in BD, where ST was the comparator for cognitive behavioural therapy, no significant difference between treatment arms was found.[28] This was attributed to shared therapeutic components, which suggests that both therapies may have been helpful in reducing relapses, but this would need to be tested in the future against a wait-list control group. In our study, shared characteristics between EMDR and ST include psychoeducation and emotional support and alliance. BD patients tend to have low levels of social support,[56] so the therapeutic alliance may be especially beneficial. Future research could include the presence of a third group receiving pharmacological treatment only to clarify non-specific therapeutic benefits.

A recent meta-analysis estimated the risk of relapse at 44% in the first year following a BD mood episode, and at 70% within five years.[57] It is difficult to put the relapse rates from our study into context, due to the inclusion criteria of current trauma symptoms, which impact negatively on BD's clinical course,[19] and a minimum of two affective episodes in the previous year, which is important as a high number of previous episodes and shorter intervals between affective episodes are both associated with a higher risk of relapse.[58] Also of note is that we applied a strict intention-to-treat rule in our analysis, meaning dropouts who abandoned the study early for reasons other than relapse were included in the analysis, contributing to shorter relapse rates. The lack of hospitalisation prevention in the EMDR group contradicted our main hypothesis, but resembled findings from other studies in severe mental disorder.[59]

Furthermore, previous meta-analysis indicated that non-euthymic patients with 13 or more lifetime affective episodes respond poorly to adjunctive psychotherapy for BD.[60] The participants in our study had subsyndromal depression (BDRS = 9.1), and the mean number of previous episodes was 14.75 (SD 17.2), and thus may have been prone to a reduced treatment response. However, at the 12-month

time point, EMDR was significantly superior to ST for reducing symptoms of depression (p=0.0006) and mania (p=0.027), which means that positive effects of EMDR appear to have been maintained for at least six months following the end of therapy. A much larger effect size was observed for the effects of EMDR on depression severity than on mania scores (d=0.969 compared to 0.513). This may partly be due to the 'ceiling effect' of the low hypomania scores at the baseline in our study.

The significant improvement in subsyndromal depressive symptoms is especially encouraging, given not only the high burden of illness and the increased risk of suicide associated with these symptoms, but also the important clinical challenge of successfully treating depressive episodes in BD.[61,62] Untreated (subsyndromal) depressive symptoms can have an important negative impact on quality of life, psychosocial functioning, and cognition,[63–65] and the improvement in these symptoms may partially explain the significant improvement in our study in psychosocial functioning at 12 months in the EMDR group (p=0.038). Psychosocial functioning tends to deteriorate in BD patients following multiple affective episodes,[66] and subsyndromal depressive symptoms should be targeted early in the disease course to improve functional outcomes,[67] so the improvement in the EMDR treatment condition in a sample of patients with a long history of affective episodes and subsyndromal depressive symptoms is promising. Poor psychosocial functioning is also associated with cognitive impairment[68] related to a worse disease course.[69] In our study, cognitive impairment scores improved significantly across conditions (t=2.615, df=42, p=0.006), although there were no between-group differences.

As this was the first multicentre randomised controlled trial on trauma-focused psychotherapy, an important aim was to investigate the safety and tolerability of EMDR. Trauma-focused treatments are safe in patients with PTSD with no comorbid psychiatric disorder,[70] but patients with severe mental disorder are usually excluded from PTSD trials, and a major concern of addressing trauma in BD patients is that it may destabilise affective symptoms.[71] Our findings of comparable relapse and dropout rates for EMDR and ST support EMDR as a safe and acceptable adjunctive psychotherapy for BD with sequelae from psychological trauma, and support the results of our pilot trial.[26] As trauma symptoms and diagnosis of PTSD are associated with a poorer prognosis in BD,[19] it may be counter-productive to leave these unaddressed for fear of destabilising the patient.

Interestingly, there was a significant reduction in trauma symptoms in both EMDR and ST conditions. This was unexpected in the ST condition, and unlikely to be due to spontaneous remission as the average interval between the traumatic event and study enrolment in our sample was 22.4 years. It is therefore in our view probable that both treatments were effective in reducing trauma symptoms as compared to baseline, but this would need to be tested against a third group which is a wait-list control. Satisfaction with treatment was very high in both groups with no significant difference between them (p=0.887), with qualitative responses frequently referencing how helpful it was to have the opportunity to receive regular therapy sessions, regardless of treatment arm. However, the impact of ST on trauma symptoms was unexpected. In non-BD populations, EMDR and trauma-focused cognitive behavioural therapy are more effective treatments for PTSD than supportive and present-centred therapies.[25] However, ST can be superior to a waitlist condition[72] and can be as effective as cognitive behavioural therapy in chronic PTSD among those who complete all the sessions.[27] Thus, ST may include elements which alleviate trauma symptoms despite not directly focusing on traumatic events. Again, the social support factor may contribute to the efficacy of EMDR and ST, as social support has been shown to moderate PTSD symptoms.[73] Similarly, difficulties in emotion regulation,

often experienced in PTSD,[74] may be ameliorated by ST. Furthermore, the evaluation and reappraisal of prior traumatic events during study assessments is likely to have impacted trauma-related symptoms, as re-telling trauma narratives can have therapeutic effects.[75] Finally, it is of note that traumatic memories were only processed once the appropriate subprotocols for clinical needs related to BD were applied, and once the patient had sufficient emotional regulation resources. Our study comprised a real-world sample of patients with a generally severe clinical profile, and a high number of previous episodes. Given this, many only began to process traumatic memories in the final therapy sessions. This, therefore, may explain the positive results with affective symptoms, and future trials may wish to extend the number of sessions to provide more opportunity for more clinically severe patients to be able to process trauma.

BD carries a high economic burden in terms of direct medical costs and indirect costs such as unemployment and reduced productivity of patients and caregivers.[76] In terms of treatment cost, both treatment arms had the same cost (968 euros). Although we cannot demonstrate cost-effectiveness of an EMDR intervention in terms of significantly reducing hospital admissions and related medical costs, the improvement in functioning may reduce indirect costs, and future studies can focus on identifying the cost-effectiveness of trauma-focused adjunctive psychotherapy in EMDR.

This study's strengths include, firstly, being the first multicentre randomised controlled trial investigating a trauma-focused psychotherapy in comparison with an active control condition (i.e. ST) in trauma exposed BD patients. Secondly, the EMDR intervention followed a strict protocol facilitating replication of the study interventions in future research as well as its implementation in clinical practice. Third, our study included both BD-I and BD-II patients which allows us to generalize findings to the bipolar spectrum. In this respect, EMDR appears to be promising for male and female BD-I and BD-II patients with trauma symptoms, who are either in a euthymic state or show subsyndromal affective symptoms.

However, there are also several limitations: firstly, our primary endpoint (relapse rates over 24 months) may have been too ambitiously chosen, not considering the putative high dropout rate in a potentially severe mental health condition as BD. Dropout rates in BD studies at 12 months have been estimated at 34%[77] and between 25% and 50% in outpatient psychiatric care,[78] whereas in our study at 12 months the dropout rate was 56%. This may be due to the long illness duration and high number of previous affective episodes in our study population, which can negatively impact dropout. Furthermore, it was a highly traumatised sample, and dropout rates in PTSD interventions are considered high as systematic reviews in the treatment of PTSD in combat veterans show, with an overall pooled dropout rate between 24%[79] and 36%.[80] Furthermore, the SARS-COV-2 pandemic may have had a negative impact in drop-out rates, particularly for the 12-month and 24-month follow-ups. Secondly, as a limitation, the final stages of the trial coincided with the first wave of the COVID-19 pandemic, meaning four subjects received part of the treatment online. We could not find any research comparing online and face-to-face psychotherapy in BD patients, but EMDR has been shown to be effective delivered online,[81] and the pandemic affected both treatment arms equally. Future research can determine whether online delivery can be considered as a possible intervention delivery mode. A third limitation is the concomitant pharmacotherapy which may have had confounding effects, although there were no significant between-group differences in pharmacological treatment. Moreover, although raters were blind to treatment allocation, patients were not blind to treatment

modality because of the nature of the interventions. We were also unable to include a sensitivity analysis for gender due to the low number of males in our sample. Finally, comorbid psychiatric disorders were not diagnosed by standardized interviews, but rather assessed by reviewing the medical history together with the patient. Furthermore, at the time the study was planned and initiated, complex post-traumatic stress disorder was not yet a recognised diagnosis in the ICD-11,[82] and the standard tool for measuring it, the International Trauma Questionnaire,[83] was not yet developed. However, complex post-traumatic stress disorder has been shown to be a frequent comorbidity in patients with severe mental disorder[84] and future studies would benefit from assessing this comorbidity.

Conclusions

In summary, the specific EMDR protocol for BD shows promise in treating affective symptoms, but was not superior to ST in reducing relapses of mood episodes or hospitalisations. This study provides valuable data supporting the safety and tolerability of trauma-focused EMDR in trauma-exposed patients with BD. Future trials should focus on exploring the therapeutic effects of EMDR on affective symptoms observed in this study. These findings pave the way for future research in treating comorbid trauma in BD, which is often associated with less favorable outcomes and chronicity.

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Table

Table 1 Sociodemographic and clinical data for EMDR and ST group

	EMDR (n=39)	ST (n=38)	Sig difference	Total (n=77)
Sex *n* (%)				
Male	8 (20.5%)	10 (26.3%)	X^2=0.110, df=1 p=0.740	18 (23.4)
Female	31 (79.5%)	28 (73.7%)		59 (76.6)
Other	0 (0.0%)	0 (0.0%)		0(0.0%)
Mean age in years (SD)	46.3 (9.4)	47.3 (7.3)	t(-0.542), df=71.412 p=0.590	46.8 (8.4)
Ethnicity *n* (%)			X^2=0.573, df=1, p=0.449[a]	
Caucasian	34 (87.2)	36 (94.5)		70 (90.9)
Latin-American	1 (2.6)	0 (0.0)		1 (1.3)
Asian	0 (0.0)	1 (2.6)		1 (1.3)
Not reported	4 (10.3)	1 (2.6)		5 (6.5)
Civil Status *n* (%)				
Single	15 (38.5)	16 (42.1)	X^2=0.586, df=2, p=0.746[b]	31 (40.2)
Married	14 (35.9)	15 (39.5)		29 (37.7)
Widowed	1 (2.6)	0 (0.0)		1 (1.3)
Separated/Divorced	9 (23.1)	7 (18.4)		16 (20.8)
Mean years education (SD)	13.6 (4.0)	14.0 (3.8)	t(-0.363), df=53.947 p=0.718	13.8 (3.9)
Education *n* (%)				
Incomplete primary	2 (5.1)	1 (2.6)	X^2=1.082, df=2, p=0.581[c]	3 (3.9)
Complete primary	2 (5.1)	3 (7.9)		5 (6.5)
Incomplete secondary	4 (10.3)	5 (13.2)		9 (11.7)
Complete secondary	10 (25.6)	9 (23.7)		19 (24.7)
Incomplete tertiary	8 (20.5)	9 (23.7)		17 (22.1)
Complete tertiary	13 (33.3)	11 (28.9)		24 (31.2)
Work status *n* (%)				
Employed full-time	5 (12.8)	8 (22.9)	X^2=0.391, df=2, p=0.822[d]	13 (16.9)
Employed part-time	2 (5.1)	1 (2.9)		3 (3.9)
Temporary sick leave	16 (41.0)	15 (42.9)		31 (40.3)
Permanent disability for mental health	7 (17.9)	7 (20.0)		14 (18.2)
Permanent disability for other reasons	1 (2.6)	0 (0.0)		1 (1.3)

Student				
Homemaker	4 (10.3)	0 (0.0)		4 (5.2)
Unemployed	0 (0.0)	1 (2.9)		1 (1.3)
Other	3 (7.7)	2 (5.7)		5 (6.5)
Not reported	1 (2.6)	1 (2.9)		2 (2.6)
	0 (0.0)	3 (7.9)		
Clinical variables				
Mean age of onset (SD)	31.3 (12.0)	28.8 (11.1)	t(1.184), df=73.988, p=0.240	30.1 (11.5)
Mean illness duration in years (SD)	15.0 (9.8)	19.3 (11.2)	t(-2.065), df=73.462, p=0.042	17.1 (10.7)
Mean number of hospital admissions (SD)	4.2 (7.0)	2.5 (3.5)	t(1.077), df=1, p=0.299	3.3 (5.6)
Mean number of episodes past year (SD)	2.4 (0.8)	2.6 (1.1)	X^2=0.105, df=1, p=0.746	2.5 (0.9)
History of psychotic symptoms *n* (%)				
No	22 (56.4)	20 (52.6)	X^2=0, df=1, p=1	42 (54.5)
Yes	17 (43.6)	17 (44.7)		34 (44.2)
Not reported	0 (0.0)	1 (2.6)		1 (1.3)
Comorbidity *n* (%)				
Axis I	8 (20.5)	9 (23.7)	X^2=0.113, df=1, p=0.952	17 (22.1)
Axis II	3 (7.7)	8 (21.1)	X^2=2.806, df=1, p=0.177	11 (14.3)
Axis III	22 (59.5)	25 (65.8)	X^2=0.321, df=1, p=0.743	47 (62.7)
BD Type *n* (%)				
BD-I	29 (74.4)	27 (71.1)	X^2=0.005, df=1, p=0.944	56 (72.7)
BD-II	10 (25.6)	11 (28.9)		21 (27.3)
Suicide *n* (%)				
History suicidal ideation	33 (84.6)	29 (76.3)	X^2=0.845, df=1, p=0.528	62 (80.5)
History suicide attempts	18 (46.2)	12 (31.2)	X^2=1.496, df=1, p=0.323	30 (39.0)
Mean number of suicide attempts (SD)	1.2 (2.9)	0.5 (0.8)	t(1.559), p=0.062)	0.9 (2.2)
Medication *n* (%)				
Mood stabilisers	36 (92.3)	32 (84.2)	X^2=4.235, df=1, p=0.123	68 (88.3)
Antipsychotics	29 (74.4)	26 (68.4)	X^2=0.693, df=1, p=0.579	55 (71.4)

Anxiolytics	15 (38.5)	17 (44.7)	X^2=0.225, df=1, p=0.813	32 (41.6)
Antidepressants	13 (33.3)	17 (44.7)	X^2=0.914, df=1, p=0.473	30 (39.0)
Other	6 (15.4)	9 (23.7)	X^2=0.758, df=1, p=0.562	15 (19.5)
Mean BDRS baseline score (SD)	9.1 (4.5)	9.0 (5.2)	t(0.069), df=73.018, p=0.946	9.1 (4.8)
Mean YMRS baseline score (SD)	2.0 (2,4)	2.5 (2.5)	t(-0.855), df=74.846, p=0.396	2.3 (2.4)
Mean IES-R baseline score (SD)	36.5 (27.0)	40.2 (24.4)	t(-0.620), df=70.981, p=0.537	38.3 (25.7)
Mean DES baseline score (SD)	11.5 (6.4)	14.7 (11.8)	t(-1.415), df=53.745, p=0.163	13.1 (9.6)
Mean FAST baseline score (SD)	29.5 (14.0)	28.5 (13.4)	t(0.317), df=73.854, p=0.752	29.0 (13.7)
Mean SCIP-S baseline score (SD)	69.1 (12.1)	68.2 (11.2)	t(0.332), df=69.961, p=0.741	68.7 (11.6)
PTSD Diagnosis *n* (%)				
Current	12 (30.7)	8 (21.1)	X^2=0.582, df=1, p=0.446	20 (26.0)
Lifetime	20 (51.3)	19 (50.0)	X^2=0, df=1, p=1	39 (50.6)

Key: EMDR=Eye Movement Desensitization and Reprocessing; ST=Supportive Therapy; SD=Standard Deviation; PTSD=post-traumatic stress disorder; df=degrees of freedom.

[a] X^2 combining “Latin-American”, “Asian”, and “not reported” in one category

[b] X^2 combining “widowed” with “separated/divorced” in one category

[c] X^2 combining “incomplete primary”, “complete primary”, and “incomplete secondary” into one category, “completed seconday” and “incomplete tertiary” into a second category, and “complete tertiary” into a third category.

[d] X^2 combining “employed full-time" and “employed part-time" into one category, “temporary sick leave” and “permanent disbability” into another category, and the rest into a third category.

Figure

Click here to access/download;Figure;Figure 1 (1).docx

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

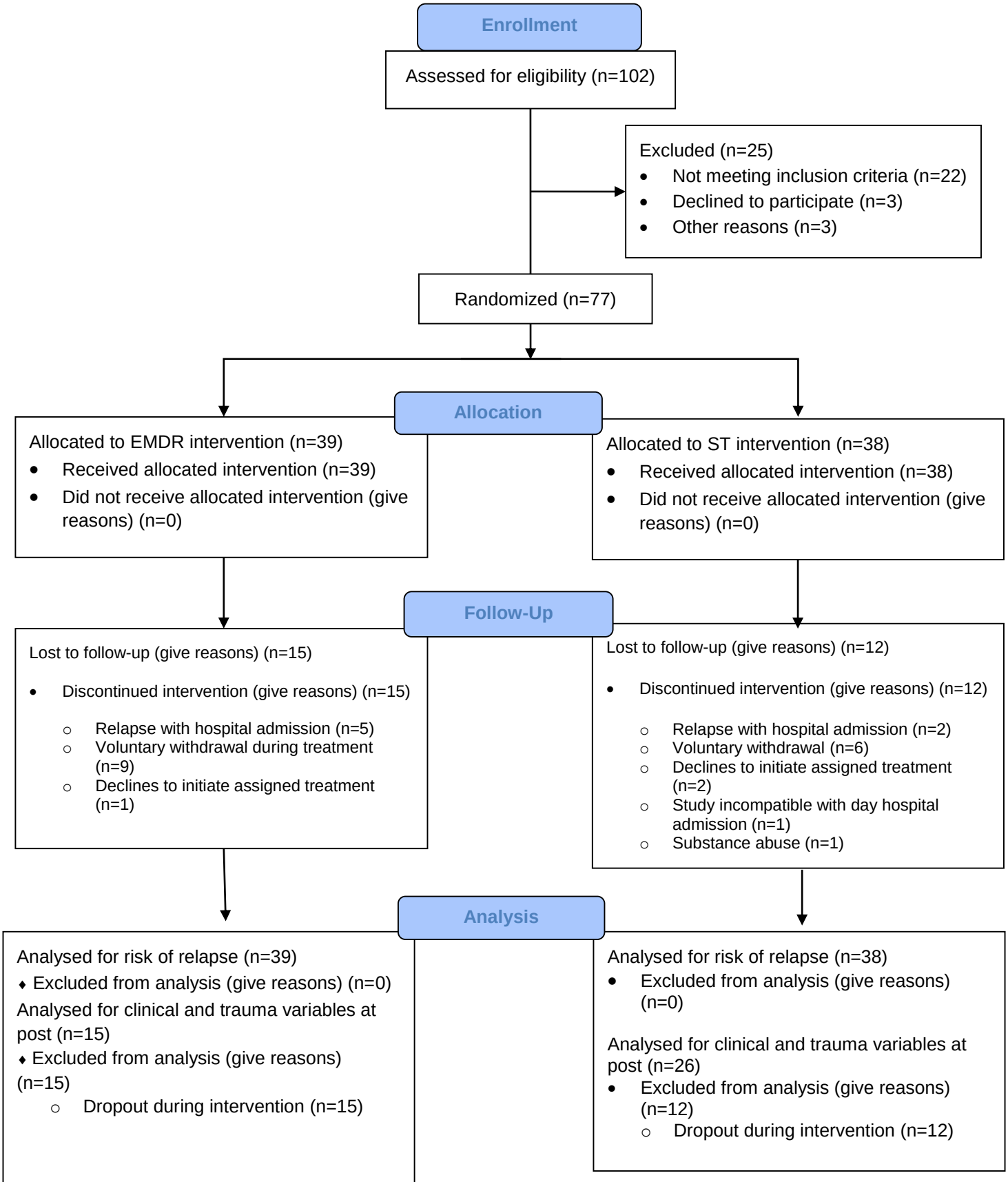
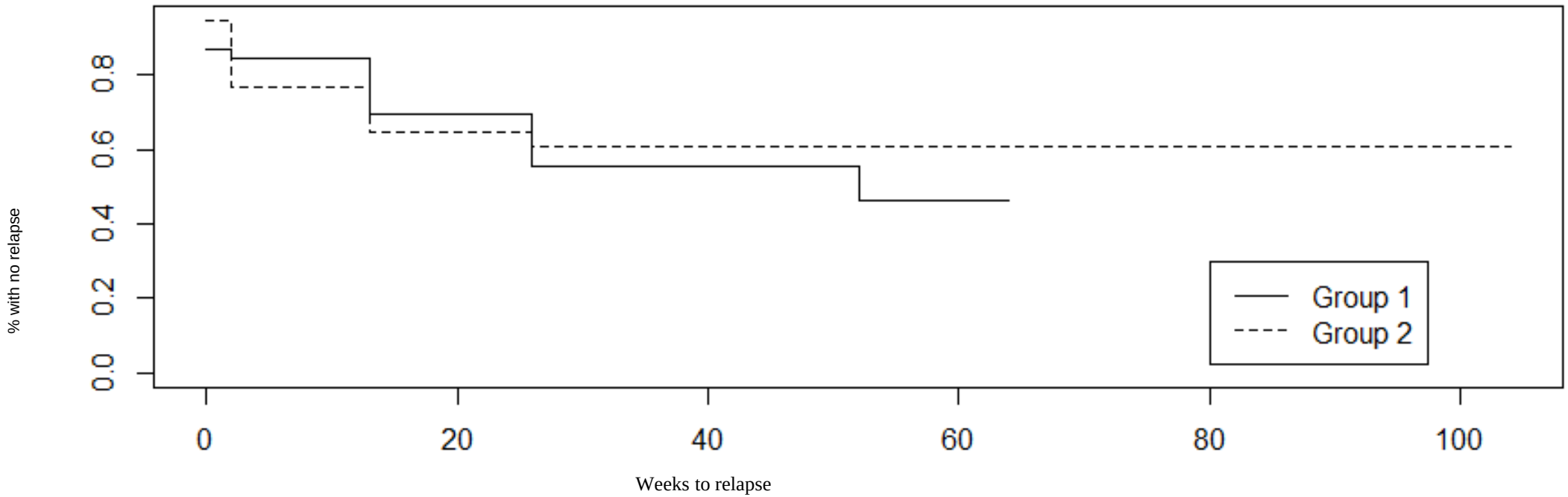
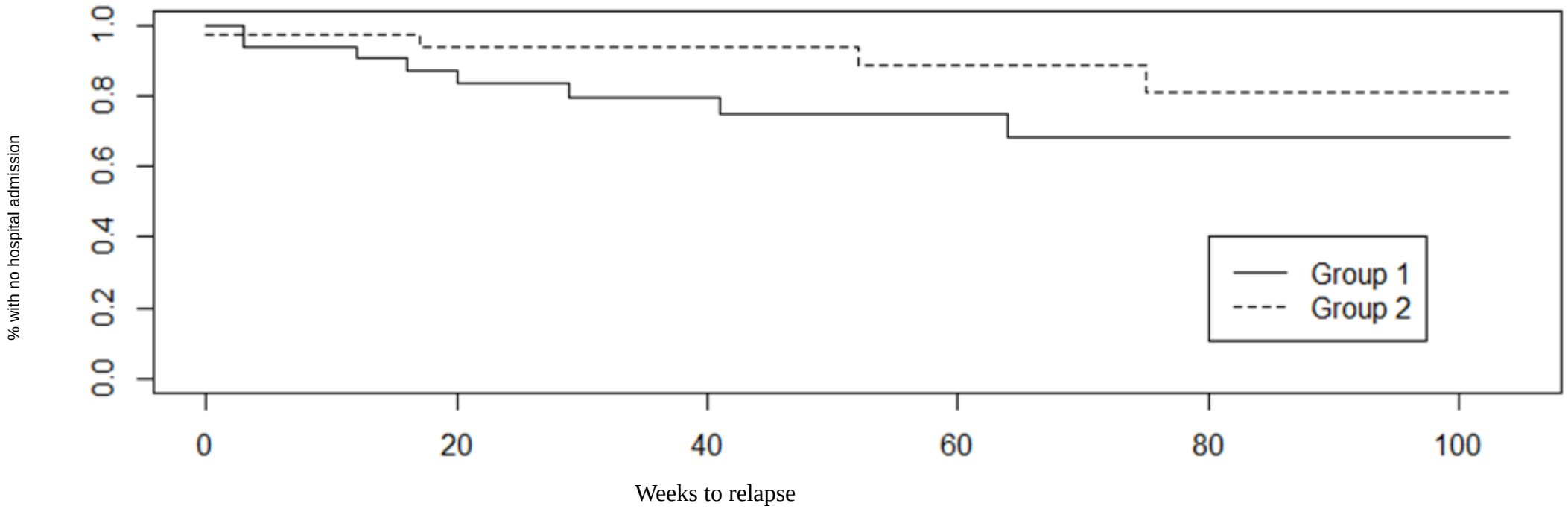


Figure 2. Risk of an affective relapse with or without hospitalization.



Key. Group 1=Eye Movement Desensitisation and Reprocessing (EMDR) Therapy, Group 2=Supportive Therapy.

Figure 3. Risk of an affective relapse with hospitalization.



Key. Group 1=Eye Movement Desensitisation and Reprocessing (EMDR) Therapy, Group 2=Supportive Therapy.

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:
No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:
Sí

- Si la respuesta es afirmativa, por favor, mencione el comité ético que aprobó la investigación y el número de registro.:
Study approval statement: Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/l). Informed consent was signed by all participants prior to enrolment in the study.
- Si la respuesta es afirmativa, por favor, confirme que los autores han cumplido las normas éticas relevantes para la publicación. :
Sí
- Si la respuesta es afirmativa, por favor, confirme que los autores cuentan con el consentimiento informado de los pacientes. :
Sí

3. ¿Su trabajo incluye un ensayo clínico?:
Sí

- Si la respuesta es afirmativa, por favor, confirme que los experimentos se han realizado según las normas CONSORT. :
Sí
- Por favor, indique la entidad en la que se ha registrado y el número de referencia.:
clinical trials (NCT02634372)
(https://classic.clinicaltrials.gov/ct2/show/NCT02634372)

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:
Sí

Dr. Benedicto Crespo Facorro, MD, PhD
Editor-in-Chief
Journal of Psychiatry and Mental Health

18th July, 2023

Dear Sir,

Please find our submission of the manuscript “EMDR therapy vs. Supportive Therapy as adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial”, to be considered for publication in the Journal of Psychiatry and Mental Health.

Bipolar disorder is a serious mental disorder where it is difficult for patients to achieve full functional recovery. This is compounded by the high rates of psychological trauma and trauma symptoms in bipolar disorder patients, as psychological trauma has been shown to negatively impact the clinical course of bipolar disorder. The study we submit represents the first multicentre study to compare the efficacy of a trauma-focused psychotherapy, in this case Eye Movement Desensitisation and Reprocessing (EMDR) therapy, with a control condition in bipolar disorder patients. EMDR therapy is recommended, alongside trauma-focused cognitive behavioural therapy, as a first-line treatment for post-traumatic stress disorder, and in our innovative study, the EMDR protocol was specifically adapted to treat trauma symptoms in a bipolar population. Furthermore, our study is strengthened by the use of an active control condition, supportive therapy, which has been found in previous studies in bipolar disorder to be a strong control condition.

Our findings show that, while EMDR therapy was not significantly superior to supportive therapy in reducing affective relapses and hospitalisations, it was superior to supportive therapy in maintaining improvements in depression, mania, and psychosocial functioning at six months following the end of treatment. These results show that EMDR therapy has promise as an innovative adjunctive psychotherapy, with potential to improve hard-to-treat outcomes in bipolar disorder, such as the remission of subsyndromal depressive symptoms. Furthermore, the results show that treating trauma did not negatively impact dropout or relapse rates. This is an important result as clinicians are often reticent about treating trauma for fear of destabilising affective symptoms, and our results provide the first evidence from a multicentre trial that it is safe to treat trauma symptoms in this population.

On the basis of the above, as the first multicentre study to test a trauma-focused psychotherapy in bipolar disorder patients, and the encouraging results, we believe these findings will be of interest to readers of the Journal of Psychiatry and Mental Health.

We declare that this manuscript is original. This article forms part of the PhD, in preparation, of the first author, and is published as a preprint in PsyArXiv

(https://psyarxiv.com/s5hrf/), with all rights reserved. It is not being considered for publication elsewhere.

As corresponding author, I confirm that the manuscript has been read and approved for submission by all the named authors.

Yours sincerely,

ALICIA VALIENTE GOMEZ / num:08393927

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Alicia Valiente-Gómez, PhD
Centre Fòrum Research Unit
C/ Llull, 410
08019 Barcelona
Spain

Many thanks for the time in reviewing the manuscript and for the opportunity to address this valuable feedback and improve our manuscript. Please find below a point by point response to each of the suggestions and comments related to the article.

[editor's comments:
Many thanks for submitting this RCT - lots of work and efforts on it and nice idea. The results are interesting, but a bit puzzle by the comparator choice (ST) and its effect. What was the rationale behind choosing this comparator? could that be developed in the text? I am uncertain whether both intervention and comparator are effective on reducing relapses or none of them are. It would be helpful having your views on it. Additionally, it would also be helpful to put a bit of economic context: how much is the estimated cost of the intervention (and the comparator?). Please see also the comments by the reviewers below.
Thanks and kind regards
Emilio

Response to editor:

Many thanks for your consideration of our article and time in reviewing our paper and the helpful comments. We have given more detail on our reasons for choosing supportive therapy as the comparator in the introduction:

> *Supportive therapy was chosen as the comparator because, firstly, it can be applied with the same frequency and duration as EMDR but has no trauma component. As research shows that trauma can have a negative impact on relapse rate in BD, comparing EMDR with a non-trauma focused therapy allows for the analysis of the specific impact of the EMDR technique focused on trauma, controlling for more general effects of Furthermore, ST has previously been used as a comparator in studies regarding BD [25,26] and PTSD.[27]*

Furthermore, we have commented more on our views on whether both ST and EMDR are effective or neither of them in the discussion, firstly regarding relapses and then regarding trauma symptoms. We make a cautious interpretation that both are effective but this would need to be tested in the future against a control condition with no therapeutic component:

> Regarding relapses: *A previous study comparing cognitive behavioural therapy with ST in reducing relapses in BD similarly found no significant difference between treatment arms,[26] which was attributed to shared therapeutic components****, which suggests that both therapies may have been helpful in reducing relapses, but this would need to be tested in the future against a wait-list control group.***
>
> *Regarding trauma: It is therefore in our view probable that both treatments were effective in reducing trauma symptoms as compared to baseline, but this would need to be tested against a third group which is a wait-list control. Satisfaction with treatment was very high in both groups with no significant difference between them (p=0.887), with qualitative responses frequently referencing how helpful it was to have the opportunity to receive regular therapy sessions, regardless of treatment arm. However, the impact of ST on trauma symptoms was unexpected.*

Thank you also for your comment regarding the cost, which is an important factor. We have included some further information about this in the discussion:

> *In terms of treatment cost, both treatment arms had the same cost (968 euros/per patient). Although we cannot demonstrate cost-effectiveness of an EMDR intervention in terms of significantly reducing hospital admissions and related medical costs, the improvement in*

functioning may reduce indirect costs, and future studies can focus on identifying the cost-effectiveness of trauma-focused adjunctive psychotherapy in EMDR.

Reviewer #1: In this article, the authors investigated the efficacy of a trauma-focused adjunctive psychotherapy for bipolar disorder, which is a significant research question, as there is a paucity of previous research on this topic. The article is meticulously written and provides a clear description of the EMDR Bipolar protocol employed.

However, some clarifications are needed to improve the reader's comprehension.
1- Clarification is needed regarding the definition of "affective episodes" and whether hypomania was included as an episode.

Response to reviewer 1: Many thanks for the time taken to review the article and the valuable comments. Regarding the first point, this is an important point to clarify. We have added this phrase to make it clear:

Affective episodes were defined as episodes meeting DSM-5 criteria for a hypomanic, manic, or depressive episode.

2- In a similar way, further explanation is required about how "relapses" were defined and identified.

Response: Thank you for this comment. We have provided more detail about this in the methods section:

Relapses were defined as the participant meeting DSM-5 criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study.

3- Patients were euthymic, but it is not specified if changes in treatments were allowed in the pre-enrolment and study phases.

Response: thank you for this. We have specified this:

Where necessary, changes in pharmacological treatment at any point throughout the study period were permitted, due to the clinical manifestations of bipolar disorder often changing over time, requiring a different pharmacological approach.

Further to this, we included an analysis to verify if there were any significant differences between groups in medication changes, which could have influenced the results, finding that there were no significant difference in pharmacological changes at any time point in the study:

The analysis in Table 1 shows no significant differences between EMDR and ST groups in pharmacological treatment at baseline. There were no significant between-group differences in terms of changes to pharmacological between baseline and post-treatment (X2 =0.188, p=0.885), between post-treatment and 12-month follow-up (X2 =1.245, p=0.448), nor between 12-month and 24-month follow-up (X2 =4.408, p=0.119).

4- Given the small sample size and the number of variables, particularly with multiple groups (e.g., 9 groups for work status), clarification is needed on whether corrections, such as Fisher's test, were applied when using the chi-square test for group comparison (the test may not be accurate if more than 20% of the cells have expected frequencies below five).

Response: Thanks for this. Yates' continuity correction was applied to all the Chi Square calculations. Where there were variables with multiple groups, we have redone these analyses combining groups with small values (e.g. widowed has been combined with separated/divorced) - these changes can be seen in Table 1.

5- While the study mentions the inclusion of both bipolar type 1 and type 2 groups as a strength, it omits a comparative analysis between them. Could the authors provide an analysis of the differences between these two diagnostic groups? Furthermore, the assertion that "EMDR appears promising for male and female BD-I and BD-II patients with trauma symptoms" appears to lack precision, as the efficacy could potentially be attributed to a sole diagnostic group, possibly as a sum effect (given that only sex was factored into the statistical models).

Response: Thank you for this comment. We agree that it is interesting to factor BD type into the analysis, and that with the current analysis we cannot justify the assertion in the text. We have included three supplementary analyses: one regarding risk of relapse according to BD type, another regarding differences between BD type at each time point, and a final analysis to understand differences between BD-I and BD-II in terms of treatment response to each treatment arms. This has been added into the text as follows:

There was no significant difference between BD-I and BD-II in terms of risk of relapse (z=-0.26, p=0.80 for a relapse of any type; z=-0.34, p=0.74 for a relapse with hospital admission).

Furthermore, there was no significant difference in BD results for BD-II as compared to BD-I at any time point, except for a possibly significant result for the SCIP at 12 months (unadjusted p=0.015), where BD-II participants scored on average higher than BD-I (see Supplementary Table 4). An analysis of differences between BD-I and BD-II in response to the different treatment arms revealed no significant differences in any variable (please see Supplementary Table 5).

6- Were there any observed differences between depressive and manic relapses that could provide further insights?

Thank you for this comment. Unfortunately we did not collect the data to make this analysis possible, but this is a very interesting point which we will keep in mind for future studies.

7- Despite the therapies' efficacy (as their safety and acceptability), a high dropout rate is noted. Could the authors offer an explanation for this trend?

Thank you for this comment. We have discussed this further in the discussion:

> *Dropout rates in BD studies at 12 months have been estimated at 34 and between 25% and 50% in outpatient psychiatric care, whereas in our study at 12 months the dropout rate was 56%. This may be due to the long illness duration and high number of previous affective episodes in our study population, which can negatively impact dropout. Furthermore, it was a highly traumatised sample, and dropout rates in PTSD interventions are considered high as systematic reviews in the treatment of PTSD in combat veterans show, with an overall pooled dropout rate between 24% and 36%. Furthermore, the SARS-COV-2 pandemic may have had a negative impact in drop-out rates, particularly for the 12-month and 24-month follow-ups*

8- The transition to internet-based interventions due to the COVID-19 pandemic is intriguing. It might be beneficial for the authors to briefly share their perspective on the feasibility of this approach as a potential standard procedure compared to in-person therapy.

Response: Many thanks. Given that we applied this approach with a very small number of patients in exceptional circumstances, we have not commented more extensively in this paper, but in more recent studies we have continued to offer EMDR online where it is more appropriate (for example, where patients have difficulties in coming to the hospital for treatment) and anecdotal evidence is that the results are similar (Faretta et al, 2022 10.3389/fpsyg.2022.964407). We have added in this sentence;

Future research can determine whether online delivery can be considered as a possible intervention delivery mode.

Reviewer #2: 1. Abstract: "This multicentre RCT included 77 patients with BD and current trauma-related Symptoms."
It is important that when utilizing the acronym 'RCT,' its expansion as 'Randomized Controlled Trial' is provided for elucidation. This practice is particularly significant within the abstract section and during the initial instance of employing this terminology.

Response: Many thanks for your time in reviewing the article and your helpful comments. Thank you for pointing this out, we have removed the acronym.

Abstract: What were the conclusions for supportive therapy? What were the conclusions for EMDR versus ST?

Response: Thank you, we have added some more detail in the abstract to make this clearer:

> *Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR* ***was superior to ST*** *in reducing of affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment.* ***Both EMDR and ST reduced trauma symptoms as compared to baseline, possibly due to a shared benefit of psychotherapy.*** *Importantly, focusing on traumatic events did not increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.*

2. Introduction: " BD has a strong genetic components…."
Please provide more in-depth explanation regarding the genetic components.

Response: Thank you, we have included more information explaining the genetic components:

> *It is considered one of the most heritable mental illnesses, and recent genome-wide association studies have shown that, while variations of the gene CACNA1C are the most widely studied and replicated,[11] there are 64 genes implicated in BD.[12] However, environmental factors as well as gene x environment interactions can best explain its aetiology.[1]*

3. Introduction: "Eye Movement Desensitization and Reprocessing (EMDR) therapy….."
Please provide a more in-depth explanation regarding what eye movement desensitization and reprocessing therapy is.

Response: Thank you, we have provided more information on this:

> *Eye Movement Desensitisation and Reprocessing (EMDR) therapy[23] is recommended, a, alongside cognitive behavioural therapy, as one of the first line treatments for PTSD according to reviews and treatment guidelines from the American Psychiatric Association, American Psychological Association, World Health Organisation, and International Society for Traumatic Stress Studies, among others[24,25] EMDR therapy comprises a structured eight-phase protocol to help patients heal from traumatic events. Each traumatic memory is processed by the client focusing on its visual, emotional, and somatic components, while the therapist applies sets of bilateral stimulation, most commonly in the form of side-to-side eye movements. Through this process, the person becomes desensitised to the traumatic memory (i.e. they can think about it without any negative emotional, cognitive, or somatic reaction), and the therapist then works with the client to install a positive reinterpretation of the traumatic event, thus helping the patient to heal from each traumatic event. Following processing of past traumatic memories, the same protocol is applied to current stressors and potential future stressors.*

4. Randomization: "Evaluators provided the study coordinator (AM-A)….., who sent theses to JR….."
Please clarify the acronyms 'AM-A' and 'JR'
Response: apologies this was not clear. These are the initials of the authors involved in the process – Ana Moreno-Alcázar and Joaquim Radua. We have included “the author” to help make this clearer.

5. Results and Discussion
Please review the format and ensure to replace 'affective relapse' with the specific context of your study, and verify that the values and interpretations accurately reflect your research findings.
Response: thank you. We have provided a more exact definition of both affective episode and relapse in the methods section to make this clearer:

> *Affective episodes were defined as episodes meeting DSM-V criteria for a hypomanic, manic, or depressive episode.*

Relapses were defined as the participant meeting DSM-5criteria for an episode of mania, depression, or hypomania, following a period of any duration of euthymia or subsyndromal symptoms not meeting criteria for a full affective episode. Relapses were categorised as either requiring hospitalisation or not requiring hospitalisation. The relapses were identified at each time point through administration of the BDRS and YMRS scales, a review of medical records, and through patient intervention. Participants with a relapse requiring hospitalisation were considered dropout in the study, due to it not being possible for them to attend the therapy sessions in this case, while participants with relapses which did not require hospitalisation continued in the study.

We have reviewed carefully the values and interpretations and have verified that they are accurate. We spotted a small error with the calculation of the effects sizes and these have been changed in the text.

6. Discussion
It is important to enhance the organization of the content and concentrate more on bipolar patients. Some redundant comments should be removed, as there is no need to repeat the same point multiple times.

Many thanks for this comment. We have reviewed the discussion in detail and attempted to ensure the organization is coherent and focused on bipolar patients, and to remove redundancies, while also amplifying other points in accordance with the requested revisions.

7. There are numerous acronyms present; it is advisable to reduce their usage to improve the readability and understanding of the text.
Thank you, we have removed the acronyms which were not present many times in the text.

8. The majority of the bibliography is more than 4 years old. A minimum of 50% should be no older than 4 years.

Response: thank you. We have added in some new references. Leaving to one side the references for the scales, which are numerous as there are all the Spanish validations in addition to the English versions, and these are generally older than four years, we have now improved the bibliography so that 50% are within the last four years.

9. Keyword: Why is the term "supportive therapy" not present?

Response: thank you, this was an oversight. We have now added this.

10.Every time new terminology is introduced, it should be accompanied by an explanation to elucidate the purpose of its incorporation. In this context, it is crucial to clarify the rationale behind utilizing such terminology, ensuring that the readers comprehend its significance within the research context. In the manuscript, some terms like ANOVA (among other examples) are used; however, they did not provide an explanation for their usage. To enhance the clarity and comprehensibility of the manuscript, it is recommended to provide concise explanations for the introduction of new terminologies.

Many thanks, we have included a definition of ANOVA; and have reviewed the text for other acronyms and have removed them where they are not helpful, and ensured the definition is next to it.