UNIVERSITAT DE BARCELONA

Self and Hetero-Aggression

Clinical Implications in Bipolar Disorder and Mixed States

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Norma Verdolini

SELF- AND HETERO-AGGRESSION: Clinical Implications in Bipolar Disorder and Mixed States

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Clinical Implications in Bipolar Disorder and Mixed States

Thesis submitted in order to obtain the academic degree of Doctor at the University of Barcelona by

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CERTIFY that they have guided and supervised this doctoral thesis entitled **"SELF- AND HETERO-AGGRESSION: Clinical Implications in Bipolar Disorder and Mixed States"**, which is presented in order to obtain the title of doctor by the candidate Norma Verdolini. They thereby assert that this thesis fulfills all the required criteria to be defended.

To all those I can call my family

To the pillars of my heart

To my roots, for the time to come

Diffidate, gente, diffidate dagli inquieti alla ricerca di novitá assurde e di cambiamenti radicali, diffidate dagli insoddisfatti di quello che sanno che vorrebbero conoscere tutto, diffidate di coloro che non accettano il nostro credo del *"parvula sed apta mihi"*. Diffidate di quelli che vogliono cambiare la loro vita per provare nuove esperienze. Diffidate soprattutto di coloro che vogliono sapere e conoscere sempre di piú, perché questa gente non avrá mai pace.

Beware, people, distrust the restless people in search of absurd innovations and radical changes, distrust those dissatisfied of what they know because they would like to know everything, distrust those who do not accept our belief in the *"parvula sed apta mihi"*. Beware of those who want to change their lives to try new experiences. Beware especially of those who want to know and know more and more, because these people will never have peace.

N.48 (Luglio 2001) - Dr. Livingstone, I suppose
I fantasmi della libertá, Paolo Pancheri

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The acknowledgements page in a PhD thesis is generally considered to be optional. On the contrary, I think that it is the most important part and the most difficult to write. Indeed, when you say thank you to somebody for his/her help you should be capable to give back at least the same amount of nobility that is intrinsic to the ability to support somebody without asking nothing in exchange.

Working in investigation is challenging but you are paid back with wonder if passion guides you. That's how I felt in these years and even if sometimes I was wandering, I was not lost at all and part of the merit goes to the people I would like to thank below.

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TABLE OF CONTENTS

FRAMEWORK

This work is presented to the University of Barcelona in fulfillment of the requirements and procedures for the degree of Doctor in the format of compendium of published articles. The published articles included in this thesis (*) are part of a line of research and a series of national and international presentations, posters and scientific papers regarding the interesting topic of self and hetero-aggression in patients suffering from bipolar disorder with a focus on mixed states and their specific clinical presentations. Furthermore, the implications of self and hetero-aggression on the prognosis and longitudinal course of bipolar disorder (particularly mixed states) as well as on the therapeutic approach have been addressed. As for the requirements, at least two of the included articles are original published articles authored by the doctorate candidate within the first two quartiles of the field of psychiatry.

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The research work presented in this thesis has been conducted at the **Bipolar Disorders Program of the Hospital Clínic de Barcelona**, part of the Insitut d'Investigacions Biomèdiques August Pi y Sunyer (IDIBAPS), the University of Barcelona (UB) and the Centro para la Investigación Biomédica en Red de la Salud Mental (CIBERSAM), in close collaboration with the **FIDMAG Germanes Hospitalàries Research Foundation**, part of the CIBERSAM, and with the **Division of Psychiatry, Clinical Psychology and Rehabilitation** of the Department of Medicine of the University of Perugia (Italy).

The thesis project had the participation and collaboration of other national and international Institutions (as reported in Figure 1).

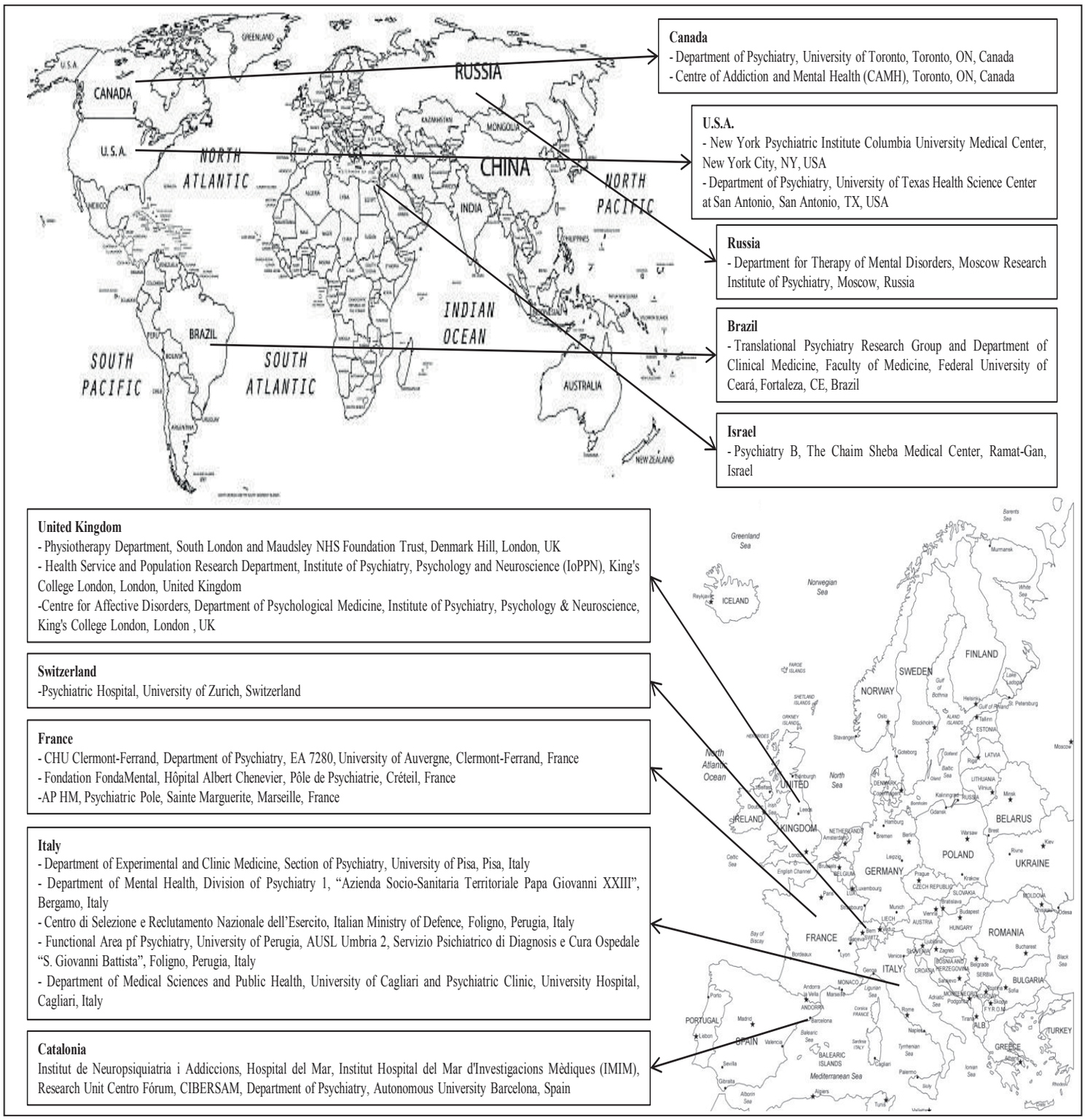

Figure 1. *List of national and international Institutions collaborating in the research line*

The indexed publications are listed below. In bold parentheses the study number determined by thematic sequence order. The Impact factor is reported for the year of publication. If it was not available, the corresponding most recent impact factor was reported.

Total research line impact factor: 22.13

* Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis. **Verdolini N**, Pacchiarotti I, Köhler CA, Reinares M, Samalin L, Colom F, Tortorella A, Stubbs B, Carvalho AF, Vieta E, Murru A. J Affect Disord. 2018 Jul 5;239:161-170. doi: 10.1016/j.jad.2018.06.050. **(Study I)**. **Impact factor 2017: 3.786**

* The aggressor at the mirror: Psychiatric correlates of deliberate self-harm in male prison inmates. **Verdolini N**, Murru A, Attademo L, Garinella R, Pacchiarotti I, Bonnin CDM, Samalin L, Pauselli L, Piselli M, Tamantini A, Quartesan R, Carvalho AF, Vieta E, Tortorella A. Eur Psychiatry. 2017 Jul;44:153-160. doi: 10.1016/j.eurpsy.2017.04.002. Epub 2017 Apr 14 **(Study II)**. **Impact factor 2017: 4.129**

* Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. **Verdolini N**, Perugi G, Samalin L, Murru A, Angst J, Azorin JM, Bowden CL, Mosolov S, Young AH, Barbuti M, Guiso G, Popovic D, Vieta E, Pacchiarotti I; BRIDGE-II-MIX Study Group. Acta Psychiatr Scand. 2017 Oct;136(4):362-372. doi: 10.1111/acps.12777. Epub 2017 Jul 25. **(Study III)**. **Impact factor 2017: 4.984**

* Sultans of swing: A reappraisal of the intertwined association between affective lability and mood reactivity in a post-hoc analysis of the BRIDGE-II-MIX study. **Verdolini N**, Menculini G, Perugi G, Murru A, Samalin L, Angst J, Azorin JM, Bowden CL, Mosolov S, Young AH, Barbuti M, Popovic D, Vieta E, Pacchiarotti I; BRIDGE-II-MIX Study Group. J Clin Psychiatry. In press. **(Study IV)**. **Impact factor 2017: 4.247**

* Mixed states in bipolar and major depressive disorders: Systematic review and quality appraisal of guidelines. **Verdolini N**, Hidalgo-Mazzei D, Murru A, Pacchiarotti I, Samalin L, Young AH, Vieta E, Carvalho AF. Acta Psychiatr Scand. 2018 May 13. doi: 10.1111/acps.12896 **(Study V)**. **Impact factor 2017: 4.984**

ABSTRACTS

English

Introduction: The poorest outcomes in bipolar disorder are represented by self-aggressive (i.e. deliberate self-harm, attempted or completed suicide) and hetero-aggressive violent behaviors. A better understanding of the clinical factors associated with both the risk of criminal behavior and the risk of self-injurious behaviors among individuals suffering from bipolar disorder may improve the course of illness and the risk management.

Aim: The main objective of this doctoral thesis was to evaluate the psychiatric correlates of self- or hetero-aggression in the context of bipolar disorder, particularly in those patients presenting mixed features.

Methodology: The five published articles included in this thesis had different study designs: **Study I.** A meta-analysis including studies on the association between bipolar disorder and violent criminal behaviors; **Study II.** A cross-sectional study assessing clinical correlates of deliberate self-harm and suicide attempts in prisoners, particularly mood disorders and bipolar disorder; **Study III.** A post-hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX multicentric study aimed at evaluating hetero-aggression as a mixed feature during a major depressive episode and its relationship with other clinical variables, such as the lifetime history of suicide attempts. **Study IV.** Another post-hoc analysis of the BRIDGE-II-Mix study focused on the clinical relevance of the intertwined association between affective lability and mood reactivity and their correlation with other mixed symptoms, particularly verbal or physical hetero-aggression. **Study V.** A critical systematic review of guidelines on the treatment of mixed states with a methodological quantitative quality assessment of included articles.

Results: One every fourteen patients suffering from bipolar disorder reported violent criminal behavior. Even though the association with violent criminality was not significant when patients suffering from bipolar disorder were compared with patients suffering from any other psychiatric disorder, the chance of committing violent criminal behavior was smaller in patients with bipolar disorder than in those suffering from psychotic disorders but higher in comparison with patients with depressive disorders. In meta-regression analyses, no significant moderators emerged. Mood disorders as well as psychoses, borderline personality disorder and poly-drug use were the most relevant clinical predictors of deliberate self-harm in prison. In the sample of affective patients evaluated during a major depressive episode, the presence of aggressive behaviors was mainly related with bipolarity and the most relevant clinical variable associated with aggression was the presence of mixed features. A significant increase of the risk for aggressive behaviors associated with the presence of lifetime

suicide attempts has been observed. Verbal or physical hetero-aggression during the index major depressive episode was inversely associated with the presence of affective lability. The identification of self- and hetero-aggressive behaviors represents the target of a tailored treatment strategy in the subgroup of bipolar disorder patients characterized by a shared psychopathological "aggressive" dimension.

Conclusions: the self- and hetero-aggressive components of bipolar disorder have been investigated in this doctoral thesis, leading to a better and broader knowledge on the topic, both in psychiatric and in correctional settings. Specific clinical characteristics, such as the mixed presentations, have been identified as possible goals of treatment.

Català

Introducció: Una mala evolució del trastorn bipolar es caracteritza per conductes violentes tant de tipus autoagressiu (incloent, entre d'altres, temptatives autolítiques o suïcidi consumat) com heteroagressiu. Una millor comprensió dels factors clínics associats al risc de cometre aquests tipus d'alteracions conductuals en individus que pateixen un trastorn bipolar podria ajudar a millorar el curs de la malaltia.
Objectiu: L'objectiu principal d'aquesta tesi doctoral ha sigut avaluar els correlats psiquiàtrics d'auto i/o heteroagressió en el trastorn bipolar, especialment en pacients amb característiques mixtes.
Mètodes: Cadascun dels cinc articles publicats inclosos en aquesta tesi presenten dissenys diferents. Estudi I: metanàlisis que inclou estudis sobre l'associació entre el trastorn bipolar i els comportaments criminals violents. Estudi II: estudi transversal que avalua els correlats clínics dels intents de suïcidi en presoners, especialment trastorns de l'estat d'ànim i trastorn bipolar. Estudi III: Anàlisi post-hoc dels trastorns bipolars - Estudi multicèntric per a la millora del diagnòstic, orientació i educació (BRIDGE)-II-MIX per avaluar l'heteroagressió com a característica mixta durant un episodi depressiu major i la seva relació amb altres variables clíniques, com ara la història d'intents de suïcidi. Estudi IV: segon anàlisi post-hoc de l'estudi BRIDGE-II-MIX centrat en la rellevància clínica de l'associació entre la labilitat afectiva i la reactivitat de l'estat d'ànim i la seva correlació amb altres símptomes mixtos, en particular l'heteroagressió verbal o física. Estudi V: revisió sistemàtica crítica de les pautes sobre el tractament dels estats mixtes amb una avaluació quantitativa metodològica de qualitat dels articles inclosos.
Resultats: Un de cada catorze pacients amb trastorn bipolar van reportar un comportament criminal violent. Tot i que l'associació amb aquesta variable no va ser significativa quan es va comparar trastorn bipolar amb algun altre trastorn psiquiàtric, la possibilitat de cometre un delicte violent va resultar menor en comparació amb pacients amb trastorns psicòtics, i major amb trastorns depressius. En els anàlisis de metaregressió no vam obtenir cap moderador significatiu. Els trastorns de l'estat d'ànim, així com els trastorns psicòtics, el trastorn límit de la personalitat i l'ús de múltiples fàrmacs es van identificar com els predictors clínics més determinants de la

conducta autoagressiva entre la mostra d'individus presos. En la mostra de pacients afectius avaluats durant un episodi depressiu major, la presència de comportaments agressius es va relacionar principalment amb la bipolaritat. Concretament, la variable clínica més rellevant associada a la conducta agressiva va ser la presència de característiques mixtes. També es va observar un increment significatiu del risc de comportaments agressius associats a la presència d'intents de suïcidi al llarg de la vida. L'heteroagressió verbal o física durant l'episodi de depressió major índex es va associar inversament a la presència de labilitat afectiva. La identificació de conductes d'auto i heteroagressivitat podria representar l'objectiu d'una estratègia de tractament dissenyat específicament per aquest subgrup de pacients amb trastorns bipolar caracteritzats per una dimensió "agressiva" psicopatològica compartida.
Conclusions: La present tesi doctoral ha investigat els components d'auto i heteroagressivitat del trastorn bipolar conduint-nos cap a un millor i més ampli coneixement sobre el tema, no només en l'àmbit psiquiàtric però també correccional. També ha identificat diferents característiques clíniques específiques, com ara les presentacions mixtes, com a possibles objectius de tractament.

Castellano

Introducción: Las consecuencias más severas que presentan pacientes con trastorno bipolar son las que ocurren por actos auto-agresivos (p. ej. autolesiones, intentos suicidas o el suicidio consumado) y comportamientos hetero-agresivos violentos. Una mejor comprensión de los factores clínicos asociados tanto con el riesgo de conducta criminal como con el riesgo de comportamientos auto-perjudiciales en los individuos que padecen de trastorno bipolar, podría contribuir a mejorar el curso de enfermedad y la gestión de los riesgos asociados.

Objetivo: El objetivo principal de esta tesis doctoral fue evaluar los correlatos clínicos de auto o hetero-agresiones, en el contexto del trastorno bipolar, con especial foco en aquellos pacientes que presentan características clínicas mixtas.

Metodología: Los cinco artículos incluidos en esta tesis tenían diseños de estudio diferentes: **Estudio I**. Meta-análisis que incluye estudios sobre la asociación entre trastorno bipolar y conductas criminales violentas; **Estudio II.** Estudio transversal que evalúa los correlatos clínicos de autolesiones e intentos de suicidio en presos, en particular trastornos afectivos y el trastorno bipolar; **Estudio III.** Análisis post-hoc del estudio BRIDGE-II-MIX, con el objetivo de evaluar la hetero-agresión considerada como característica mixta durante un episodio depresivo, y su relación con otras variables clínicas, como la historia de intentos de suicidio; **Estudio IV.** Análisis post-hoc del estudio de BRIDGE-II-MIX, enfocado en la importancia clínica de la asociación entrelazada entre la labilidad afectiva y la reactividad de humor y su correlación con otros síntomas mixtos, en particular la hetero-agresión verbal o física; **Estudio V**. Revisión crítica sistemática de guías clínicas sobre el tratamiento de estados mixtos con una evaluación cuantitativa de la calidad metodológica de los artículos incluidos.

Resultados: Uno cada catorce pacientes que padecen de trastorno bipolar presentó una conducta criminal violenta. Aunque la asociación con la criminalidad violenta no fuera significativa cuando los pacientes que sufren del trastorno bipolar fueron comparados con pacientes que sufren de cualquier otro trastorno psiquiátrico, la posibilidad de cometer una conducta criminal violenta era menor en pacientes con trastorno bipolar que en aquellos que padecen de trastornos psicóticos, pero mayor en comparación con pacientes con trastornos depresivos. Los análisis de meta-regresión no detectaron moderadores significativos.
Los trastornos afectivos así como las psicosis, el trastorno límite de personalidad y el consumo de diferentes tóxicos eran los factores clínicos de riesgo más relevantes de autolesiones en la cárcel. En la muestra de pacientes afectivos evaluados durante un episodio depresivo, la presencia de comportamientos agresivos principalmente fue relacionada con la bipolaridad y la variable más relevante clínica asociada con agresión, fue la presencia de características mixtas. Se observó además un aumento significativo del riesgo para comportamientos agresivos asociados con la presencia de intentos suicidas previos. La hetero-agresión verbal o física durante un episodio depresivo era inversamente asociada con la presencia de labilidad afectiva. La identificación comportamientos auto y hetero-agresivos representa el objetivo de una estrategia de tratamiento adaptada en el subgrupo de pacientes con trastorno bipolar, caracterizado por una dimensión psicopatológica "agresiva" compartida.

Conclusiones: Los componentes auto y hetero-agresivos del trastorno bipolar, tanto en ámbito psiquiátrico como en las cárceles han sido investigadas en esta tesis doctoral, conduciendo a un mejor y más amplio conocimiento sobre el tema. Características específicas clínicas, como las presentaciones mixtas, han sido identificadas como posibles objetivos de tratamiento.

Italiano

Introduzione: Le conseguenze più negative del disturbo bipolare sono rappresentate da comportamenti auto- (i.e. autolesionismo, tentativi di suicidio) e etero-aggressivi violenti. Una migliore comprensione dei fattori clinici associati sia con il rischio di comportamento criminale ed il rischio di comportamenti autolesivi negli individui che soffrono di disturbo bipolare può migliorare il corso clinico di malattia e la gestione di rischio.

Obiettivo: L'obiettivo principale di questa tesi di dottorato era di valutare i correlati psichiatrici di auto- e etero-aggressivitá nel contesto del disturbo bipolare, particolarmente in quei pazienti che presentano caratteristiche miste.

Metodologia: I cinque articoli inclusi in questa tesi avevano disegni di studio diversi: **Studio I.** Un meta-analisi che includeva studi sull'associazione tra disturbo bipolare e comportamenti criminale violento; **Studio II.** Uno studio trasversale che stimava i correlati clinici di autolesionismo e tentativi di suicidio, particolarmente i disturbi dell'umore e il disturbo bipolare, in detenuti; **Studio III.** Un analisi post-hoc dello studio BRIDGE-II-MIX che valorava la etero-aggressivitá come caratteristica mista durante un episodio depressivo maggiore e la sua relazione con altre variabili cliniche,

come la storia clinica positiva per tentativi di suicidio; **Studio IV.** Un altro studio post-hoc incentrato sull'attinenza clinica dell'associazione tra labilitá affettivo e la reattività dell'umore e la loro correlazione con gli altri sintomi misti, particolarmente l'etero-aggressivitá verbale o fisica; **Studio V.** Una revisione sistematica e critica sul trattamento degli stati mmisti con una valutazione quantitativa della qualità metodologica degli articoli inclusi.

Risultati: Un paziente su quattordici che soffre di disturbo bipolare riportarono un comportamento criminale violento. Anche se l'associazione con criminalitá violenta non era significativa quando nella comparazione dei pazienti con disturbo bipolare con quelli che presentavano qualsiasi altro disturbo psichiatrico, il rischio di commettere comportamento criminale violento era inferiore nei pazienti con disturbo bipolare che in quelli con disturbo psicotico ma superiore rispetto ai pazienti che presentavano disturbi depressivi. Nelle analisi di meta-regressione, non emerse nessuno moderatore significativo. I disturbi dell'umore così come le psicosi, il disturbo borderline di personalità e il poli-abuso di sostanze erano i predittori clinici piú importanti di autolesionismo. Nel campione di pazienti con disturbo affettivo valutati durante un episodio depressivo maggiore, la presenza di comportamenti aggressivi fu associata principalmente con bipolarità e la variabile clinica maggiormente associata con aggressivitá era la presenza di caratteristiche miste. Un aumento significativo del rischio di comportamenti aggressivi è stato osservato per la presenza nella storia clinica di tentativi di suicidio. L' etero-aggressivitá verbale o fisica durante un episodio depressivo era inversamente associato con la presenza di labilitá affettivo. L'identificazione di comportamenti auto- o etero-lesivi rappresenta l'obiettivo di una strategia di trattamento appositamente modellata per il sottogruppo di pazienti con disturbo bipolare caratterizzato dalla dimensione psicopatologicacondivisa definita "aggressitá".

Conclusioni: Le componenti di auto- e etero-aggressivitá del disturbo bipolare sono stati obiettivo di ricerca in questa tesi di dottorato, conducendo ad una migliore e più ampia conoscenza sul tema, sia in ambito psichiatrico che correzionale. Specifiche caratteristiche cliniche, come le presentazioni miste, sono state identificate come possibili obiettivi di trattamento.

JUSTIFICATION

Bipolar disorder (BD) is a severe chronic mood disorder characterized by episodes of mania, hypomania, and alternating or intertwining episodes of depression with the presence of subthreshold symptoms between the episodes (Grande et al., 2016). A complex and quite frequent presentation of BD is represented by the occurrence of mixed features (MFS), defined as the coexistence of three or more depressive or hypo/manic features during a hypo/manic or major depressive episodes (Solé et al., 2017).

The prognosis varies widely, depending on BD clinical features (i.e. presence of psychotic symptoms, rapid cycling, number of illness episodes, predominant polarity) and comorbid psychiatric (i.e. substance related and personality disorders) or medical comorbidities (i.e. metabolic and cardiovascular disorders). Approximately 30-40% of major mood episodes that occur over the course of BD appear to exhibit mixed features and the presence of MFS identifies a subgroup of individuals with greater illness complexity and a higher rate of psychiatric or medical comorbidity (McIntyre et al., 2015).

The poorest outcomes in BD are represented by self-aggressive behaviors, namely deliberate self-harm (DSH) and attempted or completed suicide, as well as by hetero-aggressive acts, such as violent and non-violent crimes (Goodwin et al., 2016).

Aggression is defined as an overt behavior involving intent to inflict noxious stimulation or to behave destructively towards another organism or object. In psychiatry, it is a behavioral response and it may be self-directed (Moyer, 1976). The concept of "violence" generally refers to aggression in humans and is seen as both the basis of criminal behavior and a reason for stigma in mental illness.

In BD, the risk of criminality may not be as widely appreciated as the risk for suicide, but offending is actually a more common outcome and thus associated with a higher absolute risk. The risk of violence was increased in individuals who self-harmed, particularly in BD patients (Sahlin et al., 2017). Suicide in BD is independently associated with clinical variables, particularly lifetime DSH and criminality (Webb et al., 2014), underlining the possible underpinning neurobiological role of aggression

for poor prognostic outcomes in BD. Indeed, aggression has assumed particular importance as a core feature of manic and mixed states, independently from psychosis, and often emerging as a correlate of comorbid substance abuse and suicidality (Maj et al., 2003). Nonetheless, it is not yet currently included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for mania and mixed features specifier (American Psychiatric Association., 2013).

Aggression is linked to violent crime and suicide in psychiatric and forensic populations (Sahlin et al., 2017). According to literature, the impulsive subtype of aggression is the most frequently motivating criminal behavior in BD, especially occurring during manic episodes (Siever, 2008). At the same time, impulsive aggression in mood disorders may be a reliable suicide risk marker as it seems specifically related to suicidal behaviors (Perroud et al., 2011). In addition, the combined risk of suicidality and criminality in BD was found to be substantially elevated (Webb et al., 2014).

A better understanding of the clinical factors associated with both the risk of criminal behavior and the risk of self-injurious behaviors among individuals suffering from BD could be of paramount importance. Clinical prediction rules focusing on multiple vulnerabilities of BD may improve risk management, especially when there is a history of self-injurious behaviors or criminal offending, (Webb et al., 2014).

As a consequence, the self- and hetero-aggressive components of BD needed to be better investigated, both in psychiatric and in correctional settings, in order to identify a sub-group of patients within BD individuals, particularly in those with MFS, that could represent the goal of a tailored treatment.

In order to try to compensate these unmet needs of clinic and research, we planned this line of research with the aim to better understand self- and hetero-aggression in BD, particularly in a subgroup of patients showing mixed features, trying to identify the specific clinical features that may precipitate aggressive behaviors in BD patients (see Figure 2).

The first step was to study criminal behavior as a proxy of hetero-aggression and violence in BD. We quantitatively evaluated the association between criminal behavior and BD as well as the possible moderators (i.e. clinical features, comorbid disorders)

for this association through a meta-analysis and a meta-regression approach. We investigated the risk of criminal behavior for BD in comparison with other psychiatric disorders such as major depressive disorder (MDD), schizophrenia and other psychoses, drug and alcohol related disorders and personality disorders. To our knowledge, this was the first systematic review and meta-analysis to provide a quantitative analysis of violent criminal behavior and its components in patients with BD **(Study I)**.

The second step was to determine the prevalence of DSH in inmates, as it has been less studied than suicidality in the prison setting, and we tried to establish the association between BD and DSH in prison **(Study II)**.

Furthermore, we tried to connect these previous findings in a third study **(Study III)**, a post-hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX multicentric study, aimed at evaluating hetero-aggression as a mixed feature during a major depressive episode (MDE) and its relationship with BD and other clinical variables, such as the lifetime history of suicide attempts.

Study IV was aimed at assessing the psychopathological role of affective lability as a possible mixed symptom and a clinical correlate of atypical features in depression. The study was a post-hoc analysis of the BRIDGE-II-MIX study, focused on the clinical relevance of the intertwined association between affective lability and mood reactivity and their correlation with other mixed symptoms, particularly verbal or physical hetero-aggression.

On the basis of the results of these studies, we have been able to establish the possible clinical and treatment implications for aggression in mixed states and BD. As a consequence, we decided to address the unmet need of proper indications in the treatment of mixed states. We developed a PROSPERO protocol in order to conduct a critical systematic review of existing evidence and a comprehensive overview of guidelines on the treatment of mixed states, providing every-day practice suggestions on the management and treatment of specific mixed symptoms and associated clinical features, such as hetero- and self-aggression **(Study V)**.

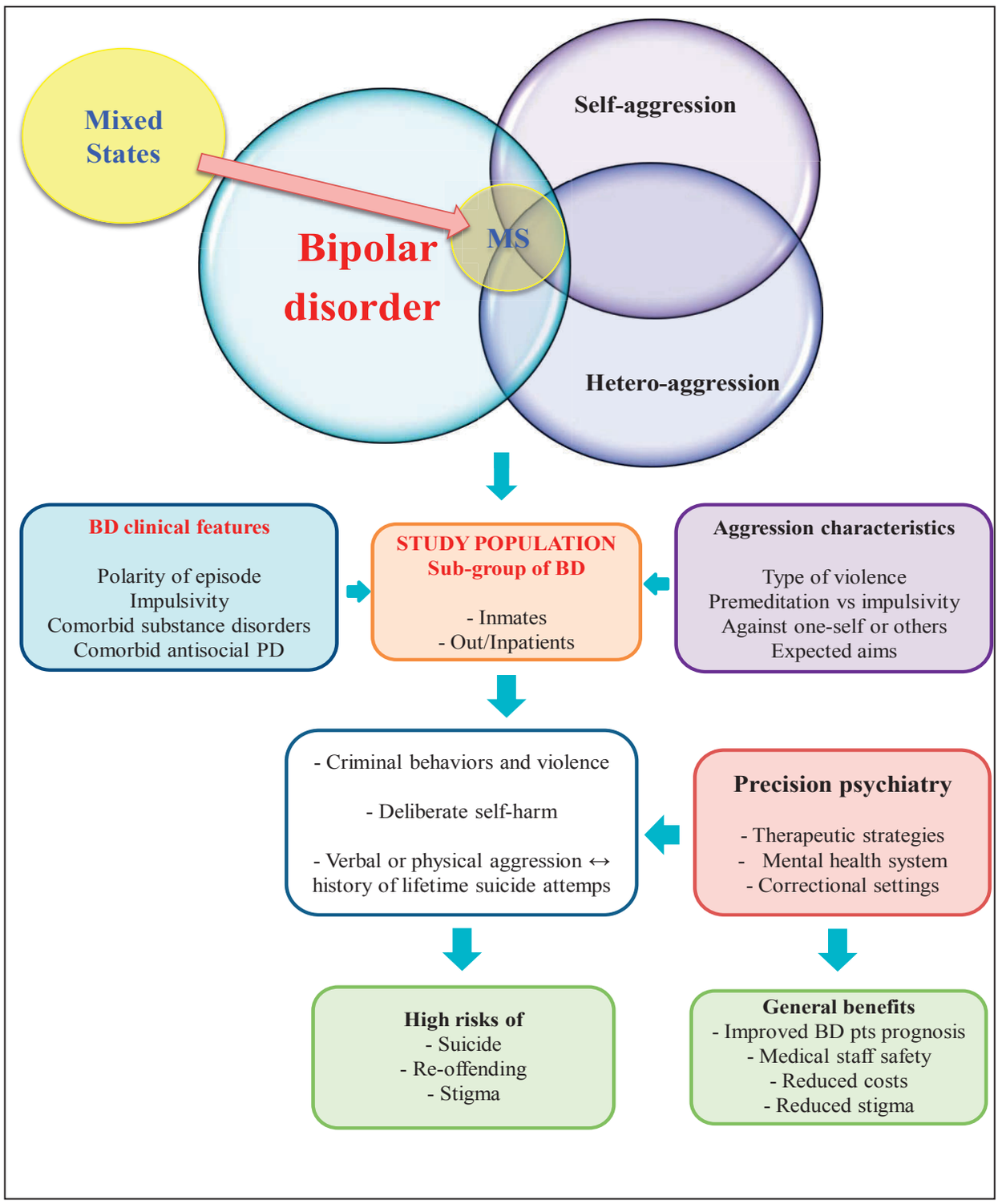

Figure 2. *Self and hetero-aggression in BD and MS; research line*
Abbreviations: ***BD****=bipolar disorder,* ***MS****=mixed states;* ***PD****=personality disorder*

INTRODUCTION

Bipolar disorder and mixed symptoms

Bipolar disorders include several different disorders of emotion, energy and thought with a severe chronic course of illness classified according to the longitudinal course in BD type I (BDI) or type II (BDII). BD expresses as recurrent episodes of changes in energy levels and behavior representing episodes of mania, hypomania, alternating or intertwining with episodes of depression with the presence of subthreshold symptoms between the episodes (Grande et al., 2016). A complex and quite frequent presentation of BD is represented by the occurrence of mixed states, historically defined as the coexistence of depressive and manic symptoms (Solé et al., 2017).

The clinical manifestation of manic episodes is represented by hyperactivity, increased self-esteem, grandiosity, reduced need for sleep, expansive mood and behavior plus psychotic symptoms whilst during depressive episodes patients generally refer decreased energy, sadness, social withdrawal, hypersomnia and low self-esteem. Psychosis can also occur during depressive episodes but occurs more frequently during mania. Hypomania is a milder and shorter form of mania, and individuals with hypomania have relatively intact judgement (Grande et al., 2016).

Bipolar depressive episodes subtly differ from unipolar depression. They are usually associated with an earlier age of onset, a family history of mania, they more frequently present a shorter duration, with an abrupt onset and off set and atypical symptoms, such as hypersomnia, lability, and weight instability. Bipolar depression is linked to comorbid substance related disorders (SUD), is triggered by stressors at early stages,

and has more post-partum risk, psychotic symptoms, psychomotor retardation and catatonia (Vieta et al., 2018).

A mixed episode was previously defined by juxtaposed full manic and depressive episodes in the diagnostic and statistical manual of mental disorders-IV-text revision (DSM-IV-TR) (American Psychiatric Association., 2000). A "with mixed features" specifier (MFS) has been incorporated in the DSM-5 (American Psychiatric Association., 2013). This specifier may be applied to manic episodes in BDI, hypomanic episodes in BDI and BDII, and to MDE experienced in BDI, BDII, BD not otherwise specified (BD-NOS) as well as in MDD (Vieta and Valentí, 2013). As a consequence, hypomanic symptoms could currently denote both MDD or BD and many individuals along the mood disorders spectrum, that were previously "orphans" of a diagnosis, could be classified according to a "mixed-categorical–dimensional" approach (McIntyre et al., 2016; Vieta and Valentí, 2013).

Approximately 30-40% of major affective episodes that occur over the course of BD appear to exhibit mixed features (Kessing, 2008; McIntyre et al., 2015; Verdolini et al., 2015). Major concerns still exist for the DSM-5 MFS. In fact, it has 100% specificity but only 5.1% sensitivity (Stahl, 2017). Specificity at the expense of sensitivity suggests that up to 95% of patients presenting with the MFS according to the DSM-5 are wrongly diagnosed as having 'pure' affective episodes (i.e., without mixed features) (McIntyre et al., 2016; Stahl, 2017). The DSM-5 workgroup excluded overlapping symptoms like distractibility, irritability, and psychomotor agitation, arguing that they may lack the ability to differentiate between manic and depressive states (Malhi et al., 2017), in the choice of a more "specific" approach at the expenses of the "sensitivity" of the classification (McIntyre et al., 2016; Vieta and Valentí,

2013). Nevertheless, when criteria that consider overlapping symptoms for the diagnosis of mixed features are used, a more balanced trade-off between sensitivity and specificity was obtained, with a specificity of 87% and a sensitivity as high as 55% (Stahl, 2017; Takeshima and Oka, 2015). In addition, it is not clear which could be the implication on the prevalence of mixed episodes of the DSM-5 MFS in comparison to previous DSM classifications, as literature findings are conflicting. In BD, DMS-5 mixed features rates were found to be threefold higher than DSM-IV-TR mixed episodes in a retrospective naturalistic study (Shim et al., 2015) whilst the Bipolar CHOICE, a randomized comparative effectiveness trial, reported that fewer patients suffering from BD met mixed criteria with the DSM-5 non-overlapping definition compared to the DSM-IV (Tohen et al., 2017). In the multicenter, multinational cross-sectional BRIDGE-II-MIX study, 7.5% of the entire sample fulfilled DSM-5 criteria for MDE with mixed features but when a broader definition including overlapping symptoms was applied, the rates of depressive mixed states were as high as 29.1% (Perugi et al., 2015).

The DSM-5 does not provide a clear rationale for not weighing certain depressive symptoms (i.e. weight loss/ gain, decreased/increased appetite, insomnia/hypersomnia) for the establishment of a MFS in the context of mania (or hypomania) (McElroy and Keck, 2017) or other clinical manifestations such as anxiety (McElroy and Keck, 2017), aggressiveness or affective lability possibly indicating underlying mixed state. A recent study identified that a four- or five-symptom cluster composed by the DSM-5 MFS symptoms racing thoughts, increased talkativeness and decreased need for sleep and by the two non-specific symptoms distractibility and irritability, was shown at baseline in a placebo-controlled trial involving patients with MDD with mixed

features (Targum et al., 2016). Hence, it has been hypothesized that the symptoms of the DSM-5 MFS are themselves nonspecific (Malhi, 2013).

Hetero-aggression in bipolar disorder and mixed symptoms

Hetero-aggression is defined as an overt behavior involving intent to inflict noxious stimulation or to behave destructively towards another organism or object (Moyer, 1976). In psychiatry, it is a behavioral or motor response associated with intent to do harm and it may be self-directed (Safer, 2009).

Several psychiatric disorders, including affective disorders, have been associated with increased rates of hetero-aggression and violent behaviors (Dolenc et al., 2015). Particularly, BD patients presented increased risk for aggressive behaviors (Ballester et al., 2014; Ng et al., 2017). In comparison with subjects suffering from other psychiatric disorders or healthy controls, BD patients previously showed increased self-reported verbal and physical hetero-aggression, particularly during acute episodes and independently from BD subtypes, severity, psychotic symptoms and current pharmacological treatments (Ballester et al., 2014, 2012).

Manic patients showed the highest odds ratio for aggressive incidents among psychiatric inpatients (Barlow et al., 2000). Several factor analyses described the clinical context of hetero-aggression in mania. Hetero-aggression was associated with paranoia and irritability, loading on the same factor ("irritable hetero-aggression") (Cassidy et al., 1998). In another factor analysis, hetero-aggression loaded on the same factor as irritability, uncooperativeness, impatience and lack of insight, suggesting the existence of a distinct subtype of mania defined as "aggressive" (Sato et al., 2002). In a more recent study, the factor analysis revealed 5 factors, and one of them was termed

‘‘Dysphoria’, with positive significant loading for hostility, uncooperativeness, and suspiciousness, representing one of the two classical aspects of manic states (Pacchiarotti et al., 2013b). In this context, hetero-aggression could represent a core feature of manic and mixed episodes of BD, and might be a persistent “trait”, appearing in the same patients across repeated episodes.

As for depressive episodes, it has been found that BDI and BDII depressed patients had more life-time hetero-aggression/hostility than unipolar depressed patients (Dervic et al., 2015). Few studies with few methodological limitations evaluated possible clinical correlates of hetero-aggression during a MDE across mood disorders (Ballester et al., 2012; Dervic et al., 2015; Dolenc et al., 2015; Garno et al., 2008; Michaelis et al., 2004; Ng et al., 2017).

Comorbidity with other disorders, namely substance and alcohol abuse and borderline personality disorder (BPD), might increase the risk of hetero-aggression in BD patients even though is still not clear the mutual implication of the different components (Garno et al., 2008; Salloum et al., 2002).

Despite these previous findings, hetero-aggression is not currently considered as a DSM diagnostic criterion of mania and consequently is not included in the DSM-5 mixed features in both bipolar and unipolar depressive episodes (American Psychiatric Association., 2013). In fact, only irritable mood represents a major defining characteristic of manic episodes since the first edition of the DSM (American Psychiatric Association, 1980) and across the different revisions of the manual up to the last DSM-5.

Violence is an overt aggressive destructive behavior with the intention to inflict harm (Látalová, 2009) resulting in injury, death or psychological harm (“World Health

Organization. Health topics-Violence," 2017). Violence is the basis of violent criminal behavior (VCB), with deleterious impact on individuals and societies (Krug et al., 2002; Látalová, 2009).

Previous research studied BD as possible risk factors for VCB, with conflicting results (Johnson et al., 2016; Lysell et al., 2014; Rihmer et al., 2010). According to national surveys, the prevalence of violence ranges from 0.8 to 34.7% in samples including individuals with mental illness, depending on the psychiatric disorder considered, whilst it is about 2% in the general population (Corrigan and Watson, 2005). Several psychiatric disorders, including mood disorders, have been associated with increased rates of aggression and violent behavior even though rates vary across studies. In the Epidemiological Catchment Area (ECA) study BD was the less reported condition associated with violent behaviors (11%), whilst in the National Comorbidity Survey (NCS) BD presented the highest frequency of violent acts (12.2%) among lifetime mental illnesses (Corrigan and Watson, 2005). In a national U.S. survey, Calabrese and colleagues assessed that the 1-year OR for being jailed, arrested and convicted of a crime was 4.87 for BD patients (Calabrese et al., 2003). BD is also associated with the highest risk of violent reoffending among the other psychiatric disorders (Chang et al., 2015).

Previous reviews (Fazel et al., 2010; Fovet et al., 2015; Látalová, 2009) attempted to summarize evidence on the association between violence and BD, but failed to include possible legal outcomes (Látalová, 2009), presented unstandardized methods or broader definitions of violence (Fovet et al., 2015), provided a quantitative analysis limited to few studies (Fazel et al., 2010) or considered BD with other psychoses, providing mixed-samples results (Fazel et al., 2009; Witt et al., 2013).

Self-aggression in bipolar disorder and mixed symptoms

BD is the affective disorder with the highest suicide rate which is up to 20-times higher than the rate among the general population (Vieta et al., 2018). About a third to a half of patients with BD attempt suicide at least once in their lifetime, and roughly 15–20% of attempts are completed (Grande et al., 2016). Risk factors for suicide attempts in BD include a younger age at onset, female sex, depressive polarity, anxiety, substance abuse and personality disorder comorbidity whilst risk factors for completed suicide include a first-degree family history of suicide and male sex (Grande et al., 2016).

Suicide has always received more attention than other self-aggressive adverse outcomes in the longitudinal course of BD, not only in the general population but also in prison samples. Indeed, acts of self-aggression encompass a wide range of behaviors which differ in severity, from minor cuts in the context of DSH to complete suicide.

For example, suicide attempts (SA), non-fatal self-directed potentially injurious behaviors with an intent to die as a result of the behavior, are one of the few predictors of subsequent completed suicide and carry their own burden, sequelae and stigma (Vieta et al., 1992).

Depressive mixed state seems to substantially increase the risk of suicidal behavior in both clinical and community samples (Barbuti et al., 2017; Benazzi, 2005a; Pacchiarotti et al., 2011; Sato et al., 2003). Recent studies have confirmed a higher frequency of suicide attempts and suicidal ideation in mixed than in non-mixed states in MDD and BD (Holma et al., 2014).

Baldessarini and colleagues in a pooled-analysis (Baldessarini et al., 2012a) evaluated a broader predominant polarity category defined depression-plus-mixed including mixed states and found that the association with suicidal acts nearly doubled, from a relative risk of 2.48 to 4.62.

In a post-hoc analysis of the BRIDGE-II-MIX study (Popovic et al., 2015), a percentage as high as 22.34% of the total sample presented a previous history of SA. In the subgroup of patients with a history of SA, the prevalence of mixed states ranged from approximately 12% with DSM-5 criteria to nearly 40% according to the RBDC criteria. The most frequent (hypo)manic symptoms in both groups were irritable mood, emotional/mood lability, distractibility, psychomotor agitation, and impulsivity. Interestingly, many of these symptoms (including irritable mood, mood lability, and psychomotor agitation) were excluded from the DSM-5 mixed features specifier.

In a factor analysis of a sample of BD-I inpatients, Pacchiarotti and colleagues (Pacchiarotti et al., 2013b) found a factor labeled "mixicity" defined by suicidality, excitement, motor hyperactivity, tension and anxiety items. This factor was significantly associated with a pure mixed course of illness and a higher number of lifetime mixed episodes as well as with family history of suicide and lifetime suicide ideation.

As for DSH, it can be conceptualized as the deliberate, voluntary and not accidental, direct destruction or alteration of body tissue without conscious suicidal intent (Favazza, 1998). Even though presentations of DSH to health systems point out to an increased prevalence, DSH was not studied as much as suicidality.

The lifetime prevalence of DSH presents great variations worldwide. In Europe and the U.S., it is about 3% to 5% (Soomro, 2008), (i.e. 3.44% in West Germany and

4.95% in France), it ranges around 3.82% in Canada, but the variations can go from less than 1% in Beirut and Taiwan to nearly 6% in Puerto Rico (Weissman et al., 1999). The percentages of lifetime DSH in adult offenders are significantly higher, ranging between 15% (Fotiadou et al., 2006) and 35% (Sakelliadis et al., 2010) in male prisoners. The rates of DSH are dramatically high among incarcerated offenders with mental disorders, ranging from 18% (Loughran and Seewoonarain, 2005) to 61% (Gray et al., 2003) while in custody and from 48% (Loughran and Seewoonarain, 2005) to 67% (Bland et al., 1999) for lifetime DSH. Unfortunately, in previous literature, information about prevalence rates of BD among DSH inmates was completely lacking.

In prison populations, DSH may represent a relevant source of morbidity and, when present, may moderate the risk of suicide (Hawton et al., 2015, 2014), especially when underlying mental disorders, particularly mood disorders, are present (Fazel et al., 2008).

Epidemiological, socio-demographic and clinical features seem to be different in offenders when compared with the general population. Despite this, relatively few studies evaluated possible clinical correlates of DSH in incarcerated samples. Most of them were epidemiological studies (Hawton et al., 2014; Ireland, 2000), whilst others bore methodological limitations. In fact, very few studies investigated specific factors independently associated with DSH in prison inmates, such as mood disorders (Carli et al., 2011; Hawton et al., 2014; Young et al., 2006). Indeed, even though the presence of mood disorders conveys an increased risk for DSH in the community, this predictor was not well studied in correctional settings (Hillbrand et al., 1996).

The association between hetero- and self-aggression in bipolar disorder and mixed symptoms

The poorest outcomes in BD are represented by hetero- and self-aggressive behaviors (Goodwin et al., 2016). Patients suffering from BD more frequently die prematurely in comparison with the general population (Crump et al., 2013) and this might be the consequence of both a higher risk of suicide and of perpetrated interpersonal violence (Webb et al., 2014). In BD, the risk of criminality may not be as widely appreciated as the risk for suicide, but offending is actually a more common outcome and thus associated with a higher absolute risk (Goodwin et al., 2016).

Previous research attempted to explain the common causal mechanisms underlying the risks of both self- and hetero-aggression in patients with BD. For example, the risk of violence was found to be increased in individuals who self-harmed, particularly in BD patients (Sahlin et al., 2017). Similarly, suicide in BD was independently associated with clinical variables, particularly lifetime DSH and criminality (Webb et al., 2014).

In particular, in a study conducted by Webb and colleagues (Webb et al., 2014) the incidence of SA among BD patients who committed violent crimes was higher than in the general population, with an Hazard Ratio as high as 1.64. In the same study, the combined risk of both suicidality and criminality was predicted by three independent factors, namely the lifetime history of attempted suicide, a diagnosed alcohol/drug disorder and the fact that the first two patient episodes for BD required admission (Webb et al., 2014).

An explanation for these multiple adverse outcomes in BD might be represented by poor impulse control since the presence of impulsivity is thought to facilitate the transition from aggressive thoughts to aggressive behaviors and this is considered a

critical symptom factor for suicidality, aggression, self-destructive behavior, and subthreshold/full bipolarity (Jiménez et al., 2012).

In a study evaluating the clinical implication of impulsivity in the course of illness of BD patients (Swann et al., 2011), those patients reporting histories of previous convictions had a recurrent course of illness with predominantly manic episodes, with increased probability of SUD and SA. Indeed, high levels of disinhibition during manic or hypomanic phases of illness associated with alcohol or drug use might represent the underpinning mechanism in violence and hetero-aggression as well as the increased risk of SA or DSH could be due to low or mixed mood induced or exacerbated by SUD during depressive phases of BD illness (Pacchiarotti et al., 2011; Webb et al., 2014).

Since the presence of aggressive behaviors exerts a significant impact on the clinical outcome of the BD illness, with major implications in terms of prognosis, management and treatment strategies, more conclusive evidence may affect assessment, treatment interventions, and clinical guidelines.

Recent guidelines recommend the need for the early detection of hetero- and self-aggressive behaviors in mood disorders (Goodwin et al., 2016; Stahl et al., 2014). The effectiveness of specific types of interventions for self and hetero-aggression both in the general population as well as in specific environments, i.e. correctional settings, should better investigated (Carter et al., 2016; Fazel et al., 2016). At the same time, improvements to both the criminal justice and the mental health systems would likely reduce the clinical severity and the likelihood of individuals suffering from BD to offend/re-offend or to committing self-harm/suicide (Bolton et al., 2015; Chang et al., 2015).

The treatment of hetero- and self-aggression is challenging even because it is somehow correlated with stigma. Yet, patients with criminal histories are sometimes still excluded from treatment programs, so that availability of proper treatments may be scant (Appelbaum, 2006). Self-injurious behaviors arouse ambivalent feelings in health professionals that quite often experience a combination of guilty and anger (Favazza, 1998).

As a consequence, increasing the efforts in providing to patients suffering from BD with a history of self- or hetero-aggression an appropriate and integrated treatment strategy should be the goal of precision psychiatry applied to the aggressive dimension of BD.

AIMS AND HYPOTHESES

Objective

The main objective of this doctoral thesis was to evaluate the psychiatric correlates of self- or hetero-aggression in the context of bipolar disorder, particularly in those patients suffering from mood episodes with mixed features of the opposite pole.

Primary aims

1. To establish the prevalence of criminal behavior, considered as a proxy of hetero-aggression and violence, in bipolar disorder as well as the moderators of a possible association between bipolar disorder and violent criminal behavior (**Study I**).

2. To determine the prevalence of deliberate self-harm in prisoners and to study clinical variables (i.e. mood disorders and bipolar disorder) specifically related to the occurrence of deliberate self-harm in inmates (**Study II**).

3. To assess the relationship between the presence of aggressive behaviors during a major depressive episode with mixed features within the context of bipolar and clinical features such as lifetime suicide attempts (**Study III**).

4. To investigate the psychopathological link between affective lability and mood reactivity and the clinical implications of the association with other mixed symptoms, particularly verbal or physical hetero-aggression (**Study IV**).

5. To critically summarize available evidence and to provide a comprehensive review of recently updated guidelines on the treatment of mixed states and symptoms, addressing challenging clinical aspects such as hetero- and self-aggression (**Study V**).

Secondary aims

1. To investigate the risk of violent criminal behavior for bipolar disorder in comparison with other psychiatric disorders such as major depressive disorder,

schizophrenia and other psychoses, drug and alcohol related disorders and personality disorders **(Study I).**

2. To assess clinical variables other than mood disorders that might predict the occurrence of deliberate self-harm in inmates **(Study II).**

3. To identify if the presence of aggression might represent a diagnostic clinical indicator of mixicity in patients with bipolar depression **(Study III).**

Hypotheses

1. Psychiatric disorders have been studied as possible risk factors for violent criminal behavior with higher risk of hetero-aggression and violence in psychiatric populations. Previous research attempted to summarize evidence on the association between violence and bipolar disorder with conflicting results or methodological limitations. We hypothesized that *patients suffering from bipolar disorder present high prevalence of violent criminal behavior compared to the general population, with identifiable possible risk factors such as comorbid substance related disorders or manic symptoms* **(Study I).**

2. *We hypothesize that the risk of violence in bipolar disorder is higher in comparison with other psychiatric conditions such as anxiety and depressive disorders. On the contrary, the risk of violence in bipolar disorder is lower than in schizophrenia or psychotic disorders* **(Study I).**

3. As in the general population and in psychiatric cohorts, *self-aggressive behaviors such as deliberate self-harm do not distribute homogeneously in the inmate population, showing association with specific socio-demographic and clinical features, such as mood disorders* **(Study II).**

4. Since hetero- and self-aggressive behaviors seem to be linked dysfunctional behaviors, we postulate that *patients suffering from mood disorders could report high rates of hetero-aggression that are associated with self-aggressive behaviors, such as lifetime history of suicide attempts* **(Study III).**

5. We hypothesize that *hetero-aggressive behaviors are differently shown by patients suffering from a mood disorder depending on the specific phase of illness, particularly during mania or in patients presenting a depressive episode but with mixed features of the different pole, mainly in those with a diagnosis of bipolar disorder rather than a major depressive disorder, independently from comorbid*

disorders, such as borderline borderline personality or substance related disorders **(Study I** and **III).**

6. Other clinical features of mixed episode, such as affective lability, could be correlated with self- and hetero-aggression. In particular, affective lability may diminish effortful control resources in the attempt to regulate the intense emotional fluctuations. We postulate that *depressive mixed patients presenting labile emotions might be more prone to both self- and hetero-aggressive behaviors towards others* **(Study IV).**

7. We assume that *establishing a proper treatment in the perspective of a personalized pharmacological and psychological treatment for the aggressive component of BD and providing the appropriate management and follow-up in mental health outpatients units represent important steps to reduce the risk of aggression in mood disorders* **(Study I, II, III, V).**

METHODOLOGY

In order to study the relationship between self-injurious behaviors and hetero-aggression in BD, we planned five studies based on the corresponding aims and hypotheses of this doctoral thesis. The published articles included in this thesis had different study designs in order to provide the most comprehensive assessment of the aggressive component in BD.

Study I: criminal behaviors in the context of bipolar disorder

Study design

Systematic review and meta-analysis.

Search strategy

The MEDLINE/PubMed, EMBASE and PsycInfo databases have been searched using the search strategy: ("Bipolar Disorder"[Mesh]) AND (violen*[Title/Abstract] OR crim*[Title/Abstract] OR prison*[Title/Abstract] OR inmates[Title/Abstract] OR jail[Title/Abstract]).

Eligibility criteria

Original peer-reviewed articles published in any language have be considered for inclusion if satisfying the following criteria: observational studies; more than 95.0% of sample participants aged 18+; assessing CB or violent behavior (through self-assessing instruments used in large-scale epidemiological surveys); a diagnosis of BD established in accordance to ICD and/or DSM criteria; studies have to provide data on the prevalence of VCB in BD or the association between VCB and BD.

A working definition of VCB was used: Any record of conviction, involvement in the judicial system or charge for violent crime, namely homicide, attempted homicide, assault, robbery, arson, threat or intimidation, and all sexual offenses (Webb et al., 2014). Studies reporting on self-assessed VCB evaluated in large-scale epidemiological surveys, namely the National Epidemiologic Survey on Alcohol and

Related Conditions (NESARC) (Pulay et al., 2008), NCS (Corrigan and Watson, 2005), and the ECA (Swanson et al., 1990), were also deemed eligible.

Animal studies, intervention studies, case reports, letters to the editor, studies that include youths, that do not provide the prevalence or association of CB in individuals with BD, studies providing the prevalence or association in BD with non-VCB only; studies not providing comparison with general population have been be excluded.

Data extraction, collection and methodological quality assessment of included articles

An independent search and extraction of data according to an a priori elaborated data extraction checklist was performed and a standardized extraction platform was developed in Microsoft Access 2010. For each study, the prevalence of VCB in participants with BD was extracted as well as the full contingency tables to estimate crude ORs, considering the general population controls without psychiatric disorders and controls with any psychiatric disorder other than BD (including severe mental illness, depression, anxiety disorders, psychotic disorders, alcohol or drug abuse disorders, or personality disorders). The type of assessment (record-based vs. self-report) was also coded.

The methodological quality of included studies have been assessed through the Newcastle-Ottawa Scale (Stang, 2010). For purposes of normalization, the % of criteria met was considered as a proxy of the overall methodological quality. The inter-rater reliability of independent reviewers was high (92.8%).

Statistical analysis

A random-effects meta-analysis estimated the prevalence of VCB in BD. The effect size (ES) for the association measures were estimated as OR and 95% CI. Separate estimates were calculated considering the general population controls without psychiatric disorders or controls with any psychiatric disorder other than BD.

Heterogeneity across studies was assessed with the Cochran's Q test (Bowden et al., 2011). Inconsistency across studies was estimated with the I^2 metric (Higgins et al., 2003). Evidence of publication bias was assessed with funnel plot graph and the Egger's regression test (Egger et al., 1997). When evidence of publication bias was

observed, ES estimates were adjusted with the trim-and-fill procedure (Fazel et al., 2007).

Potential sources of heterogeneity were explored with subgroup and meta-regression analyses. Meta-regression analyses were conducted when data from at least five independent datasets were available.

All analyses were conducted in Stata MP software version 14.0 ("Stata MP software version 14.0, Stata Corp, College Station, TX, USA," 2018) using the metan package. Statistical significance was considered at an alpha level of .05.

Study II: deliberate self-harm in prison

Study design

Cross-sectional study.

Sample size

The convenience sample included inmates detained in the Spoleto Prison (Umbria, IT) in the time period October the 1st, 2010 - September the 30th, 2011 at the Spoleto Prison. During the 12-month study period, 670 male inmates were and considered for evaluation. The final sample of included inmates was composed of 526 individuals (92.6% of potentially eligible participants), with 93 out of 526 (17.7%) inmates that reported at least 1 lifetime DSH behavior.

Inclusion/exclusion criteria

Male inmates, aged 18+ years were deemed eligible. Leading bosses in organized criminality or inmates awaiting trial were excluded from the study, as well as those with mental retardation, severe cognitive impairment or unwilling to provide written informed consent.

Study procedures

Eligible inmates underwent a comprehensive psychiatric evaluation. The interviewers were specifically trained to discriminate between lifetime suicide attempts (SA) and

DSH.

Measures and data collection

Participants were interviewed and the following measures were collected:

-The *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)* assessing DSM-IV Axis I disorders.

-The *Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)* for the assessment of Axis II personality disorders (PD).

-The *Addiction Severity Index-Expanded Version (ASI-X)* evaluates the use of alcohol and other substances as well as their impact on functioning in several areas (medical, employment, support, legal, family/social, psychiatric). The interviewers also assessed both reported SA, lifetime and in the last month, and severe suicidal thoughts according to the specific ASI-X items. SA were defined as acts of self-harm with intent to die that were not self-mutilatory in nature.

-The *Deliberate Self-Harm Inventory (DSHI)* is a 17-item, behaviorally based, self-report questionnaire that assesses frequency, severity, duration, and type of different self-harm behaviors.

Socio-demographic and clinical variables (drug and alcohol, medical and psychiatric status, prescribed treatments and use of services) were also collected through the specific ASI-X form.

Statistical analysis

A dichotomous DSH variable have been derived when inmates affirmatively answered to any of the first 16 items on the DSHI, or when the answer to the item 17 ("Have you ever intentionally done anything else to hurt yourself that was not asked about in this questionnaire? If yes, what did you do to hurt yourself?") described a behavior consistent with the conceptual definition of DSH. Bivariate analyses were performed with Chi-square tests, independent-samples t-test, or Mann-Whitney U test (according to type of distribution of the variable).

A partial correlation permitted to assess the relationship between the number of SA and the number of lifetime episodes of DSH, after adjustment for age.

A multivariable hierarchical logistic regression analysis was finally performed. The accuracy of the model in detecting DSH (Yes/No) in inmates was explored in receiver operating characteristic (ROC) analysis.

Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All p values were two-tailed and statistical significance was set at $p<0.05$.

Study III: BRIDGE-II-MIX study post-hoc analysis of aggression

Study design

A BRIDGE-II-MIX study post-hoc analysis of aggression. The BRIDGE-II-MIX study was a multicenter, international, non-interventional, cross-sectional study conducted between June 2009 and July 2010 in 239 centers in Bulgaria, Egypt, Morocco, the Netherlands, Portugal, Russia, Spain, and Turkey aimed at establish the frequency of depressive mixed states. The objective of this post-hoc analysis was to assess the specific features of patients with (MDE-A) or without (MDE-N) aggression.

Sample size

A total of 2,811 patients presenting with a MDE agreed to participate and represented the full analysis population. Among them, 399 patients (14.2%) presented verbal or physical aggression (MDE-A group) during the index MDE.

Inclusion/exclusion criteria

In the BRIDGE-II-MIX study, hospital-based or community psychiatrists enrolled consecutively 10-20 eligible adult patients aged 18 or older, consulting for a MDE according to DSM-IV criteria during a three month recruiting period.

Reasons for nonparticipation were: refusal to participate, patient unable to complete the questionnaire and patients presenting with an acute non-psychiatric condition/emergency or any psychiatric condition other than a MDE.

Study procedures

In the post-hoc analysis, an operational clinical definition of aggression has been used, defined by the presence of at least one of the following behaviors during the index MDE: 1. Physical Aggression (PHY): a. ever threatened or b. hit people, or c. got into fights more than most people or d. become so mad to have broken things; 2. Verbal Aggression (VER): a. to argue a lot with other people, or b. to can't help getting into arguments when people disagree, or c. to get very angry for no good reason with troubles in self-controlling.

Measures and data collection

The psychiatrists completed a case report, incorporating inclusion criteria, socio-demographic variables (age, gender, marital status), inpatient or outpatient status, history of psychiatric symptoms (affective symptoms, postpartum depression, SA), and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the Diagnostic and Statistical Manual of Mental Disorders-forth edition, text revised (DSM-IV-TR) (American Psychiatric Association., 2000) diagnostic criteria for BD, known risk factors for BD (e.g., family history of BD and postpartum depression), previous response to antidepressants, psychiatric comorbidity, current treatment were recorded.

The functional status was determined by the investigator using the Global Assessment of Functioning (GAF) (Endicott et al., 1976) and the global illness severity was assessed through the Clinical Global Impression-Bipolar Version (CGI-BP) (Spearing et al., 1997).

Statistical analysis

The Chi-square test and the Student's t-test were used for comparison between groups for categorical and continuous variables. To minimize the problem of type I errors, a Bonferroni-corrected threshold for statistical significance was set. A stepwise backward logistic regression model was performed to identify the association between aggression and significant variables at the bivariate analyses. The stepwise modeling procedure consist, for each step, in eliminating the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p<0.1$. Odds ratios with 95% confidence intervals will be used for

observed associations. All tolerance values in the regression analyses were > 0.2 and all variance inflation factors were < 2, thereby indicating that multicollinearity was be a source of bias in the regression models. All p values were two-tailed and statistical significance was set at $p<0.05$. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA).

Study IV: BRIDGE-II-MIX study post-hoc analysis of the intertwined association between affective lability and mood reactivity

Study design

A BRIDGE-II-MIX study post-hoc analysis investigating the psychopathological construct of affective lability (AL) in unipolar and bipolar depression and its clinical correlates, assessing specific features of depressed patients with (MDE-AL) or without (MDE-noAL) AL. The clinical implications of the association between AL and atypical features in depression, particularly mood reactivity (MR), were also assessed.

Sample size

The total sample consisted of 2,811 patients presenting with a MDE. Patients diagnosed with comorbid BPD (n = 187) and Attention deficit hyperactivity disorder (ADHD) (n = 61) have been excluded from the analysis in order not to bias the possible correlation between AL and mixed depression due to the trait-like characteristic of AL in BPD (American Psychiatric Association., 2013; Links et al., 2000) and in ADHD (Broome et al., 2015). The final total sample of the post-hoc analysis was composed by 2,577 patients. Among them, 694 patients (26.9%) presented AL (MDE-AL group) and 1035 (40.2%) presented MR (MDE-MR group).

Inclusion/exclusion criteria

As in **Study III**.

Study procedures

An operational clinical definition has been adopted, delineating AL as a state feature represented by marked and rapid shifts between different mood states, in response to

positive or negative environmental stimuli and with subsequent influences on behavior. In adapting a definition of AL to the BRIDGE-II-MIX study, the steering committee of the BRIDGE-II-MIX study decided to combine different previous classifications of AL (Harvey et al., 1989; Links et al., 2000; Siever and Davis, 1991; Thompson et al., 2011), but chose to consider it not as a trait symptom. In fact, AL was considered as a state feature of mixed depression, as highlighted in the Koukopoulos´ diagnostic criteria for mixed depression (Sani et al., 2018, 2014).

AL has been distinguished from MR, defined according to DSM-5 as a variation of mood in depressed patients following only positive stimuli (American Psychiatric Association., 2013).

The presence of mixed features was defined according to the DSM-5 "with mixed features" specifier (DSM-5-MXS).

Measures and data collection

As in **Study III**.

Statistical analysis

The Chi-square test and the Student's t-test were used for comparison between groups for categorical and continuous variables. To minimize the problem of type I errors, a Bonferroni-corrected threshold for statistical significance was set. A stepwise backward logistic regression model was performed to identify the association between AL and 14 significant variables (depression "with mixed features" according to DSM-5, BDII diagnosis, MDD diagnosis, depression "with atypical features" according to DSM-5, severity of mania, severity of depression, age at first depressive episode, number of previous mood episodes, comorbid anxiety disorder, hyperphagia, hypersomnia, MR, treatment with mood stabilizers, treatment with antipsychotics). BDI was excluded from the model because violating the assumption of multicollinearity. Subsequently, a stepwise logistic regression model was performed in order to differentiate AL from MR, testing the correlations between MR and the same clinical variables included in the previous model, plus leaden paralysis. The diagnosis of depression "with atypical features" according to DSM-5 was excluded from the model because violating the assumption of multicollinearity. Finally, two further

stepwise logistic regression models were performed in order to assess the associations between AL or MR and the 14 mixed symptoms of the research-based diagnostic criteria for mixed depression. All p values were two-tailed and statistical significance was set at $p<0.05$. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA).

Study V: Systematic review and quality appraisal of guidelines on mixed states in bipolar and major depressive disorders

Study design

Systematic literature review with methodological qualitative and quantitative assessment of included guidelines.

Study procedures

A study protocol was registered with PROSPERO and published a priori (CRD42018078199). The systematic procedures followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (Moher et al., 2009).

Search Strategy and eligibility criteria

The MEDLINE/PubMed and EMBASE databases were searched up to March 21st, 2018 looking for international guidelines for the treatment of mixed episodes, manic/hypomanic (in BDI, BDII and BD-NOS) or depressive episodes (in BDI, BDII, BD-NOS and MDD) with mixed features published in any language.

International guidelines were defined as guidelines performed by: 1. an international organization, representing more than a single country; 2. a panel of experts from different countries; 3. a national organization providing that experts from at least 3 different countries participated in the development of the guideline.

Study procedures

Treatment recommendations were extracted for both acute and long-term treatment and options were specified for the depressive or manic polarities of mixed episodes or features.

As for efficacy evidence, treatment options were categorized into category of evidence (CE) as first-line, second-line and not recommended treatments. Specifications on safety and tolerability issues were also extrapolated when available. Safety and tolerability aspects were integrated with the CE assigned to each compound leading to different recommendation grades (RG).

A methodological quality assessment of included guidelines was carried out with the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool (Brouwers et al., 2010), designed to provide a framework to assess the quality of guidelines judging the methods used for developing the guidelines, the components of the final recommendations and the factors that were linked to their uptake on the basis of six domains (i.e. scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability and editorial independence). The scores rated by two different reviewers for the 23 items of the AGREE II, for the six domains and for the overall quality of the guideline were calculated and scaled according to the AGREE II scoring instructions.

PUBLICATIONS LIST

Study I

Verdolini N, Pacchiarotti I, Köhler CA, Reinares M, Samalin L, Colom F, Tortorella A, Stubbs B, Carvalho AF, Vieta E, Murru A. Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis. J Affect Disord. 2018 Jul 5;239:161-170. doi: 10.1016/j.jad.2018.06.050.

Impact factor 2017: 3.786

Study II

Verdolini N, Murru A, Attademo L, Garinella R, Pacchiarotti I, Bonnin CDM, Samalin L, Pauselli L, Piselli M, Tamantini A, Quartesan R, Carvalho AF, Vieta E, Tortorella A. The aggressor at the mirror: Psychiatric correlates of deliberate self-harm in male prison inmates. Eur Psychiatry. 2017 Jul;44:153-160. doi: 10.1016/j.eurpsy.2017.04.002. Epub 2017 Apr 14.

Impact factor 2017: 4.129

Study III

Verdolini N, Perugi G, Samalin L, Murru A, Angst J, Azorin JM, Bowden CL, Mosolov S, Young AH, Barbuti M, Guiso G, Popovic D, Vieta E, Pacchiarotti I; BRIDGE-II-MIX Study Group. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. Acta Psychiatr Scand. 2017 Oct;136(4):362-372. doi: 10.1111/acps.12777. Epub 2017 Jul 25.

Impact factor 2017: 4.984

Study IV

Verdolini N, Menculini G, Perugi G, Murru A, Samalin L, Angst J, Azorin JM, Bowden CL, Mosolov S, Young AH, Barbuti M, Popovic D, Vieta E, Pacchiarotti I; BRIDGE-II-MIX Study Group. Sultans of swing: A reappraisal of the intertwined association between affective lability and mood reactivity in a post-hoc analysis of the BRIDGE-II-MIX study. J Clin Psychiatry. In press.

Impact factor 2017: 4.247

Study V

Verdolini N, Hidalgo-Mazzei D, Murru A, Pacchiarotti I, Samalin L, Young AH, Vieta E, Carvalho AF. Mixed states in bipolar and major depressive disorders: Systematic review and quality appraisal of guidelines. Acta Psychiatr Scand. 2018 May 13. doi: 10.1111/acps.12896.

Impact factor 2017: 4.984

Total thesis impact factor: 22.13

RESULTS SUMMARIES

Study I

Violent criminal behavior in the context of bipolar disorder:

Systematic review and meta-analysis

Journal of affective disorders

JCR-2017: Impact factor = 3.786

Position in Psychiatry = 37/142, Quartile = 2

The goals of the study were to assess the prevalence of VCB in BD, establishing the relative risk for VCB in BD compared to the general population and other psychiatric conditions. Possible risk or protective factors for increased VCB in patients with BD have been evaluated.

This systematic review and meta-analysis included 12 articles with data from 9,020,778 participants, in particular 58,475 patients with BD, 8,962,303 general population controls and 231,587 patients with any psychiatric disorder. Participants presenting any VCB were 91,387.

The prevalence of VCB in individuals with BD was 7.1% (95% CI, 3.0–16.5; k=4).

Violent criminal behavior in BD patients versus general population

The association of BD and VCB compared to general population was significant (OR=5.206; 95% CI, 1.338–20.251; k=12; p<.001; Figure 3).

Since the comparator group in one of the included studies (Fazel et al., 2007) did not have any VCB events, he OR was large, possibly biasing further analysis. Excluding this study from sensitivity analyses, the association between BD and VCB was no longer significant (OR=2.784; 95% CI, 0.687–11.287, p=.152; Figure 4).

Between-study heterogeneity was very large (I^2=99.9%) and significant (Q=8,090.26, P<.001, df=11). No evidence of publication bias was verified (p=.759; Egger's test).

Main subgroup and meta-regression analyses were conducted without the aforementioned study by Fazel et al. (Fazel et al., 2007). The association between BD and VCB was significant only in cross-sectional (k=4) studies, in studies in which

VCB was assessed through self-reported measures, and in studies conducted in the USA. In meta-regression analyses, no significant moderators emerged.

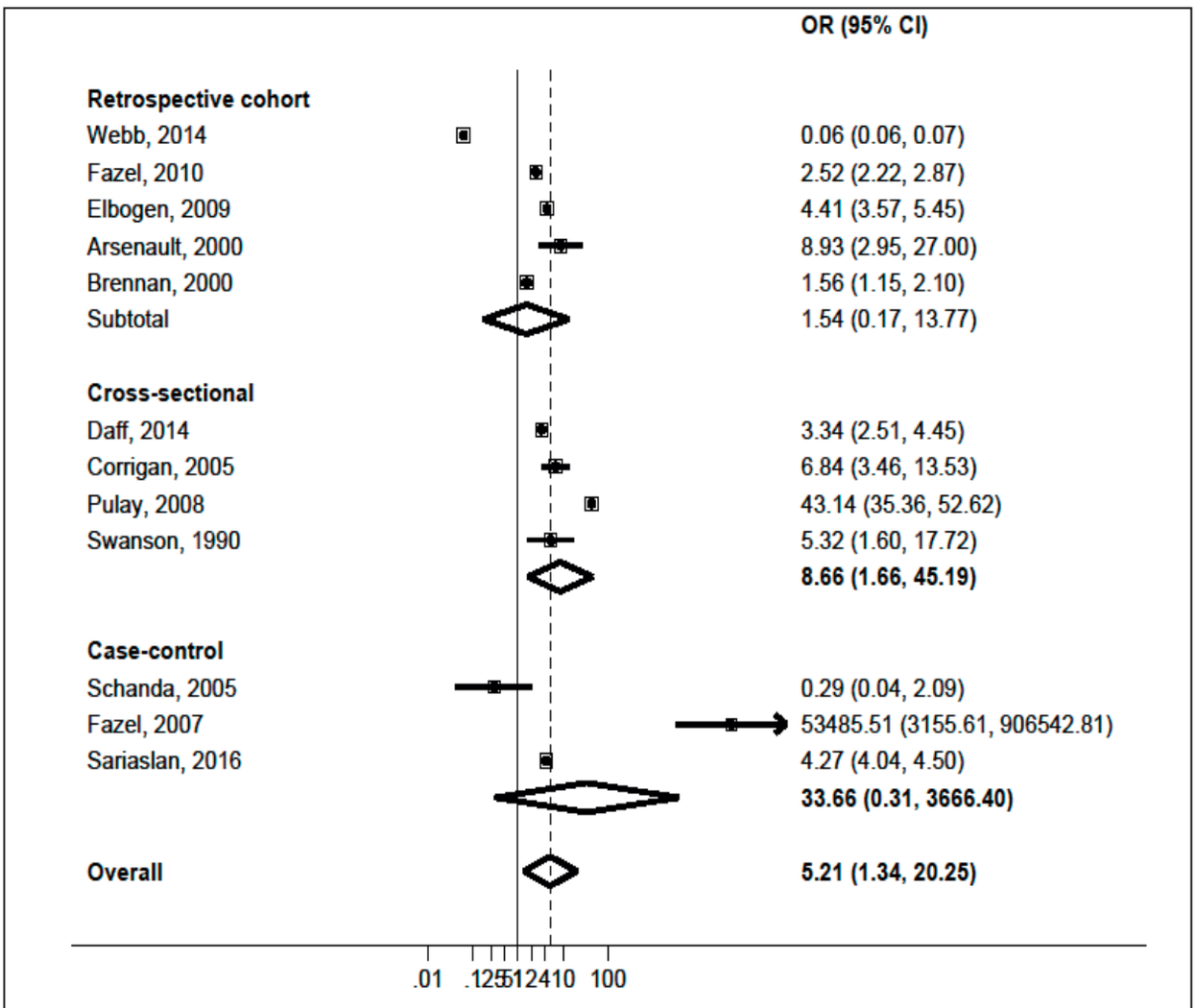

Figure 3. *Forest plot of the association of violent criminal behavior in BD subjects in comparison to the general population*

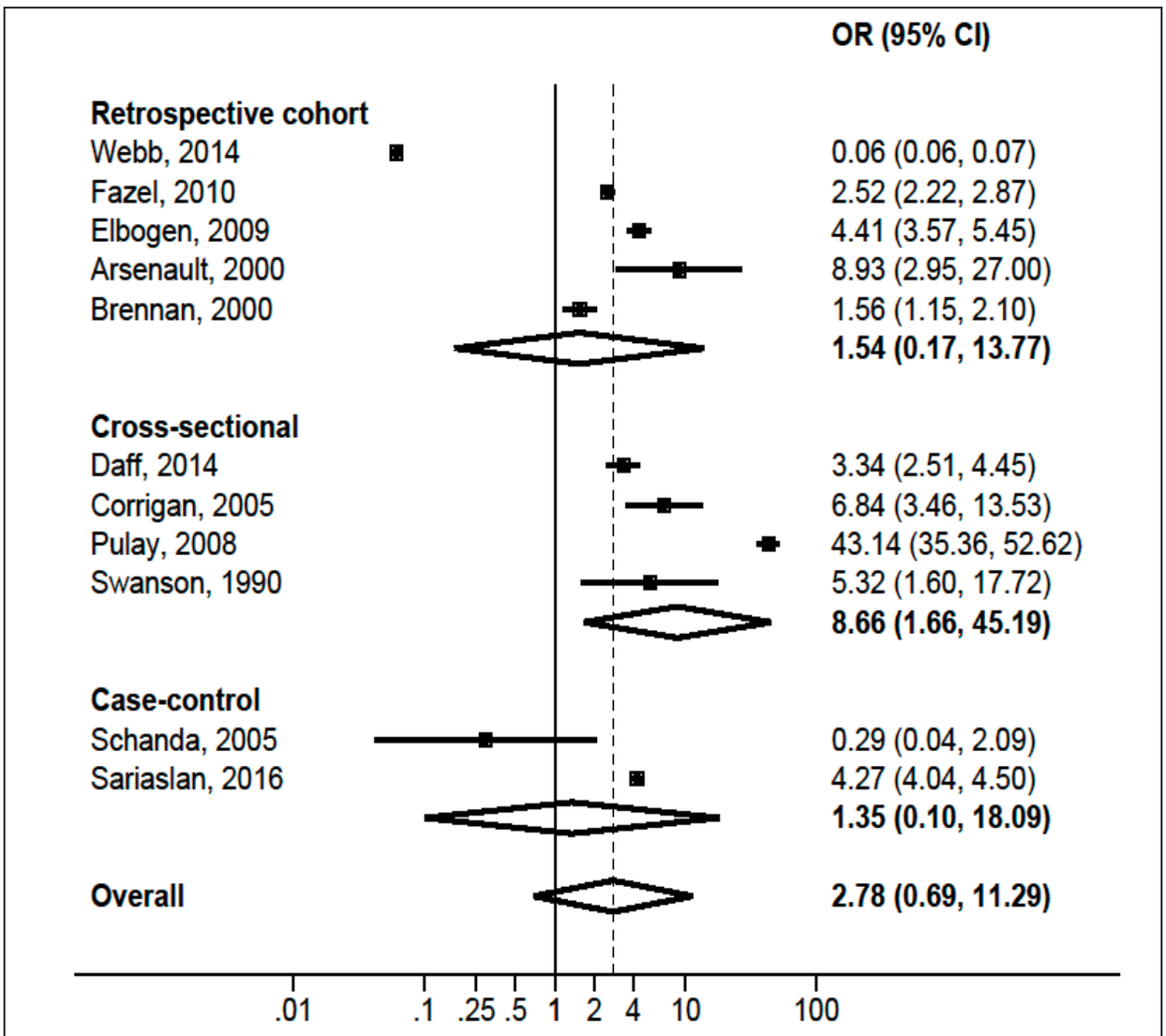

Figure 4. *Forest plot of the association of violent criminal behavior in BD subjects in comparison to the general population (Fazel et al. 2007 excluded)*

Violent criminal behavior in BD patients versus controls with any psychiatric disorder

The association between BD and VCB compared to controls with any psychiatric disorder was not significant (OR=0.783; 95% CI, 0.438–1.398; k=9; p=.407; Figure 5). The association between BD and VCB was significant only in cross-sectional (k=3) or case-control studies (k=3). The chance to present VCB was increased in studies conducted in the USA or using self-report to assess VCB. In meta-regression analyses, no significant moderators emerged.

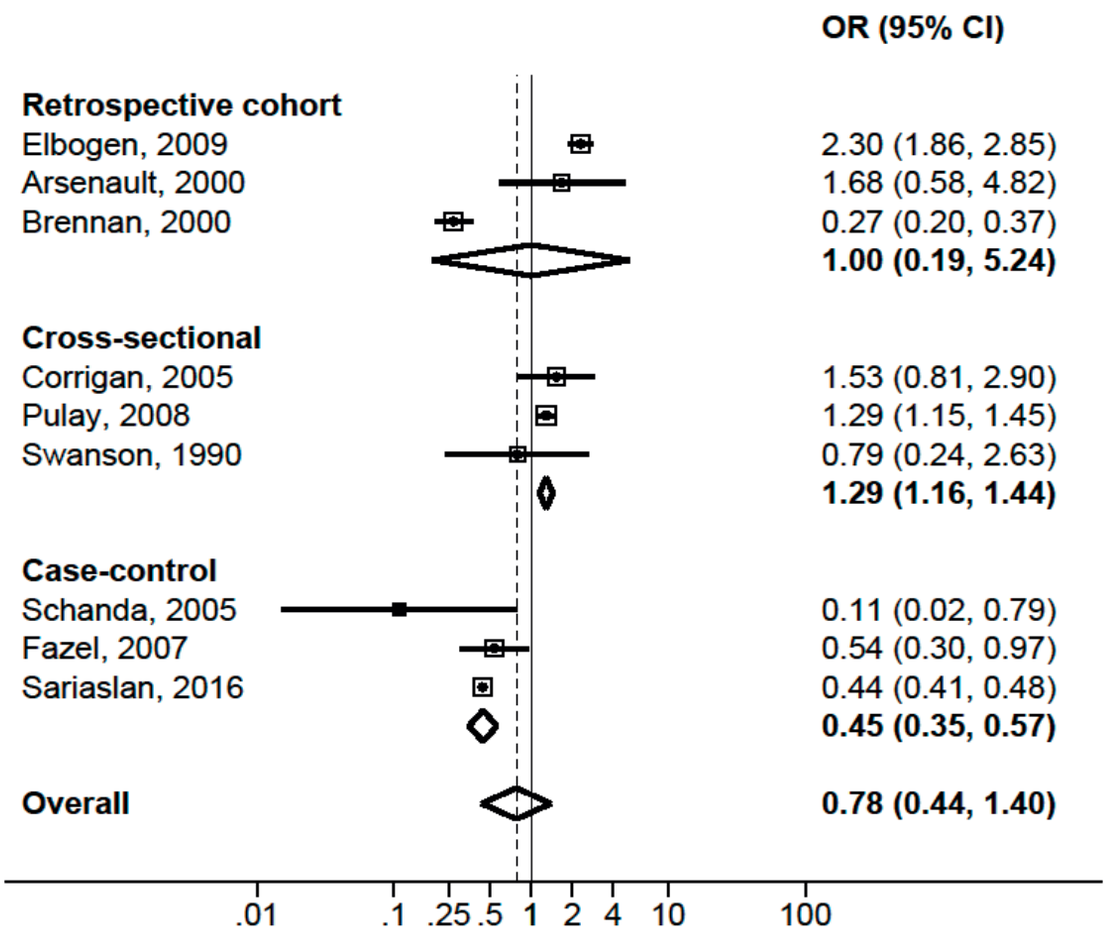

Figure 5. *Forest plot of the association of violent criminal behavior in BD subjects in comparison to a comparator group with any psychiatric disorder*

Violent criminal behavior in BD patients versus controls with major depressive disorder

Seven studies investigated VCB in BD patients compared to controls with MDD (N=141,345), finding a significant association in individuals suffering from BD that had a higher chance of VCB than those suffering from MDD (OR=2.313; 95% CI, 1.721–3.110; k=7; p<.001; Figure 6).

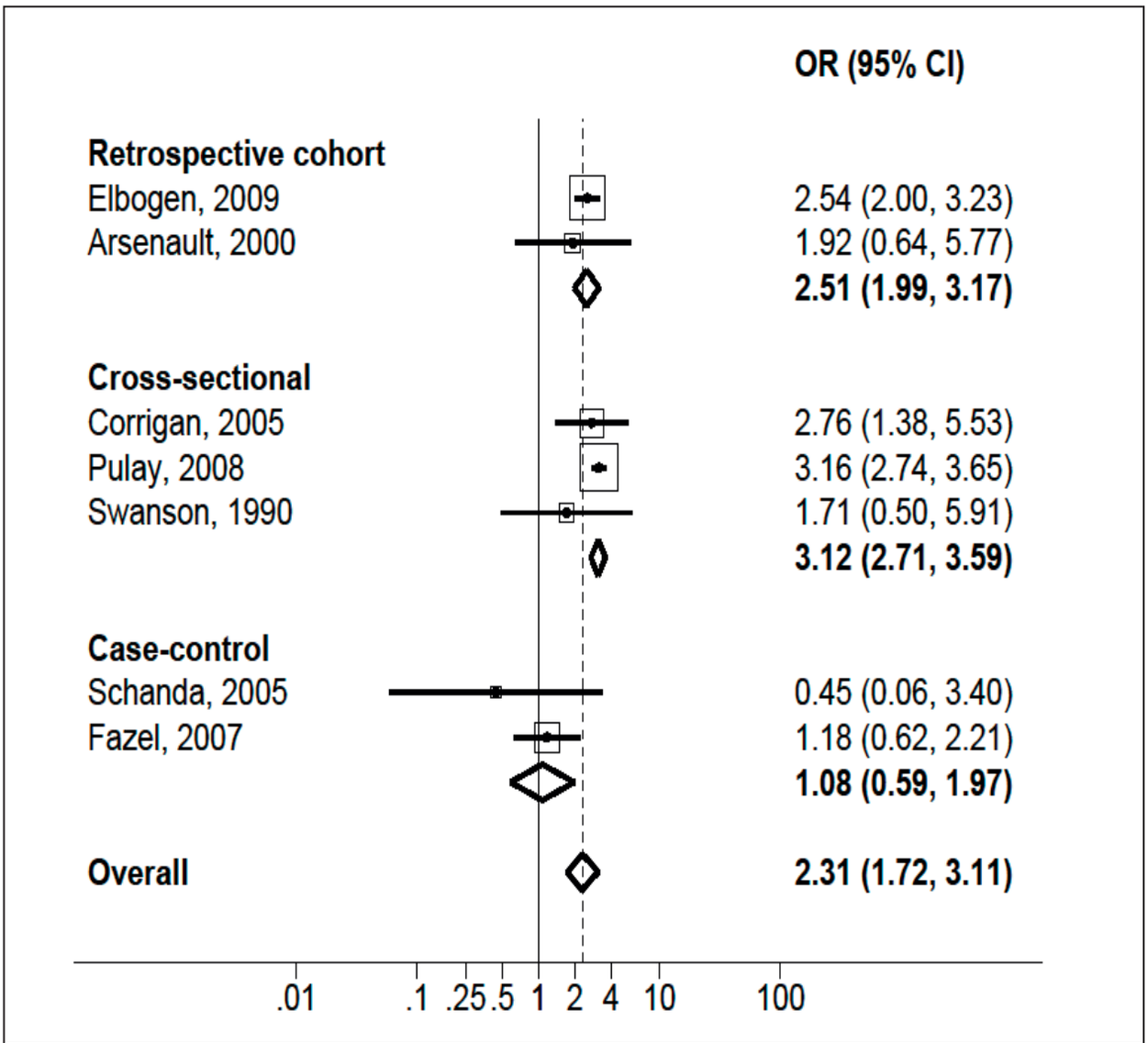

Figure 6. *Forest plot of the association of violent criminal behavior in BD subjects in comparison to subjects with MDD*

Violent criminal behavior in BD patients versus controls with psychotic disorders

Eight studies investigated VCB in BD patients compared to controls with psychotic disorders (N=55,285). Individuals suffering from BD had a smaller chance of VCB than those suffering from psychoses (OR=0.498; 95% CI, 0.329–0.751; k=8; p=.001; Figure 7).

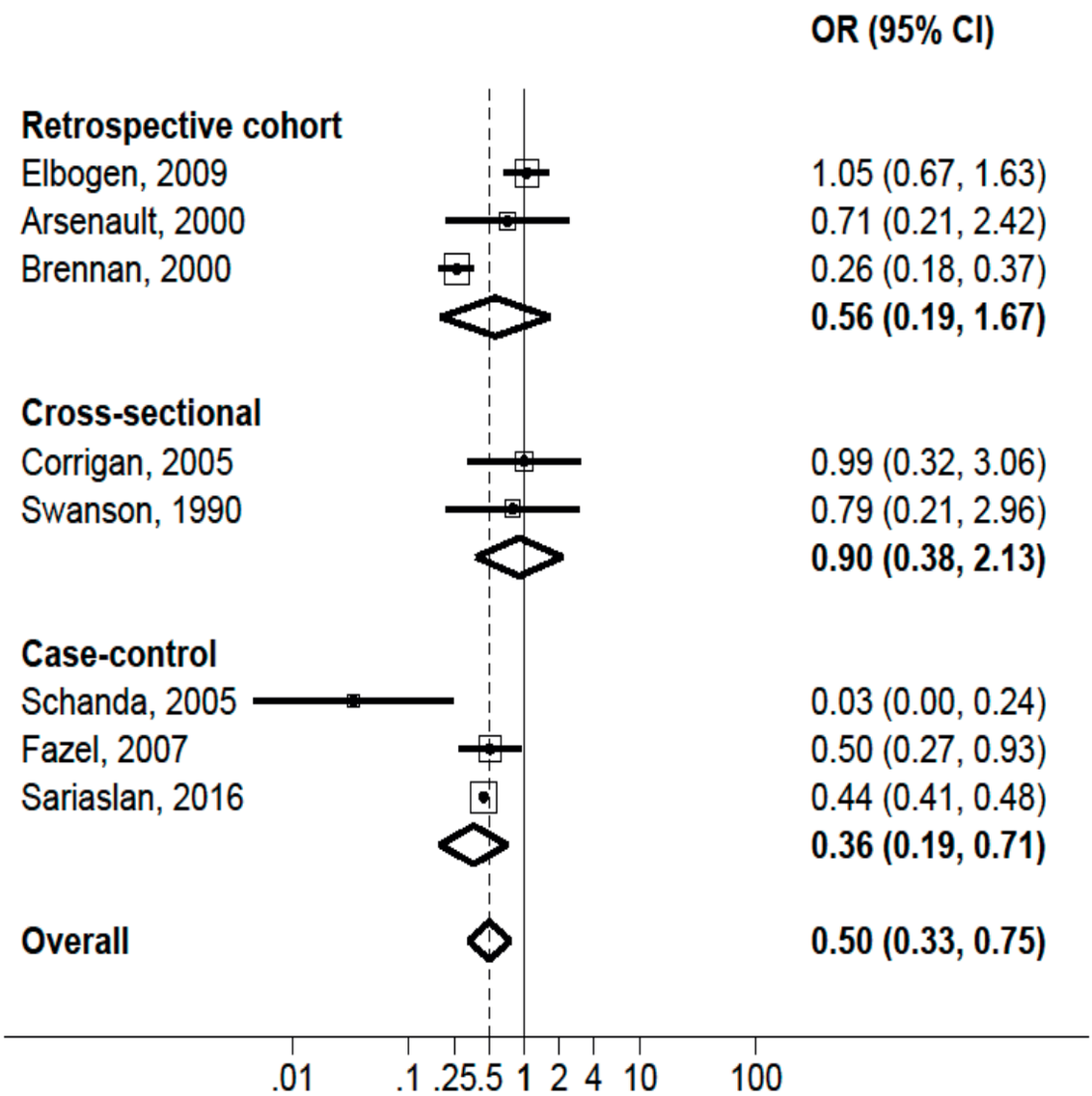

Figure 7. *Forest plot of the association of violent criminal behavior in BD subjects in comparison to subjects with MDD*

Violent criminal behavior in BD patients versus controls with other psychiatric disorders

Five studies investigated VCB in BD patients compared to controls with anxiety (N=11,391). The association was not significant (OR=1.771; 95% CI, 0.978–3.207; k=5; p=.059).

Five studies investigated VCB in BD patients compared to controls with alcohol abuse/dependence disorders (N=13,572). The association was not significant (OR=0.454; 95% CI, 0.093–2.213; k=5; p=.328).

Six studies investigated VCB in BD patients compared to controls SUD (N=12,668). The association was not significant (OR=0.980; 95% CI, 0.609–1.576; k=6; p=.933).

Only two studies investigated VCB in BD patients compared to controls with personality disorders (N=5,764). The association was not significant (OR=0.388; 95% CI, 0.022–6.742; k=2; p=.516).

Methodological quality assessment

Studies followed cross-sectional (k=4), case-control (k=3), or prospective (k = 5) designs. The mean % of criteria met in the NOS scale across studies was 82.1 (SD=17.3).

A half of the included studies had a poor methodological quality. Nine out of twelve of the included studies used representative samples and only four specified in the methodology a diagnostic assessment with a structured interview.

In summary, even though one every fourteen patients suffering from BD reported VCB, the association with violent criminality was not significant in comparison with the general population. The chance of committing VCB was smaller in patients with BD than in those suffering from psychotic disorders but higher in comparison with patients with depressive disorders. In meta-regression analyses, no significant moderators emerged.

Study II

The aggressor at the mirror: Psychiatric correlates of deliberate self-harm in male prison inmates

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European Psychiatry

JCR-2017: Impact factor = 4.129

Position in Psychiatry = 29/142, Quartile = 1

The 17.7% of the total sample of inmates reported at least 1 lifetime DSH behavior. The 11% reported a last DSH act while in prison.

The prevalence of SA in the total sample was 10.6% and in the DSH subsample it was significantly higher than in those without lifetime DSH (44.1% versus 3.5%, $p<0.001$). A significant positive correlation between the number of SA and the number of DSH episodes ($r=0.3$, $p=0.004$), after adjusting for age, was observed.

Patients with lifetime DSH have been diagnosed more frequently than those without DSH with all Axis I diagnoses with the exception of adjustment disorders. As for mood disorders, a percentage of inmates as high as 28% among those with DSH reported these diagnoses, particularly BD in 6.5%, depressive disorders in 16.1% and mood disorder not otherwise specified in 5.4% of DSH inmates. Regarding DSM-IV Axis II disorders, significantly more participants with a lifetime history of DSH had BPD ($p<0.001$), antisocial PD ($p=0.024$), and schizotypal PD ($p<0.001$) compared to those who did not self-harm. Inmates with a lifetime history of DSH also reported more frequent misuse of multiple substances ($p<0.001$) particularly a longer-lasting lifetime use of cocaine ($p=0.008$) and cannabis ($p=0.012$), also presenting a significantly younger age at onset of cocaine ($p=0.031$) and cannabis ($p=0.024$) use.

Inmates with lifetime DSH more frequently reported a history of physical abuse ($p=0.047$) and more than one type of abuse ($p=0.050$). Furthermore, they reported more familiar difficulties such as maternal and paternal substances use issues ($p=0.001$) and psychiatric problems ($p<0.001$).

In the hierarchical multiple regression model, DSH was independently associated with current psychotic disorders (aOR=6.227, p=0.001), BPD (aOR=6.004, p<0.001), mood disorders (aOR=2.856, p=0.006) and misuse of multiple substances (aOR=2.024, p=0.021).

The ROC analysis that we developed in order to assess the utility of the model revealed that the variables in the model performed significantly better than chance in predicting DSH in inmates with an area under the curve (AUC)=0.854 (standard error (SE)=0.022, 95% CI=0.811-0.897, p<0.001) (Figure 8).

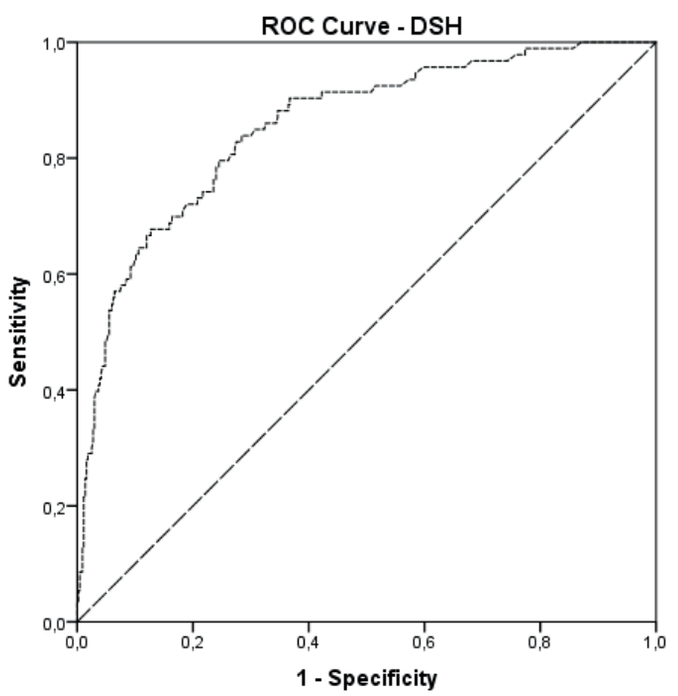

Figure 8. *ROC curve of the predictive model of DSH in inmates*

The results of the study on self-aggression in inmates highlighted that DSH and SA, although being correlated, did not represent behaviors depicting a unique self-aggressive dimension. Indeed, these behaviors are associated to similar, yet different populations and risk factors.

As for DSH, since it should be considered not as an illness but as a behavior, its management should be largely dependent on the underlying problems (Skegg, 2005) such as PD and SUD, as already known from previous literature, but according to our

findings also on mood disorders and psychotic. Indeed, the presence of mood disorders may confer a higher risk of suicide among male prisoners with lifetime DSH.

Study III

Aggressiveness in depression: A neglected symptom possibly associated to bipolarity and mixed features

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Acta Psychiatrica Scandinavica

JCR-2017: Impact factor = 4.984

Position in Psychiatry = 20/142, Quartile = 1

The 14.2% of the total sample presented verbal or physical aggression during the index MDE. The patients that presented with verbal or physical aggression at the psychiatric evaluation were more frequently diagnosed with BD, in particular BDI but not BDII, whilst the presence of aggressiveness was negatively associated with the diagnosis of unipolar depression ($p<0.001$). The index MDE more frequently presented mixed features in those patients with verbal or physical aggression.

Patients found to be aggressive more frequently reported a current substance abuse but not a current alcohol abuse even though the alcohol or substance abuse was not in the context of dependence of alcohol or substance dependence. These patients more frequently reported recurrent alcohol- and substance-related legal problems as well.

As for functioning and severity, patients who presented aggressiveness had a more severe clinical condition (higher levels of CGI-BD) and a poorer functioning (lower GAF scores) with more marked impairment in social/occupational functioning.

The presence of previous SA (31.6%) was more frequently reported in patients with aggression.

Aggressive patients were more frequently not under a psychiatric treatment. In general, these patients were less frequently prescribed with antidepressants however, in those taking this type of treatment, an antidepressant-induced hypomania/mania during the current MDE was more frequently observed.

Clinical variables associated with aggressiveness

In the stepwise backward multivariate model, the clinical variables associated with

aggression were the severity of mania, the diagnosis of BD, the comorbidity with BPD but not with substance abuse, the absence of current psychiatric treatments, the presence of psychotic symptoms and the marked impairment in social/occupational functioning. The age at first depressive episode was significantly associated with aggression but the association followed a negative pattern. A mixed depressive presentation was the clinical variable that highly associated with aggression (OR=3.8) (Figure 10).

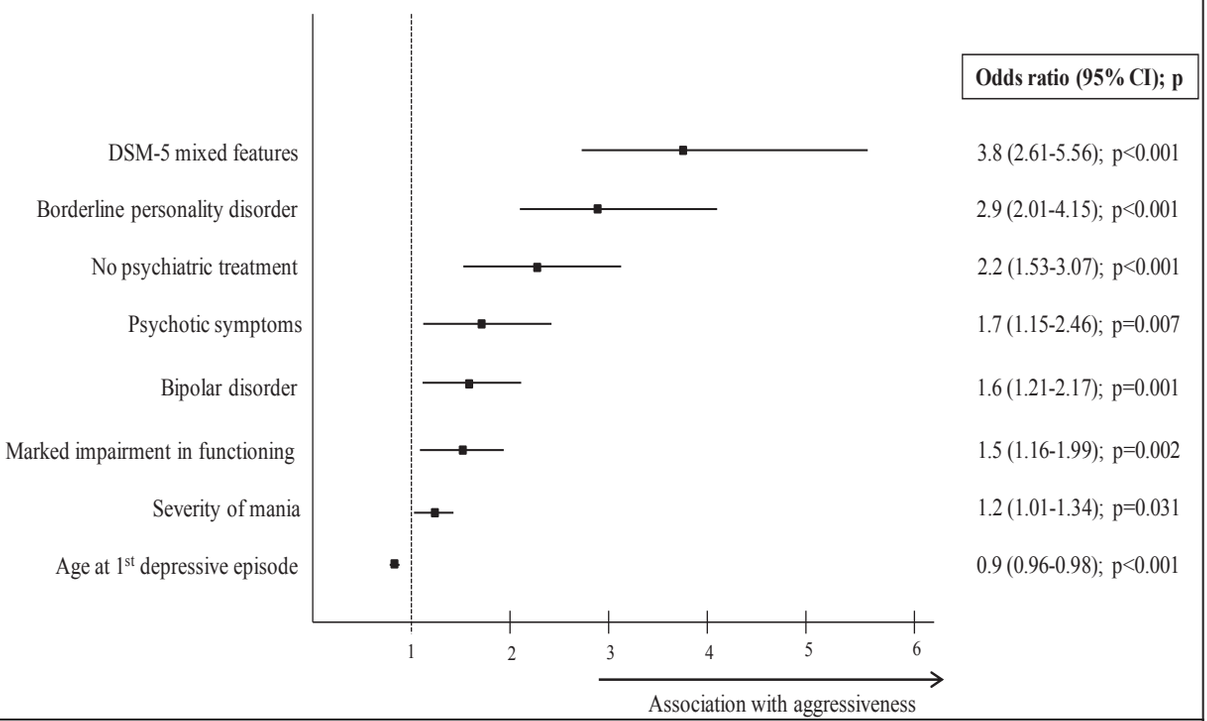

Figure 10. *Logistic regression: Significant clinical variables associated with aggression*

In order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviors, we performed a second stepwise backward multivariate modeling procedure excluding the variable of BPD comorbidity. The presence of mixed symptoms during the depressive index episode still remained the clinical variable with the highest significant association with aggressiveness (OR=3.9). The association with BD diagnosis still remained significant whilst the presence of lifetime SA became significant at the logistic regression when BPD comorbidity was excluded supporting the hypothesis that aggression might be associated with bipolarity per se, independently from comorbid disorders such as BPD

or substance abuse (Figure 11).

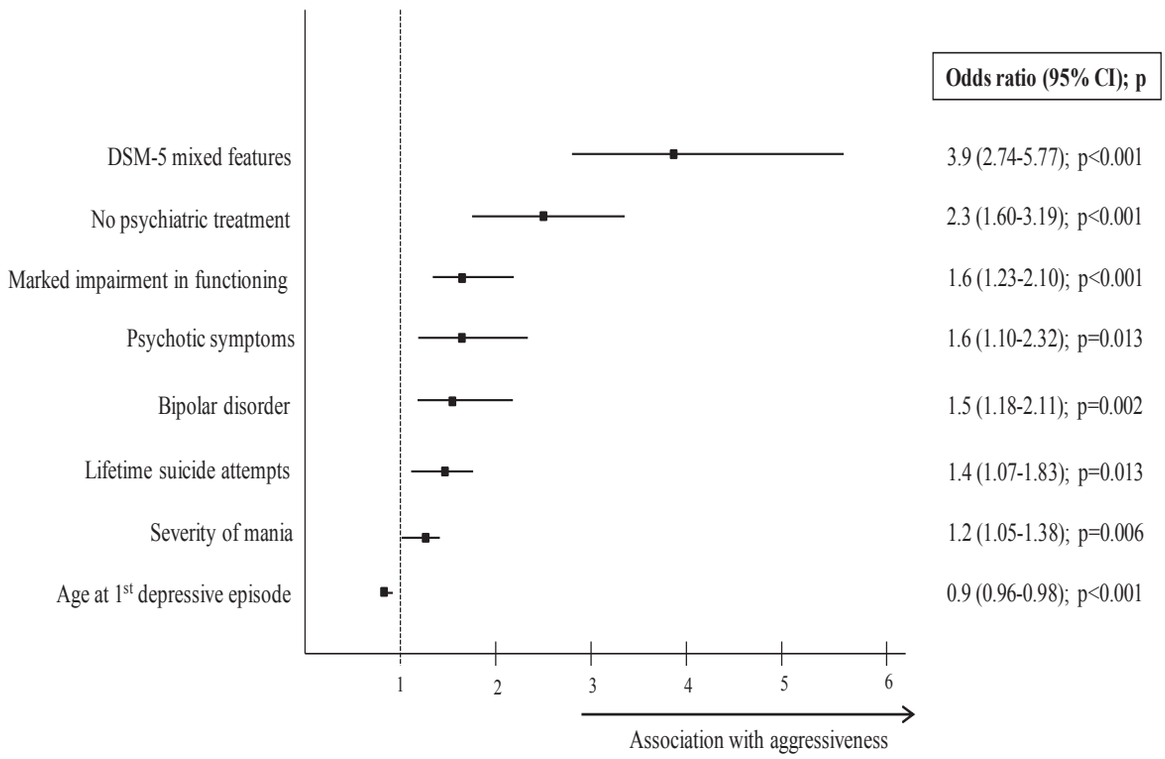

Figure 11. *Logistic regression: Significant clinical variables associated with aggressiveness (borderline personality disorder excluded)*

Study IV

Sultans of swing: A reappraisal of the intertwined association between affective lability and mood reactivity in a post-hoc analysis of the BRIDGE-II-MIX study

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The Journal of Clinical Psychiatry

JCR-2017: Impact factor = 4.247

Position in Psychiatry = 26/142, Quartile = 1

Affective lability (AL) is defined as the predisposition to rapidly reversible and marked shifts in affective states that are extremely sensitive to environmental events with intense behavioral responses (Siever and Davis, 1991). According to the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5), these abrupt switches are characterized by a few hours duration and can represent a response to both pleasant and unpleasant events (American Psychiatric Association., 2013; Thompson et al., 2011).

On the contrary, in the DSM-5 mood reactivity (MR) represents a core criterion for depressive "atypical features" and is defined as a change of mood, but restrictively in response to positive stimuli (American Psychiatric Association., 2013).

AL assumed a central role as a trait-like clinical feature in mixed episodes, especially in those with depressive polarity (Azorin et al., 2012; Benazzi, 2005b; Solé et al., 2017) and represented one of the three most frequent state features in mixed depression, together with agitation and irritability (Sani et al., 2014). Despite this, AL was excluded from the DSM-5 "with mixed features" specifier and has been poorly studied as a state clinical feature in large samples of patients in course of a MDE.

In the BRIDGE-II-MIX study sample, 694 patients (26.9%) presented AL (MDE-AL group) and 1035 (40.2%) presented MR (MDE-MR group).

The presence of AL was positively associated with BDI (odds ratio [OR] = 2.1; 95% Confidence Intervals [CI], 1.62-2.79, $P < 0.001$) and BDII (OR = 2.2; 95% CI, 1.58-3.04, $P < 0.001$), and negatively associated with a diagnosis of MDD (OR = 0.4; 95%

CI, 0.34-0.54, $P < 0.001$). In addition, the MDE-AL group was more frequently diagnosed with mixed (OR = 10.5; 95% CI, 7.10-15.49, $P < 0.001$) and atypical features (OR = 2.7; 95% CI, 1.92-3.64, $P < 0.001$) according to the DSM-5 criteria.

The MDE-AL group differed significantly from the MDE-noAL group regarding age at onset of first depressive episode (mean (M)±standard deviation (SD) = 34.37 ±12.368 versus M±SD = 36.34±12.634, t = 3.529, $P < 0.001$) and total number of previous mood episodes (M±SD = 5.17±5.389 versus M±SD = 4.36±5.645, t = -3.303, $P = 0.001$). Patients in the MDE-AL group presented higher severity of mania (M±SD = 1.69±1.028 versus M±SD = 1.13±0.541, t = -13.052, $P < 0.001$) evaluated with the CGI-BP and a lower severity of depression (M±SD = 4.40±0.951 versus M±SD = 4.52±0.947, t = 2.868, $P = 0.004$) compared to those in the MDE-noAL group. The total number of lifetime SA was not different between patients those with or without AL (M±SD = 0.44 ± 2.102 versus M±SD = 0.32 ± 0.860, t = -1.537, $P = 0.125$).

Clinical variables associated with affective lability and mood reactivity

In the stepwise backward multiple logistic regression modeling procedure ($\chi^2(5) = 546.632$, $P < .001$) with AL as the dependent variable, statistical significance persisted for the presence of mixed features according to DSM-5 (OR = 3.0; 95% CI, 2.43-3.77); severity of mania (OR = 2.0; 95% CI, 1.71-2.30); MR (OR = 3.7; 95% CI, 2.98-4.57) which were positively associated with AL; severity of depression (OR = 0.9; 95% CI, 0.77-0.97), that showed a negative correlation with AL. The variables most significantly associated with AL were MR and the presence of mixed features according to DSM-5 (see Figure 12).

To test the differences between AL and MR, a second stepwise backward logistic regression was performed, using MR as the dependent variable ($\chi^2(7) = 317.795$, $P < .001$). Variables significantly associated with MR were the presence of mixed features according to DSM-5 (OR = 1.5; 95% CI, 1.21-1.76); AL (OR = 3.7; 95% CI, 3.01-4.57); leaden paralysis (OR = 1.6; 95% CI, 1.29-1.92); hyperphagia (OR = 1.4; 95% CI, 1.05-1.77); hypersomnia (OR = 1.3; 95% CI, 1.05-1.76); comorbidity with anxiety disorders (OR = 1.5; 95% CI, 1.2-1.8). The strongest correlation with MR was presented by AL. All the variables were positively correlated (see Figure 12).

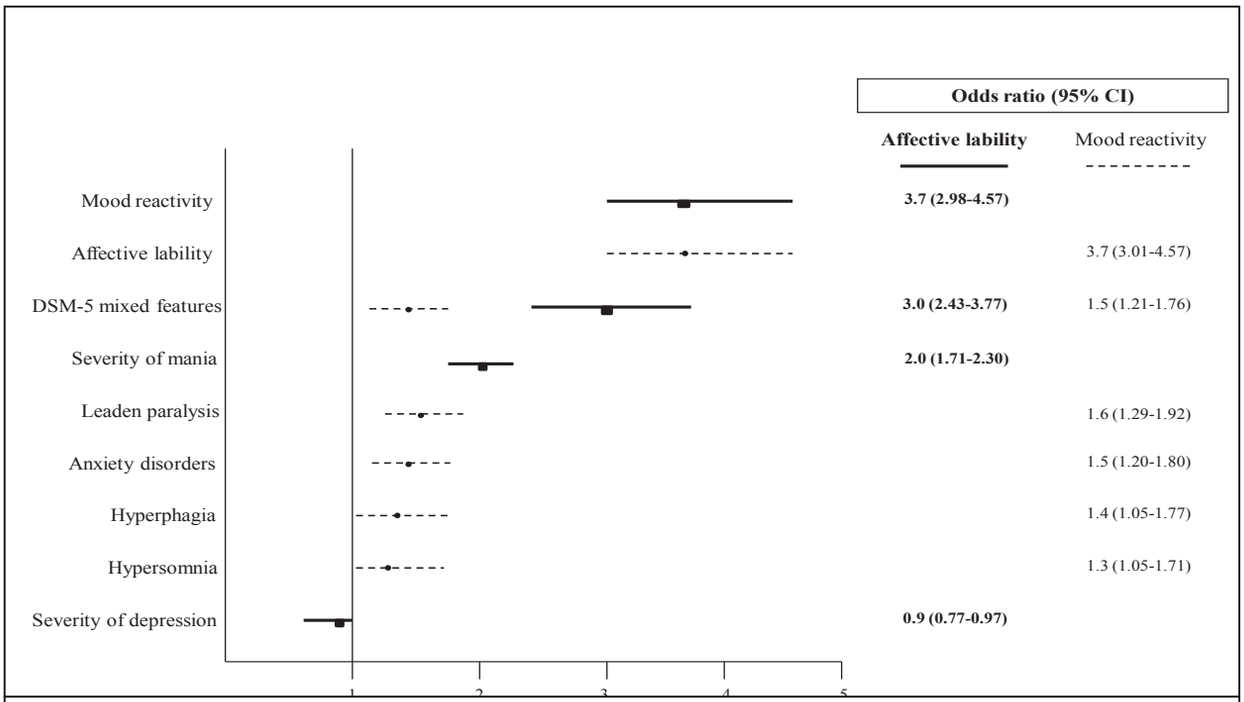

Figure 12. *Logistic regression: Significant clinical variables associated with affective lability and mood reactivity*

Abbreviations: CI = confidence interval

The findings of this study suggest that mixed depression and atypical depression lie on the same continuum from unipolar melancholic depression to BDI manic episodes. The underpinning matrix might be the emotional hyperreactivity experienced by the patient. The difference between the two types of depression was represented by the presence of swings due to negative actual or perceived stimuli, within the construct of AL (Henry et al., 2007). Indeed, MR and AL are strongly associated in terms of reaction to positive stimuli but are differentiated by the response to negative stressors (see Figure 13).

As for the mixed symptoms according to the Research based diagnostic criteria, irritable mood, racing thoughts, more talkative/pressure to keep talking, distractibility and impulsivity were directly significantly associated with both AL and MR. Elation was directly significantly associated with AL, verbal or physical aggression were inversely significantly associated with AL whilst risky behavior was inversely associated with MR (see Table 1).

Table 1 *Stepwise backward multiple logistic regression model of RBDC-MXS hypo/manic symptoms associated with AL or MR*

	MDE-AL vs MDE-noAL*			MDE-MR vs MDE-noMR†		
Variables in the equation	**Wald**	**OR (95% CI)**	***P***	**Wald**	**OR (95% CI)**	***P***
Irritable mood	187.978	5.4	< .001	15.341	1.5	< .001
Racing thoughts	16.279	2.1	< .001	6.203	1.5	.013
More talkative/pressure to keep talking	22.884	2.5	< .001	10.694	1.7	.001
Distractibility	82.459	3.1	< .001	12.382	1.5	< .001
Increased energy	-	-	-	2.805	1.4	.094
Impulsivity	16.314	2.0	< .001	12.655	1.7	< .001
Risky behavior	3.220	0.6	.073	8.153	0.6	.004
Grandiosity	2.958	1.8	.085	-	-	-
Elation	18.572	3.4	< .001	-	-	-
Verbal or physical aggression	3.800	0.7	.051	-	-	-

AL=affective lability; **MDE**=major depressive episode; **MDE-AL**=patients with a major depressive episode with affective lability; **MDE-noAL**=patients with a major depressive episode without affective lability; **MDE-MR**=patients with a major depressive episode with mood reactivity; **MDE-noMR**=patients with a major depressive episode without mood reactivity; **MR=**mood reactivity; **RBDC-MXS**=research-based diagnostic criteria for depressive mixed states.
*Chi-square=869.808; df=5; $P < .001$; variables not in the equation: psychomotor agitation, hyperactivity, increased energy, hyper-sexuality. †Chi-square=178.965; df=7; $P < .001$; variables not in the equation: psychomotor agitation, verbal or physical aggression, hyperactivity, grandiosity, elation, hyper-sexuality

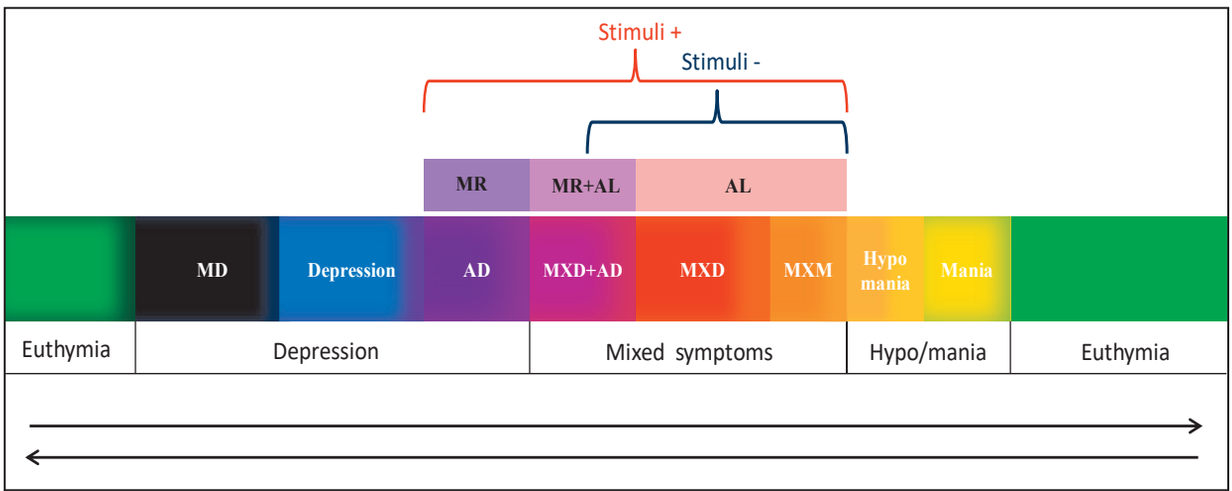

Figure 13. *Mood spectrum revised*
Abbreviations: AD=atypical depression; **AL**=affective lability; **MD**=melancholic depression; **MR**=mood reactivity; **MXD**=mixed depression; **MXM**=mixed mania
Note: The figure refers to the dimension of depression-hypomania/mania

Study V

Mixed states in bipolar and major depressive disorders:

Systematic review and quality appraisal of guidelines

Acta Psychiatrica Scandinavica

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The identification of mixed features in BD and MDD is an open challenge in psychiatry since an accurate diagnosis is a pre-requisite for the initiation of adequate therapeutic approaches (Marneros, 2001; Joshua D Rosenblat and McIntyre, 2017; Stahl, 2017).

Up to now, no drug treatment has been approved by major regulatory agencies for the management of mood episodes with a MFS (Grunze et al., 2018). The treatment of mixed episodes is an important challenge for psychiatrists since the available evidence is undermined by the methodological limitations of previous Randomized Clinical Trials (RCT). Generally, the response to pharmacological agents of patients presenting a manic episode with depressive mixed symptoms had been extrapolated from post-hoc or pooled analyses of RCT evaluating treatment response in mania (Grunze et al., 2009). In addition, these studies generally did not provide data for the mixed subgroup (Grunze et al., 2018). The evidence for mixed depression is even more scant since patients presenting mixed symptoms are generally excluded by depression RCT (Cuomo et al., 2017). As a consequence, the generalizability of the results of previous RCT may be partly suitable for the treatment of mania with mixed features but are less likely applicable to the treatment of depression with mixed features (Joshua D. Rosenblat and McIntyre, 2017).

Since mixed features represent a challenge for clinicians at the diagnostic, classification and pharmacological treatment levels, the aim of this work was to summarize available evidence and to provide a comprehensive review of recently

updated guidelines. A critical approach has been applied in order to identify areas of consensus and controversy, to underline the strengths and limitations of available evidence, and also the methodological quality of international guidelines that provided evidence for the management of mixed states in the context of BD and MDD.

The main findings of this study were:

1. Olanzapine seemed to be the most effective compound for the treatment of acute mixed hypo/manic or depressive states as well as for the prevention of mood episodes of any polarity, even though the available evidence was still scant.

2. Aripiprazole and paliperidone in monotherapy could be effective alternatives in the treatment of acute hypo/manic mixed states whilst lurasidone and ziprasidone (in combination with treatment as usual) in the treatment of acute depressive manifestations. As for the maintenance treatment, valproate was effective in the prevention of new mixed episodes. Lithium and the combination treatment of quetiapine were useful in preventing mood episodes of all polarities.

3. Antidepressant monotherapy should be avoided whilst clozapine and electroconvulsive therapy were effective options in treatment resistant patients.

As for the risk of suicide, several studies found an association between lifetime mixed episodes, higher rates of AD use and increased risk of suicide behaviors (Baldessarini et al., 2012b; Pacchiarotti et al., 2011; Valentí et al., 2011). It is for this reason that the ISBD task-force recommended that AD in BD patients should be prescribed only as an adjunct to mood-stabilizing medications (Pacchiarotti et al., 2013a). AD may protect from depressive recurrences in a small minority of patients with mixed features, both in bipolar and in unipolar patients (Stahl et al., 2017; Vieta et al., 2005), but should be prescribed in combination with antimanic agents.

As for aggression in mixed depressive episode, lurasidone was the only compound to have been investigated for the treatment of MDE with MFS in the context of MDD. A randomized, double-blind, placebo-controlled study (Suppes et al., 2016) and three post-hoc analyses of the same RCT have been conducted specifically in MDD patients with mixed features. The first post-hoc analysis (Swann et al., 2017) evaluated the efficacy of lurasidone in treating MDD with mixed features including irritable features based on the presence of both Young Mania Rating Scale (YMRS) items 5

(irritability) and 9 (disruptive-aggressive behavior) criteria at study baseline, with significant greater improvement versus placebo at week 6 of MADRS, YMRS and CGI–S scores. Treatment-emergent adverse events occurred with an incidence ≥5% were nausea and abdominal discomfort (8.7%). Up to now, lurasidone is the only medication with a completed trial in patients with MDD with MFS (Ostacher and Suppes, 2018). Finally, the California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines (Stahl et al., 2014) recommended avoiding the use of AD in patients with suspected bipolar disorder because of the possible worsening of irritability/aggression.

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Review article

Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis

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ABSTRACT

Background: Despite the potential importance of understanding violent criminal behavior (VCB) in individuals suffering from bipolar disorder (BD), previous findings are conflicting. The aims of the present study are to clarify the association of VCB and BD in comparison to general population and other psychiatric conditions.
Methods: A systematic review of literature from January 1st, 1980 through January 16th, 2017 from 3 electronic databases (MEDLINE/PubMed, EMBASE and PsycInfo), following the PRISMA and the MOOSE statements. Original peer-reviewed studies reporting data on VCB in BD were included. A random-effects meta-analysis was performed. Potential sources of heterogeneity were examined through subgroup and meta-regression analyses. The protocol was registered in PROSPERO, CRD42017054070.
Results: Twelve studies providing data from 58,475 BD participants. The prevalence of VCB in BD was 7.1% (95%CI = 3.0–16.5%; k = 4). The association of BD and VCB compared to general population was not significant (OR = 2.784; 95% CI, 0.687–11.287, P = .152). The association was significant only in cross-sectional studies, in studies in which VCB was assessed through self-reported measures, and in studies conducted in the USA. BD was more likely to be associated with VCB when BD patients were compared to controls with depressive disorders, whilst it was found to be less associated with VCB when BD was compared to psychotic disorders.
Limitations: 1. the methodological heterogeneity across the included studies. 2. causal inferences were precluded by the inclusion of cross-sectional studies.
Conclusions: These findings might provide a more balance portrait of the association between BD and VCB to clinicians, law enforcement and general public.

Abbreviations: BD, bipolar disorder; BD-I, bipolar disorder, type I; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECA, Epidemiological Catchment Area study; ES, effect size; ICD, International Classification of Disease; MDD, major depressive disorder; MOOSE, Meta-analyses Of Observational Studies in Epidemiology; NCS, National Comorbidity Survey; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SUD, drug abuse/dependence disorders; UCR, Uniform Crime Reporting; USA, United States of America; VCB, violent criminal behavior

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1. Introduction

Violence is an overt destructive behavior with the intention to inflict harm (Látalová, 2009) resulting in injury, death or psychological harm ("World Health Organization. Health topics-Violence," 2017). Violence is the basis of violent criminal behavior (VCB), with deleterious impact on individuals and societies (Krug et al., 2002; Látalová, 2009). Mass media often emphasized mental illness as the leading cause of violence in mass-shootings and terrorist attacks, and cinematographic depictions of the mentally ill are often sensationalized, contributing to stigma (Teplin, 1984; Varshney et al., 2016).

Risk factors for VCB include male sex, young age (Sher and Rice, 2015), parental criminality (Thapar, 2015), prior VCB (Johnson et al., 2016), childhood maltreatment (Jaffee et al., 2004) and victimization (Johnson et al., 2016). Psychiatric disorders have been studied as possible risk factors for VCB, with conflicting results (Johnson et al., 2016; Lysell et al., 2014; Rihmer et al., 2010).

Previous reviews (Fazel et al., 2010; Fovet et al., 2015; Látalová, 2009) attempted to summarize evidence on the association between violence and BD, but failed to include possible legal outcomes (Látalová, 2009), presented unstandardized methods or broader definitions of violence including aggressiveness (Fovet et al., 2015), provided a quantitative analysis limited to few studies (Fazel et al., 2010) or considered BD with other psychoses, providing mixed-samples results (Fazel et al., 2009; Witt et al., 2013).

1.1. Aims of the study

The present systematic review and meta-analysis aimed at: 1. Assessing the prevalence of VCB in BD; 2. Establishing the relative risk for VCB in BD compared to the general population and other psychiatric conditions; 3. Evaluating possible risk or protective factors for increased VCB in patients with BD.

2. Methods

This systematic review and meta-analysis adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) and the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) (Stroup et al., 2000) statements. The protocol was prospectively registered in PROSPERO (CRD42017054070). Two investigators (NV and IP) independently performed the literature search, title/abstract screening, full-text review, data extraction and methodological quality assessment. A third investigator was consulted whenever a consensus could not be achieved (AM).

2.1. Data sources and searches

The MEDLINE/PubMed, EMBASE and PsycInfo databases were searched from January 1st, 1980 through January 16th, 2017, augmented through the hand-searching of the reference lists of included articles. Detailed search strings are provided in the supplementary material that accompanies the online version of this article (Appendix S1).

2.2. Study selection

The following inclusion criteria were applied: original peer-reviewed articles published in any language; observational studies; > 95.0% of sample participants aged ≥ 18 years; BD diagnosis established according to International Classification of Disease (World Health Organization, 1992) and/or Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association., 2013) criteria; studies had to provide data on the prevalence or the association between VCB and BD.

A crime is violent when a victim is harmed by or threatened with violence ("National Institute of Justice," 2017). Its definition may vary depending on national legal definitions according to: type of acts included (e.g. sexual crimes excluded in New Zealand) ("New Zealand Recorded Crime Tables," 2017), intensity of the VCB (e.g. minor violent acts excluded in France) ("European Sourcebook of Crime and Criminal Justice Statistics – 2010," 2010), age of the offender (overall in Europe, limiting comparison even between member Countries) (Aebi et al., 2014). In the United States of America (USA), two main crime databases report on VCB. In the Federal Bureau of Investigation's Uniform Crime Reporting (UCR) VCB are defined as those offenses involving force or threat of force, namely murder and nonnegligent manslaughter, legacy and revised rape, robbery and aggravated assault ("Uniform Crime Reporting Statistics," 2017). The Bureau of Justice Statistics's National Crime Victimization Survey (NCVS) provide measures for non-fatal violence reporting on rape and sexual assault, robbery, and aggravated and simple assault ("Bureau of Justice Statistics," 2017).

In the present study, the following working definition of VCB was used: Any record of conviction, involvement in the judicial system or charge for violent crime, namely homicide, attempted homicide, assault, robbery, arson, threat or intimidation, and all sexual offenses (Webb et al., 2014). Self-reported VCB assessed in large-scale epidemiological surveys, namely the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Pulay et al., 2008), NCS (Corrigan and Watson, 2005), and the ECA (Swanson et al., 1990), were also deemed eligible.

The following exclusion criteria were applied: animal studies; meeting abstracts; case reports; letters to the editor; > 5.0% of the study population < 18 years; studies not providing the prevalence or association of VCB in BD; studies providing the prevalence or association in BD with non-VCB only; studies not providing comparison with general population; intervention studies.

2.3. Data extraction

A standardized extraction platform was developed in Microsoft Access 2010 ("Microsoft Access 2010, Microsoft Corporation, Redmond, Washington, USA," n.d.). For each study, we extracted the prevalence of VCB in participants with BD (see Appendix S2 for the complete list). The full contingency tables to estimate crude ORs were also extracted, considering the general population controls without psychiatric disorders and controls with any psychiatric disorder other than BD (including severe mental illness, depression, anxiety disorders, psychotic disorders, alcohol or drug abuse disorders, or personality disorders). The type of assessment (record-based vs. self-report) was also coded.

2.4. Methodological quality assessment

The methodological quality of included studies was rated through the Newcastle-Ottawa Scale [NOS] (Stang, 2010). An adapted version was used for cross-sectional studies (Herzog et al., 2013). For purposes of normalization, the % of criteria met was considered as a proxy of the overall methodological quality. The inter-rater reliability of independent reviewers was high (92.8%).

2.5. Statistical analysis

A random-effects meta-analysis estimated the prevalence of VCB in BD. The effect size (ES) measure used to estimate the prevalence of criminal behavior in BD was the proportion, but all analyses were conducted by converting proportions into logits. Simple proportions could underestimate the size of the 95% CI across the mean proportion, and could also overestimate the degree of heterogeneity across studies. Conversion into logits could circumvent these methodological shortcomings (Lipsey and Wilson, 2000).

The ES for the association measures were estimated as OR and 95% CI. Separate estimates were calculated considering the general population controls without psychiatric disorders or controls with any psychiatric disorder other than BD. Heterogeneity across studies was assessed with the Cochran's Q test (Bowden et al., 2011). Inconsistency across studies was estimated with the I^2 metric (Higgins et al., 2003). Evidence of publication bias was assessed with funnel plot graph and the Egger's regression test (Egger et al., 1997). When evidence of publication bias was observed, ES estimates were adjusted with the trim-and-fill procedure (Fazel et al., 2007).

Potential sources of heterogeneity were explored with subgroup and meta-regression analyses. The specific subgroup analyses considered a priori were reported in the Appendix S3. Meta-regression analyses were conducted when data from at least five independent datasets were available.

All analyses were conducted in Stata MP software version 14.0 ("Stata MP software version 14.0, Stata Corp, College Station, TX, USA," n.d.) using the metan package. Statistical significance was considered at an alpha level of 0.05.

3. Results

The database search generated 1,031 hits, 46 articles were identified after searching the references of included articles. After duplicates removal, the title/abstracts of 773 references were screened for eligibility; of those, 558 were excluded. Full-texts of 192 references were scrutinized in detail for eligibility, with 180 excluded (see Table S1 in the supplementary material for reasons), and 12 references included for systematic review and meta-analysis (see flowchart in Fig. 1, characteristics in Table S2). Overall, data from 9,020,778 participants (58,475 patients with BD, 8,962,303 general population controls and 231,587 patients with any psychiatric disorder) were included. Participants presenting any VCB were 91,387. Studies have followed cross-sectional ($k = 4$), case-control ($k = 3$), or prospective ($k = 5$) designs. The mean % of criteria met in the NOS scale across studies was 82.1 (SD = 17.3) (Table S3). A half of the included studies had a poor methodological quality. Nine out of twelve of the included studies used representative samples and only four specified in the methodology a diagnostic assessment with a structured interview.

3.1. Violent criminal behavior in bipolar disorder

The prevalence of VCB in individuals with BD was 7.1% (95% CI, 3.0–16.5; $k = 4$; Table 1). Heterogeneity was very large ($I^2 = 96.9\%$) and significant ($Q = 97.00$, $P < .001$). No evidence of publication bias was observed ($P = .458$; Egger's test) (funnel plot in Figure S1).

The association of BD and VCB compared to general population was significant (OR = 5.206; 95% CI, 1.338–20.251; $k = 12$; $P < .001$; Table 2, Fig. 2A). The comparator group in the study by Fazel et al. (Fazel et al., 2007) did not have any VCB events, therefore the OR was large, possibly biasing further analysis. In sensitivity analyses, where this study was not included in main analysis, the association was no longer significant (OR = 2.784; 95% CI, 0.687–11.287, $P = .152$; Table 2, Fig. 2B). Between-study heterogeneity was very large ($I^2 = 99.9\%$) and significant (Q = 8,090.26, $P < .001$, df = 11). No evidence of publication bias was verified ($P = .759$; Egger's test) (funnel plot in Figure S2). Main subgroup and meta-regression analyses were conducted without the aforementioned study by

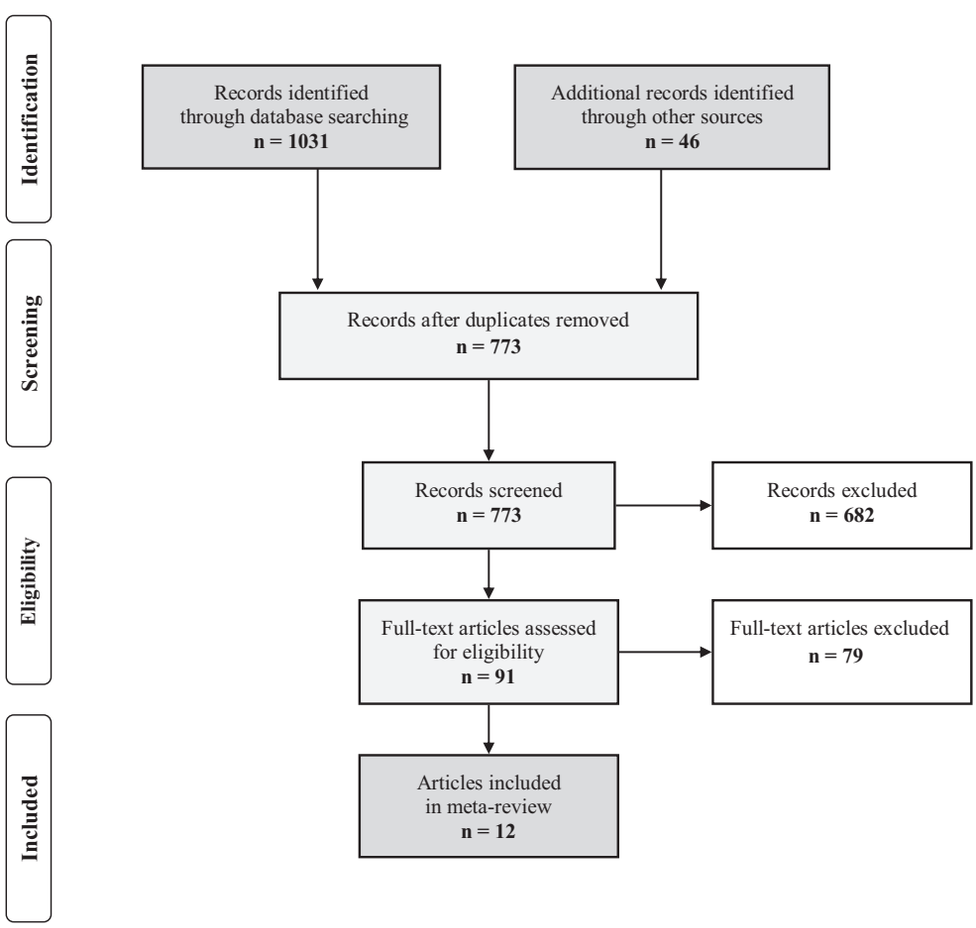


Fig. 1. PRISMA flowchart of study selection for systematic review and meta-analysis.

Table 1
Prevalence of criminal behavior in individuals with bipolar disorder. Data from four cross-sectional studies. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	BD prevalence			Heterogeneity		
		%	95%	CI	I^2	Q	*P*-value
Overall	4	7.07	3.04	16.45	96.9	97	< 0.001
Crime report type							
Self-report	2	9.28	4.79	18.01	74.0	7.71	< 0.001
Geographic region							
US	2	9.28	4.79	18.01	74.0	7.71	< 0.001

Moderator	N studies	Meta-regression				Meta-regression		
		Slope	95%	CI	*P*-value	Intercept	*z*	*P*-value
% Newcastle-Ottawa Scale score	4	0.026	−0.006	0.057	0.113	−3.955	−3.026	.002
Publication year	4	−0.002	−0.092	0.087	0.959	2.795	0.031	.976

Abbreviations: BD = bipolar disorder; *CI* = confidence interval.

Fazel et al. (2007). The association between BD and VCB was significant only in cross-sectional (k = 4) studies (Table 2, Fig. 2B), in studies in which VCB was assessed through self-reported measures, and in studies conducted in the USA (Table 2). In meta-regression analyses, no significant moderators emerged (Table 2).

The association between BD and VCB compared to controls with any psychiatric disorder was not significant (OR = 0.783; 95% CI, 0.438–1.398; k = 9; P = .407; Table 3, Figure 3). Between-study heterogeneity was very large (I^2 = 98.1%) and significant (Q = 429.35, P < .001, df = 8). No evidence of publication bias was verified (P = .559; Egger's test) (funnel plot in Figure S4). The association between BD and VCB was significant only in cross-sectional (k = 3) or case-control studies (k = 3) (Table 3, Fig. 3). The likelihood to present VCB was smaller for subjects with BD than for controls with any psychiatric disorder in case-control studies, (OR = 0.493), whilst it was increased in cross-sectional studies (OR = 1.285). The chance of VCB in BD was significantly lower in studies where VCB was assessed from records or in studies conducted in European Countries (Table 3). Chance was increased in studies conducted in the USA or using self-report to assess VCB. In meta-regression analyses, no significant moderators emerged (Table 3).

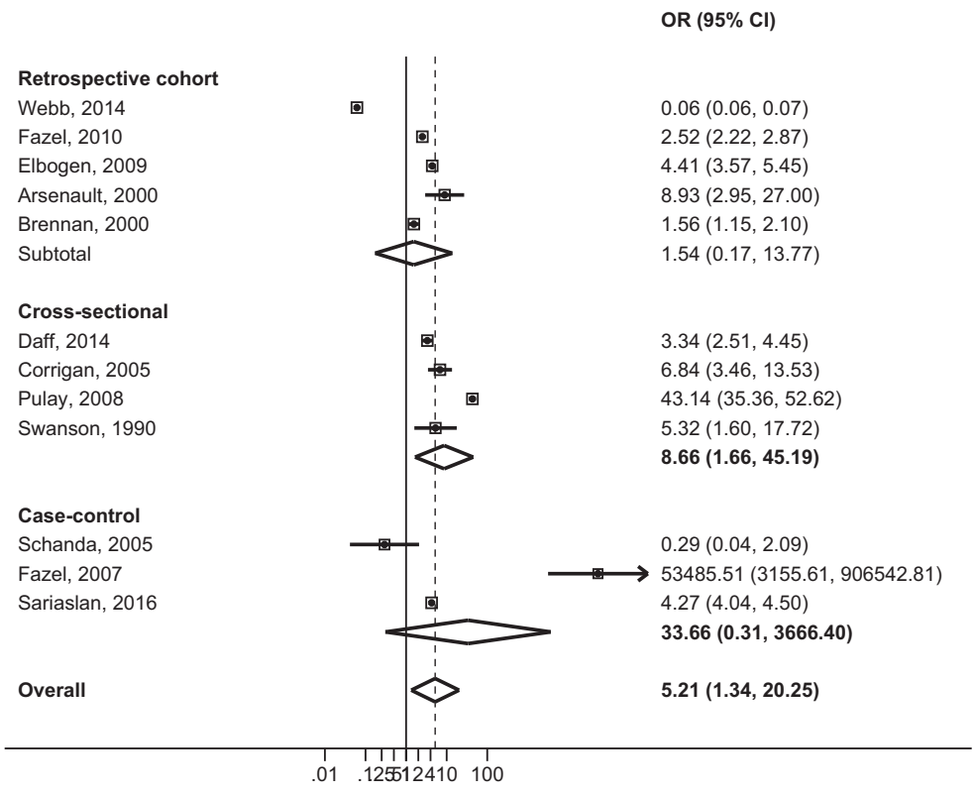
Seven studies investigated VCB in BD patients compared to controls with major depressive disorder (MDD) (N = 141,345), finding a significant association (OR = 2.313; 95% CI, 1.721–3.110; k = 7; P < .001; Figure S5 and Table S5). Heterogeneity was large (I^2 = 59.3%) and significant (Q = 14.76, P = .022, df = 6). Egger's test

Table 2
Association of bipolar disorder and criminal behavior in comparison to general population controls. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	Meta-analysis				Heterogeneity		
		OR	95%	CI	*P*-value	I^2	Q	*P*-value
Overall	12	5.206	1.338	20.251	.017	99.9	8090.26	< 0.001
Excluding Fazel et al. (2007)	11	2.784	0.687	11.287	.152	99.9	8038.78	< 0.001
Crime-report type								
Self-report	4	9.339	2.06	42.333	.004	98.8	0.36	< 0.001
Record-based	7	1.395	0.233	8.35	.715	99.9	0.71	< 0.001
Study design								
Retrospective cohort	5	1.542	0.173	13.771	.698	99.9	0.05	< 0.001
Cross-sectional	4	8.663	1.66	45.194	.010	98.6	0.67	< 0.001
Case-control	2	1.35	0.101	18.093	.821	86	0.14	.008
Geographic region								
US	4	9.339	2.06	42.333	.004	98.8	0.36	< 0.001
EU	4	1.007	0.092	11.061	.996	100	0.09	< 0.001
Oceania	3	2.753	0.785	9.658	.114	77.6	0.92	.012

Moderator	N studies	Meta-regression				Meta-regression		
		Slope	95%	CI	*P*-value	Intercept	*z*	*P*-value
% Newcastle-Ottawa Scale score	11	−0.007	−0.070	0.055	.817	1.642	0.612	.54
Publication year	11	−0.054	−0.200	0.092	.469	109.497	0.732	.464
% Female	4	−0.378	−1.991	1.235	.646	−0.082	−0.052	.958
% Any substance use disorder	4	0.127	−0.182	0.436	.421	−0.997	−0.616	.538

Abbreviations: BD = bipolar disorder; *CI* = confidence interval; **NOS** = not otherwise specified.



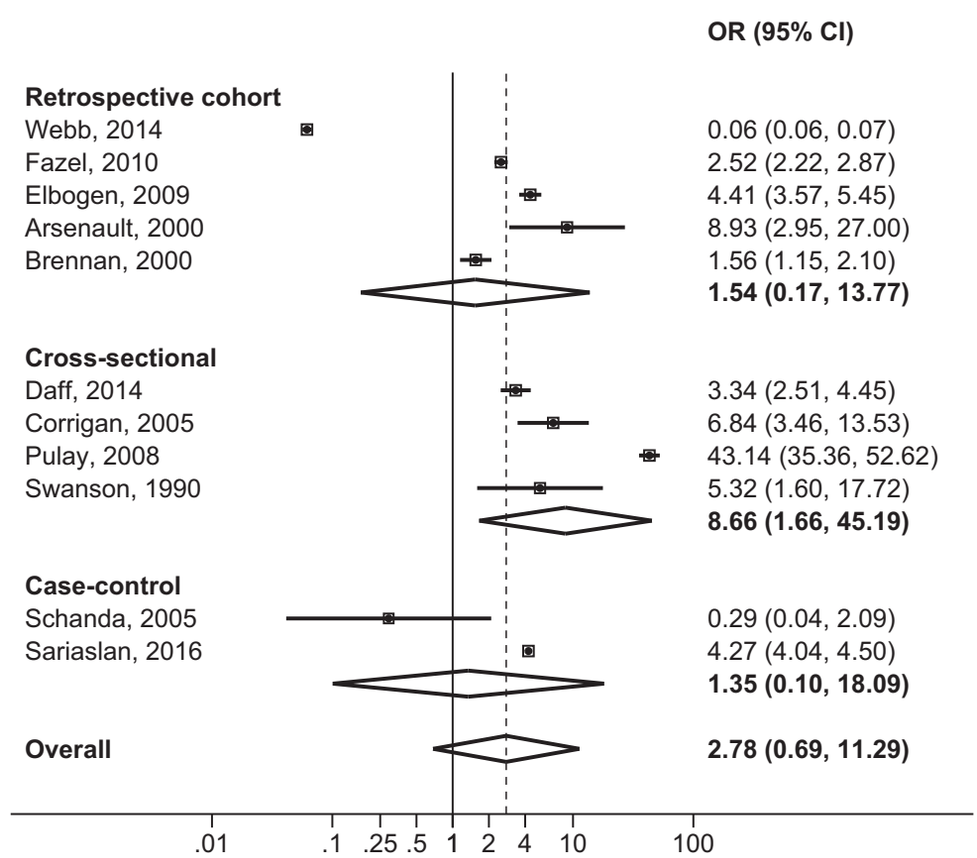


Fig. 2. Forest plot of the association of violent criminal behavior in BD subjects in comparison to the general population. Subgroup estimates are provided in accordance to study design. Effect sizes are reported as OR and 95% CIs. The sizes of the squares are proportional to sample sizes, and diamonds depict pooled effect size estimates through random-effects modeling. Panel A shows the meta-analysis of all 12 included studies, whilst panel B shows the meta-analysis excluding the study by Fazel et al. (2007).

Table 3
Association of bipolar disorder and criminal behavior in comparison to controls with any psychiatric disorder. Sources of heterogeneity were explored through subgroup and meta-regression analyses.

Subgroup	N studies	Meta-analysis				Heterogeneity		
		OR	95%	CI	*P*-value	I^2	*Q*	*P*-value
Overall	9	0.783	0.438	1.398	.407	98.1	429.35	< 0.001
Crime-report type								
Self-report	4	1.551	1.006	2.394	.047	87.0	23.04	< 0.001
Record-based	5	0.438	0.289	0.665	< 0.001	77.0	17.37	.002
Study design								
Retrospective cohort	3	1.000	0.191	5.236	1.000	98.4	121.58	< 0.001
Cross-sectional	3	1.291	1.155	1.444	< 0.001	0.0	0.92	.632
Case-control	3	0.447	0.353	0.565	< 0.001	16.0	2.38	.304
Geographic region								
US	4	1.551	1.006	2.394	.047	87.0	23.04	< 0.001
EU	3	0.392	0.272	0.564	< 0.001	78.3	9.22	.010

Moderator	N studies	Meta-regression				Meta-regression		
		Slope	95%	CI	*P*-value	Intercept	*z*	*P*-value
% Newcastle-Ottawa Scale score	9	0.012	−0.021	0.045	.471	−1.252	−0.877	.381
Publication year	9	0.003	−0.087	0.093	.945	−6.593	−0.072	.943
% Female	3	−0.563	−7.895	6.769	.880	−1.124	−1.509	.131

Abbreviations: BD = bipolar disorder; *CI* = confidence interval; **NOS** = not otherwise specified.

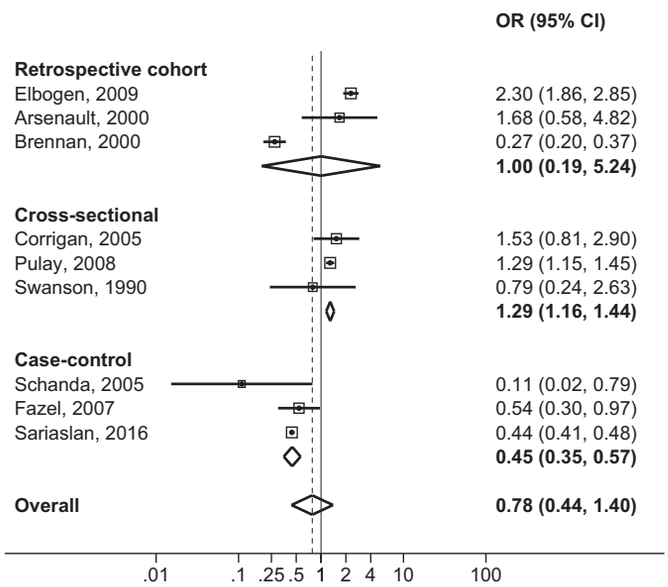


Fig. 3. Forest plot of the association of violent criminal behavior in BD subjects in comparison to a comparator group with any psychiatric disorder. Subgroup estimates are provided in accordance to study design. Effect sizes are reported as OR and 95% CIs. The sizes of the squares are proportional to sample sizes, and diamonds depict pooled effect size estimates through random-effects modeling.

(P = .035) and funnel plot suggest publication bias (Figure S6). In subgroup analyses, the association was significant and without heterogeneity in studies that used a self-report for VCB, cross-sectional design or were conducted in the USA (Table S5). No moderators were significant in meta-regression analyses (Table S6).

Eight studies investigated VCB in BD patients compared to controls with psychotic disorders (N = 55,285). Individuals suffering from BD had a smaller chance of VCB (OR = 0.498; 95% CI, 0.329–0.751; k = 8; P = .001; Figure S7, Table S5). Heterogeneity was very large (I^2 = 79.4%) and significant (Q = 33.93, P < .001, df = 7). No evidence of publication bias was observed (P = 0.802; Egger's test) (funnel plot in Figure S8). Subgroup analyses showed that the association was maintained in studies using a record-based assessment for VCB, case-control design or conducted in the USA (Table S5). No moderators were significant in meta-regression analyses (Table S6).

Five studies investigated VCB in BD patients compared to controls with anxiety (N = 11,391). The association was not significant (OR = 1.771; 95% CI, 0.978–3.207; k = 5; P = 0.059; Figure S9 and Table S5). Heterogeneity was large (I^2 = 4.7%) and significant (Q = 15.78, P = .003, df = 4). No evidence of publication bias was observed (P = .290; Egger's test) (funnel plot in Figure S10). Subgroup analyses showed a significant association (OR = 2.628) for 3 studies that used cross-sectional design, a self-report instrument and were conducted in the USA. No moderators emerged in meta-regression analyses.

Five studies investigated VCB in BD patients compared to controls with alcohol abuse/dependence disorders (N = 13,572). The association was not significant (OR = 0.454; 95% CI, 0.093–2.213; k = 5; P = .328; Figure S11, Table S5). Heterogeneity was very large (I^2 = 97.1%) and significant (Q = 138.17, P < .001, df = 4). No evidence of publication bias was observed (P = 0.139; Egger's test) (funnel plot in Figure S12).

Six studies investigated VCB in BD patients compared to controls with drug abuse/dependence disorders (SUD) (N = 12,668). The association was not significant (OR = 0.980; 95% CI, 0.609–1.576; k = 6; P = .933; Figure S13, Table S5). Heterogeneity was very large (I^2 = 87.7%) and significant (Q = 40.741, P < .001, df = 5). No evidence of publication bias was observed (P = 0.516; Egger's test) (funnel plot in Figure S14).

Only two studies investigated VCB in BD patients compared to controls with personality disorders (N = 5,764). The association was not significant (OR = 0.388; 95% CI, 0.022–6.742; k = 2; P = .516), and heterogeneity was very large (I^2 = 98.0%) and significant (Q = 50.68, P < .001, df = 1).

4. Discussion

To the best of our knowledge, this is the first meta-analysis

providing a comprehensive quantitative assessment of VCB and its components in individuals with BD.

The prevalence of VCB in BD individuals was lower than previous epidemiological studies, reporting estimates from 11% (Swanson et al., 1990) up to 25.34% (Pulay et al., 2008).

BD was not significantly associated with VCB compared to general population controls or to patients with any psychiatric disorder. In both cases, a significant association between BD and VCB emerged when VCB was not based on criminal records but assessed from self-report and in cross-sectional surveys or conducted in the USA. This could be explained with the quite broad definition of self-reported VCB provided in the three USA surveys (Corrigan and Watson, 2005; Pulay et al., 2008; Swanson et al., 1990) deemed acceptable for inclusion in the present meta-analysis. However, the estimated prevalence of VCB in the general population in these surveys (from 0.66% (Pulay et al., 2008) to 2.05% (Swanson et al., 1990)) is lower than the prevalence reported in the included record-based studies (from 0.8% (Webb et al., 2014) to 8.9% (Daff and Thomas, 2014)). Self-reported and official records of VCB are highly correlated but the concordance between them varies, as individual traits and characteristics might influence the relative accuracy of records (Forrest et al., 2014).

In this meta-analysis, BD was significantly associated with VCB in cross-sectional surveys. This is not surprising as cross sectional studies are generally used to determine prevalence, although they cannot help assessing a possible causal relationship.

As for the significant association in the USA samples, speculative reasons derived from official reports about the geographic distribution of crimes may be provided. Crime rates across Countries are complicated as crime recordings vary heavily. Yet, rates of VCB are generally higher in the USA than in Oceania and Europe (Dubow et al., 2014). USA have a homicide rate higher than Canada, Australia and UK ("United Nations Office on Drugs and Crime Statistics Online, Homicide counts and rates (2000–2015)," 2017), especially for homicides committed by firearms ("International firearm injury prevention and policy," 2017). Additional correlates to VCB explaining these different rates should also be addressed, such as Countries differences in accessing firearms (Appelbaum, 2006).

No moderators were identified to explain the associations. Neither comorbid SUD nor socio-demographic factors significantly moderated the risk of BD individuals to commit VCB. This is conflicting with previous findings in BD (Daff and Thomas, 2014; McCabe et al., 2013; Webb et al., 2014) or in the general population (Corrigan and Watson, 2005). A strong relation between SUD and violence is often assumed (Fazel et al., 2009). Nonetheless, genetic influences unrelated to SUD partially explained the correlation between VCB and BD (Sariaslan et al., 2015). Interestingly, sex did not significantly moderate the association between BD and VCB, despite male sex is a well-known risk factor for VCB in the general population (Sher and Rice, 2015) and in psychotic samples (Fazel et al., 2009).

In this meta-analysis, increased OR for the association of VCB in BD emerged when BD patients were compared to controls with depressive disorders, in USA cross-sectional studies assessing self-reported VCB. On the contrary, BD was less associated with VCB when BD was compared to psychotic disorders. The association was significant mainly in the USA, in case-control studies, or in studies reporting a record-based assessment of VCB.

The OR for incarceration was as high as 1.34 in BD patients compared with MDD patients in an USA sample (Hawthorne et al., 2012) whilst in a Swedish case-control study, schizophrenia was a stronger predictor of violence than BD (Sariaslan et al., 2015). In a study analyzing cross-sectionally the first NESARC wave (2001–2002) (Pulay et al., 2008), the risk for VCB was as high as 3.72 in BD-I whilst it was 1.73 in MDD. With some discrepancy, similar results are observed in European studies. In Swedish population studies, the OR for VCB was 3.0 for MDD (Fazel et al., 2015), 2.6 for BD (Fazel et al., 2010), and 6.3 for schizophrenia (Fazel and Grann, 2006). In the Dunebin cohort study (Arseneault et al., 2000) the risks for court-convictions and/or self-reported violence were 2.1 in MDD, 3.5 in BD and 5.4 schizophrenia.

The risk for re-offending VCB seems to keep the previous progression among diagnoses (2.06 in schizophrenia, 1.96 in BD and 1.41 in MDD) (Chang et al., 2015).

4.1. Clinical implications

Despite specific manic symptoms (e.g. social indiscretions, reckless driving) predicted criminal involvement in previous studies (Christopher et al., 2012; McCabe et al., 2013), in the present meta-analysis mania was not a significant moderator of the association between VCB and BD. Yet, past affective episodes have strong implications on the course of life of BD patients, due to an increased risk for social drift (e.g. worse educational and working achievement, family and relational problems) compared to the general population and positively associated to VCB in BD (Elbogen and Johnson, 2009). Ensuring an early diagnosis, establishing a proper treatment and providing the appropriate management and follow-up in mental health outpatients units could represent important steps to reduce the risk of VCB in BD (Goodwin et al., 2016).

Treatments for BD exert an overall control over all symptoms dimensions, encompassing aggressive symptoms (Fazel et al., 2014). Psychiatric patients with a criminal history would benefit the most from treatment programs, that often exclude them (Appelbaum, 2006). Criminal history should be an indicator of an increased need for more integrated approaches, rather than a reason for treatment exclusion (Matejkowski et al., 2014). Recent clinical guidelines provide assistance, both in inpatient and outpatient units, for the identification of triggers and treatment strategies for violence (NICE, 2015; Stahl et al., 2014).

Patients already tracked in the justice system might benefit from an integrated case-management model within both criminal and mental health systems. The implementation of court liaison and diversion programs aims at reducing the clinical severity and the likelihood of VCB in such populations (McNiel and Binder, 2007). Specific treatment algorithms for the treatment of BD in the correctional setting should be improved and their efficacy tested (Kamath et al., 2013).

The association between BD and VCB should also be considered on the likelihood of BD patients to be victims of crimes. Unluckily in the present meta-analysis the study of victimization as a possible moderator of VCB was not possible due to scant evidence justifying a meta-regression. In the past, violent victimization among psychiatric patients was observed more frequently than VCB (Choe et al., 2008), yet this raised less attention by media than violent offending (Varshney et al., 2016). As patients victims of violence are more likely to engage in VCB (Latalova et al., 2014), avoidance of this potential, dangerous loop is warranted. Victimization is a serious medical and social problem that should be included in the clinical assessment and care for BD patients (Latalova et al., 2014).

4.2. Research implications and unmet needs

The comparison between existing studies in this meta-analysis was difficult because of differences in the VCB classification systems with consequent high heterogeneity. Methodological quality of included studies was varied. Better quality, multicenter, longitudinal studies are required to disentangle the timing of the association between BD and VCB.

The identification of a worldwide accepted operational definition of VCB might help achieving generalizable and reliable results. A wide range of structured tools assessing violence is present, often with poor-to-moderate accuracy, scant external validations, especially in women or ethnic minorities (Douglas et al., 2017). Well-defined and generalized risk-assessment indicators and outcomes of VCB, early identification of potential offenders and effectiveness of interventions are still

lacking and represent possible subjects of future research.

In terms of public health perspective, research focus should be switched from relative to absolute risk measured, i.e. population-attributable risk. Identifying the percentage of VCB that can be ascribed to BD would help reducing stigmatization (Varshney et al., 2016). Possible confounders, i.e. social and cultural variables or comorbidity-related factors, should be controlled. In this meta-analysis SUD did not represent a moderator for the association between BD and VCB. This was probably related to the heterogeneity in the assessment of SUD across the included studies, with only few of them (Abram and Teplin, 1991; Alnıak et al., 2015; Shaffer et al., 2007) separated recent from past SUD.

VCB should be considered in randomized controlled trials and adequately researched as a specific treatment outcome of antipsychotics and mood stabilizers. The tendency towards manic relapses should be properly addressed (Samalin et al., 2016) as well as the depressive polarity to avoid self-injuries representing predictors of both criminality and suicide in BD (Sahlin et al., 2017; Verdolini et al., 2017; Webb et al., 2014).

Future studies should examine the possible underlying genetic risk for VCB in BD. The significant heterogeneity of the association between VCB and BD could be explained with the phenotypic variability of BD (ALDA, 2004) that should be studied at a genetic level, possibly through a mendelian randomization experiment (Burgess et al., 2015). Recently, genetic influences unrelated to SUD were found to explain a fifth of the correlation with VCB in BD (Sariaslan et al., 2015), but implications for these findings are still to be ascertained.

4.3. Limitations

This meta-analysis presents limitations. First, the considerable methodological heterogeneity across the included studies. Second, the exploratory nature of the meta-analysis has to be taken into account and negative findings should be carefully considered. Also, the generalizability of the findings should be limited due to the absence of studies proceeding from Asia, Africa and South America. Furthermore, a third of the included studies were cross-sectional, precluding causal inferences and limiting the deduction of the directionality between BD and VCB. Finally, excluding the risk of publication bias is not possible.

4.4. Conclusions

One every fourteen patients suffering from bipolar disorder reported violent criminal behavior. Overall, the association with violent criminality was not significant when bipolar disorder was compared with the general population. Despite this, the association between bipolar disorder and violent criminal behavior was significantly higher than in depressive disorders whilst the chance was smaller in comparison with psychoses. Since the associations varies depending on the comparison group and the type of methodology, predictors of violent behavior should be further investigated in bipolar disorder, differentiating between those properly related to the illness and those possibly biased by confounders. The limitations in the included articles do not allow for definitive conclusions regarding the prevalence or causes of violent criminal behavior in bipolar disorder. Nonetheless, clinicians should promote awareness in order to minimize stigmatization. From a clinical perspective, increasing the efforts in providing to patients suffering from bipolar disorder, with or without a criminal history, appropriate and integrated treatment strategies is strongly warranted.

Declaration of interest form

Dr. Norma Verdolini is funded by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a "Río Hortega" contract (CM17/00258) and reports no competing interests.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author contributions

Prof Vieta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Verdolini, Murru, Pacchiarotti, Carvalho, Vieta.

Acquisition, analysis, or interpretation of data: Verdolini, Köhler, Pacchiarotti, Murru.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Köhler.

Administrative, technical, or material support: Köhler, Verdolini, Vieta.

Study supervision: Murru, Carvalho, Vieta, Colom, Reinares, Tortorella, Samalin, Stubbs.

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Supplementary materials

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Original article

The aggressor at the mirror: Psychiatric correlates of deliberate self-harm in male prison inmates

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ABSTRACT

Background: Deliberate self-harm (DSH) causes important concern in prison inmates as it worsens morbidity and increases the risk for suicide. The aim of the present study is to investigate the prevalence and correlates of DSH in a large sample of male prisoners.
Methods: A cross-sectional study evaluated male prisoners aged 18+ years. Current and lifetime psychiatric diagnoses were assessed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* - DSM-IV Axis I and Axis II Disorders and with the Addiction Severity Index-Expanded Version. DSH was assessed with The Deliberate Self-Harm Inventory. Multivariable logistic regression models were used to identify independent correlates of lifetime DSH.
Results: Ninety-three of 526 inmates (17.7%) reported at least 1 lifetime DSH behavior, and 58/93 (62.4%) of those reported a DSH act while in prison. After multivariable adjustment (sensitivity 41.9%, specificity 96.1%, area under the curve = 0.854, 95% confidence interval CI = 0.811–0.897, $P < 0.001$), DSH was significantly associated with lifetime psychotic disorders (adjusted Odds Ratio aOR = 6.227, 95% CI = 2.183–17.762, $P = 0.001$), borderline personality disorder (aOR = 6.004, 95% CI = 3.305–10.907, $P < 0.001$), affective disorders (aOR = 2.856, 95% CI = 1.350–6.039, $P = 0.006$) and misuse of multiple substances (aOR = 2.024, 95% CI = 1.111–3.687, $P = 0.021$).
Conclusions: Borderline personality disorder and misuse of multiple substances are established risk factors of DSH, but psychotic and affective disorders were also associated with DSH in male prison inmates. This points to possible DSH-related clinical sub-groups, that bear specific treatment needs.

1. Introduction

Acts of self-harm encompass a wide range of behaviors, which differ in severity, from minor cuts to violent suicide attempts [1]. Some experts suggest that both deliberate self-harm (DSH) and suicide attempts could be conceptualized on *a continuum* of lethality, while a dichotomous differentiation between those two sets of behavior may be arbitrary and of limited clinical utility

Abbreviations: aOR, adjusted Odds Ratio; ASI-X, Addiction Severity Index-Expanded Version; AUC, area under the curve; CI, confidence interval; DSH, deliberate self-harm; DSHI, Deliberate Self-Harm Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; OR, Odds Ratio; PD, personality disorders; ROC, receiver operating characteristic; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders; SD, standard deviation.

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[2,3]. Despite these controversies, DSH and suicide attempts could be identified as distinct psychopathological phenomena, with meaningful differences related to lethality, aims of the act, the presence of suicidal intent, among other clinical characteristics [1,4].

DSH can be conceptualized as the deliberate, voluntary and not accidental, direct destruction or alteration of body tissue without conscious suicidal intent [5]. In prison populations, DSH was not studied as much as suicidality [6]. Yet, it may represent a relevant source of morbidity and, when present, may moderate the risk of suicide [7,8], especially when underlying mental disorders are present [9]. The prevalence of lifetime DSH in adult offenders ranges between 15 [10] and 35% [11] in male prisoners. Rates are smaller for those who self-harm while in custody, ranging between 5 [7] and 15% [10], whilst they significantly increase among inmates with mental disorders (up to 53% [12] for lifetime DSH and 61% [13] for DSH while in custody).

Relatively few studies evaluated possible clinical correlates of DSH in incarcerated samples [12,14–16]. Most of them were epidemiological studies [7,17], whilst others bore methodological limitations, such as a non-standardized assessment of personality disorders (PD) [18,19]. Finally, very few studies investigated specific factors independently associated with DSH in prison inmates [7,11,19,20].

The objectives of the present study are:

- to estimate the prevalence of DSH in a large sample of male prisoners;
- to explore whether DSH and suicide attempts lie on a same continuum, or otherwise might be more accurately characterized as separated psychopathological entities;
- to investigate socio-demographic, clinical, and treatment-related variables independently associated with DSH in this sample.

2. Methods

2.1. Participants

The sample was collected from October the 1st, 2010 to September the 30th, 2011 at the Spoleto Prison (Umbria, Italy). In this prison, 4 groups of criminals serve their time:

- common criminals;
- organized crime prisoners, except for leading bosses;
- protected inmates (e.g., serving for pedophilia, rape, or cooperating witnesses);
- leading bosses in organized criminality.

This study was approved by the local Ethics Review Board, by the Regional Penitentiary Committee and by the Italian Psychiatric Association. All participants provided written informed consent.

2.2. Inclusion/exclusion criteria

Male inmates, aged 18+ years, serving for crime groups 1, 2, 3 as detailed in the "Participants" section were eligible for this cross-sectional survey.

Inmates serving for crime type 4 or inmates awaiting trial were excluded from the study, as well as those with mental retardation, severe cognitive impairment or unwilling to provide written informed consent.

2.3. Study procedures

Eligible inmates underwent a comprehensive psychiatric evaluation performed by medical doctors (LA and RG) with at least 3 years of training in psychiatry. The interviewers were specifically trained to discriminate between suicide attempts and DSH.

2.4. Measures

Participants were interviewed and the following measures were collected:

- the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)* [21,22], which was shown to provide an accurate assessment of Axis I disorders in correctional settings [23];
- the *Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)* [24,25], whose reliability has been tested [26], has been widely used in correctional settings for the assessment of Axis II PD [27,28];
- the *Addiction Severity Index-Expanded Version (ASI-X)* [29] is a semi-structured interview validated for use in Italian samples [30] that evaluate the use of alcohol and other substances as well as their impact on functioning in several areas (medical, employment, support, legal, family/social, psychiatric). The reliability of the ASI-X has been previously demonstrated [31,32] and it was validated in prison populations [33,34]. In the psychiatric status area, misuse of substances was reported. The interviewers also assessed both reported suicide attempts, lifetime and in the last month, and severe suicidal thoughts according to the specific ASI-X items [35]. Suicide attempts were defined as acts of self-harm with intent to die that were not self-mutilatory in nature [36]. In the legal status area, specific information about charges was collected. In the family/social relationships area, questions about past 30 days and lifetime emotional, physical, sexual abuse and sexual harassment, as well as family history of legal/substances/psychiatric disorders were presented.

The Deliberate Self-Harm Inventory (DSHI) [37]. The DSHI is a 17-item, behaviorally based, self-report questionnaire that assesses frequency, severity, duration, and type of different self-harm behaviors. Interviewers recorded for each self-harm behavior information regarding the age of onset of a DSH behavior, the last time (in months) presenting that behavior, the total duration (in years) of that behavior, and whether a DSH-derived hospitalization or medical care had been required. Psychometric and language-specific characteristics of DSHI are presented elsewhere [37–39]. DSHI was previously used to assess DSH in male inmates [39].

Socio-demographic and clinical variables (drug and alcohol, medical and psychiatric status, prescribed treatments and use of services) were also collected through the specific ASI-X form.

Inmates' records at the Spoleto Prison were also reviewed to collect further information.

2.5. Statistical analysis

The dichotomous DSH variable was derived when inmates affirmatively answered to any of the first 16 items on the DSHI, or when the answer to the item 17 ("Have you ever intentionally done anything else to hurt yourself that was not asked about in this questionnaire? If yes, what did you do to hurt yourself?") described a behavior consistent with the conceptual definition of DSH [37]. Normality of distribution for continuous variables was evaluated with the Kolmogorov-Smirnov test, visually and with the skewness and kurtosis values. Bivariate analyses were performed with Chi-square tests, independent-samples *t*-test, or Mann-Whitney U test (according to type of distribution of the variable). Partial correlations were used to assess the relationship between the number of suicide attempts and the number of lifetime episodes of DSH, after adjustment for age. A multivariable

hierarchical logistic regression analysis was performed to investigate whether psychiatric diagnoses and other clinical features were independently associated with DSH, after adjusting for age. Predictor variables were chosen basing on:

- past research (i.e. physical abuse and substance abuse [19]);
- significant results from bivariate analyses coherent with previous research (i.e. borderline [20], antisocial PD [40] and psychiatric family history [11]);
- without a well-defined knowledge (i.e. affective [1,4], psychotic [41] and anxiety [40] disorders).

Variables already known as being less strongly associated with DSH and with doubtful clinical importance (i.e. schizotypal PD) [40] were not included due to the statistical limits imposed by the logistic regression model). Age was entered at Step 1 in order to control for its influence on DSH. Afterwards, other predictors were entered at Step 2. All tolerance values in the hierarchical regression analyses were > 0.2 and all variance inflation factors were < 2, thereby indicating that multicollinearity was not a source of bias in the regression models [42]. The accuracy of the model in detecting DSH in inmates was explored in receiver operating characteristic (ROC) analysis.

According to a two-tailed, alpha value of 0.05, the statistical power of the study population (0.94 for DSH) was sufficient to detect small effect sizes of about Cohen's $d = 0.24$, when comparing the groups for continuous variables.

Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA).

3. Results

3.1. Sample characteristics

During the 12-month study period, 670 male inmates were detained in the Spoleto Prison and considered for inclusion. Among those, 102 (15.2%) inmates were not eligible due to the following exclusion criteria: 20 (3%) were awaiting trial, and 82 (12.3%) were serving for type 4 crimes. Of the 568 eligible participants, 42 (7.4%) refused to take part in the study.

The final sample of included inmates was composed of 526 individuals (92.6% of potentially eligible participants) [43].

3.2. Lifetime deliberate self-harm

Among inmates, 93/526 (17.7%) reported at least 1 lifetime DSH behavior, with a median of 2 (range 1–57) lifetime DSH episodes. In addition, 43 out of 93 inmates (46.2%) reported engaging in more than one type of DSH behavior in their life (see Supplementary Table 1 for additional information on the type of DSH).

Fifty-eight individuals (62.4% of the DSH sub-sample, 11% of the total sample) reported a last DSH act while in prison.

Socio-demographic differences between inmates who did versus those who did not self-harm are reported in Table 1.

The prevalence of suicide attempts in the total sample was 10.6% (56/526) and in the DSH subsample it was significantly higher than in those without lifetime DSH (44.1% versus 3.5%, $P < 0.001$). Inmates with a lifetime history of DSH reported significantly more lifetime suicide attempts (Median = 0, 0–10, versus Median = 0, 0–4, $P < 0.001$) and significantly more frequently serious thoughts of suicide compared to prisoners who did not exhibit DSH (57% versus 12.7%, $P < 0.001$). A significant positive correlation between the number of suicide attempts and the number of DSH episodes ($r = 0.3$, $P = 0.004$), after adjusting for age, was observed.

As for psychiatric diagnoses, all Axis I current diagnoses were significantly more represented in the DSH group, with the exception of adjustment disorders (Table 2). Regarding DSM-IV Axis II disorders, significantly more participants with a lifetime history of DSH had borderline PD ($P < 0.001$), antisocial PD ($P = 0.024$), and schizotypal PD ($P < 0.001$) compared to those who did not self-harm.

In addition, inmates with a history of DSH more frequently received both outpatient ($P < 0.001$) and inpatient ($P < 0.001$) psychiatric treatment compared to those prisoners without a lifetime history of DSH.

Inmates with a lifetime history of DSH also reported more frequent misuse of multiple substances ($P < 0.001$) particularly a longer-lasting lifetime use of cocaine ($P = 0.008$) and cannabis ($P = 0.012$), also presenting a significantly younger age at onset of cocaine ($P = 0.031$) and cannabis ($P = 0.024$) use (Table 3).

Table 1
Socio-demographic characteristics of DSH inmates.

Lifetime variables (yes listed)	No DSH ($n = 433$)	DSH ($n = 93$)	χ^2	P
Area of the prison	*n*, %	*n*, %		
Common criminals	167 (38.6)	37 (39.8)	0.01	0.919
High-surveillance	190 (43.9)	39 (41.9)	0.052	0.82
Protected	76 (17.6)	17 (18.3)	< 0.001	0.986
Nationality				
Italian	289 (66.7)	56 (60.2)	1.171	0.279
EU[a]	82 (18.9)	10 (10.8)	3.009	0.083
Non EU	66 (15.2)	27 (29)	9.077	0.003
Marital status				
Married	178 (41.1)	44 (47.3)	0.967	0.325
Single	179 (41.3)	41 (44.1)	0.138	0.71
Separated/divorced/widowed	76 (17.6)	8 (8.6)	3.927	0.048
Lifetime variables	Mean (SD) Median (range)	Mean (SD) Median (range)	t/U	P
Age (years)	41.16 (11.82)	38.49 (10.23)	2.016	0.044
Education (years)	8 (0–17)	8 (0–15)	17595.5 (U)	0.044
Longest period of regular employment (months)	60 (0–540)	26 (0–240)	13080 (U)	< 0.001
Longest period of unemployment (months)	56 (0–444)	37 (0–420)	14928 (U)	0.279

DSH: deliberate self-harm; EU: European Union; *n*: number; SD: standard deviation.
[a] Italians excluded.

Table 2
Clinical variables associated with deliberate self-harm.

Variables (yes listed)	No DSH ($n = 433$)	DSH ($n = 93$)	$\chi 2$	P
Axis I psychiatric disorders	*n*, %	*n*, %		
Affective disorders	27 (6.2)	26 (28.0)	37.504	< 0.001
Bipolar disorders	5 (1.2)	6 (6.5)	10.491	0.006
Depressive disorders	18 (4.2)	15 (16.1)	16.68	< 0.001
Affective disorder NOS	4 (0.9)	5 (5.4)	9.025	0.011
Psychotic disorders	8 (1.8)	17 (18.3)	45.662	< 0.001
Alcohol and drug related disorders	90 (20.8)	39 (41.9)	17.377	< 0.001
Anxiety disorders	101 (23.3)	32 (34.4)	4.408	0.035
Adjustment disorders	40 (9.2)	5 (5.4)	1.007	0.316
Impulse control disorders	2 (0.5)	5 (5.4)	14.081	0.002
Axis II personality disorders				
Borderline PD	58 (13.4)	61 (65.6)	116.188	< 0.001
Antisocial PD	63 (14.5)	23 (24.7)	5.082	0.024
Histrionic PD	24 (5.5)	1 (1.1)	3.375	0.101
Narcissistic PD	26 (6.0)	3 (3.2)	0.664	0.415
Paranoid PD	29 (6.7)	6 (6.5)	< 0.001	1
Schizoid PD	28 (6.5)	3 (3.2)	0.924	0.331
Schizotypal PD	2 (0.5)	9 (9.7)	31.754	< 0.001
Obsessive-compulsive PD	13 (3.0)	1 (1.1)	1.097	0.482
Avoidant PD	15 (3.5)	2 (2.2)	0.422	0.749
Dependent PD	2 (0.5)	0 (0.0)	0.431	1
Depressive PD	8 (1.8)	4 (4.3)	2.067	0.24
Passive-aggressive PD	20 (4.6)	2 (2.2)	1.164	0.397
Lifetime treatments	Median (range)	Median (range)	U	P
Previous psychiatric inpatient[a]	0 (0–10)	0 (0–12)	14549 (U)	< 0.001
Previous psychiatric outpatient[a]	0 (0–90)	1 (0–30)	11831 (U)	< 0.001

DSH: deliberate self-harm; *n*: number; PD: personality disorders; SD: standard deviation.
[a] Assessed by means of the Addiction Severity Index-Expanded Version (ASI-X).

Regarding legal status, DSH inmates reported significantly more lifetime charges (Median = 4, 0–81 versus Median = 2, 0–27, $P < 0.001$), with more charges resulting in conviction (Median = 3, 0–81 versus Median = 2, 0–23, $P < 0.001$), such as crimes against property (Median = 1, 0–25 versus Median = 0, 0–15, $P < 0.001$), crimes of violence (Median = 1, 0–80 versus Median = 1, 0–23, $P = 0.005$) and crimes with disorderly conduct, vagrancy and public intoxication (Median = 0, 0–11 versus Median = 0, 0–10, $P = 0.001$) than those without a lifetime history of DSH. Furthermore, inmates with lifetime DSH reported a longer duration of lifetime incarcerations in months, compared to their counterparts who did not self-harm (Median = 79, 0–99 versus Median = 55, 0–99, $P = 0.040$).

Inmates with lifetime DSH more frequently reported a history of physical abuse ($P = 0.047$) and more than one type of abuse ($P = 0.050$). Furthermore, they reported more familiar difficulties such as maternal and paternal substances use issues ($P = 0.001$) and psychiatric problems ($P < 0.001$).

3.3. Multivariable analysis

Hierarchical multiple regression was used to assess possible predictors of DSH, after controlling for the influence of age. At Step 1, age was significantly related to DSH (χ^2 (1) = 4.165, $P = 0.041$), and explained between 0.8% (Cox and Snell R square) and 1.3% (Nagelkerke R squared) of the variance in lifetime DSH, and had a small protective influence on DSH (odds ratio OR = 0.979, $P = 0.045$) (Table 4). After entry of the independent variables (affective, anxiety and psychotic Axis I diagnoses, Axis II borderline and antisocial PD, positive history of physical abuse, parental psychiatric problems and misuse of multiple substances) at Step 2, the predictive power of the model significantly improved ($\chi^2(8) = 134.088$, $P < 0.001$) and the total variance explained by the model as a whole ranged between 23.1% (Cox and Snell R square) to 38.1% (Nagelkerke R squared). DSH was independently associated with current psychotic disorders (aOR = 6.227, $P = 0.001$) and borderline PD (aOR = 6.004, $P < 0.001$). Other important predictors were affective disorders (aOR = 2.856, $P = 0.006$) and misuse of multiple substances (aOR = 2.024, $P = 0.021$). The overall sensitivity of the model was 41.9% whilst its specificity was 96.1%. The positive predictive value was 69.6% and the negative predictive value was 88.5%.

The ROC analysis supported the utility of the model and its variables because it performed significantly better than chance in predicting DSH in inmates with an area under the curve (AUC) = 0.854 (standard error [SE] = 0.022, 95% CI = 0.811–0.897, $P < 0.001$) (Fig. 1).

4. Discussion

A history of DSH was not uncommon in the correctional setting, with a prevalence as high as 17.7%, consistent with previous studies in which lifetime DSH in adult offenders ranged between 15 [10] to 35% [11] in male prisoners.

In the current study, DSH was associated in the multivariable model to affective and psychotic but not anxiety disorders. Furthermore, it was independently associated with borderline but not antisocial PD. Finally, the misuse of multiple substances was significantly related to DSH but no association was found between DSH and both lifetime physical abuse and psychiatric problems in the parents.

4.1. Axis I disorders

The presence of a current psychotic disorder was the strongest independent predictor of DSH in this study. This finding has been conflicting and unclear across studies. Hence, the role of psychotic disorders as an independent predictor of either DSH or suicide attempts remain unclear [4]. In previous studies, psychotic disorders emerged as a strong independent predictor of DSH,

Table 3
Drugs/alcohol use and related features[a].

Lifetime variables (yes listed)	No DSH ($n=433$) n, %	DSH ($n=93$) n, %	χ^2	P
Alcohol over threshold	65 (15.0)	40 (43.0)	35.832	<0.001
Heroin	43 (9.9)	37 (39.8)	50.621	<0.001
Methadone	29 (6.7)	27 (29.0)	37.832	<0.001
Cocaine	147 (33.9)	62 (66.7)	32.87	<0.001
Amphetamines	7 (1.6)	12 (12.9)	28.011	<0.001
Cannabis	92 (21.2)	46 (49.5)	30.052	<0.001
Hallucinogens	13 (3.0)	8 (8.6)	6.263	0.02
Other (opiates, analgesics, psychodrugs)	3 (0.7)	10 (10.8)	32.142	<0.001
Misuse of multiple substances	95 (21.9)	52 (55.9)	42.212	<0.001

Lifetime variables (n listed)	Mean (SD) Median (range)	Mean (SD) Median (range)	t/U	P
Alcohol				
Age at first use	19 (7–48)	18 (9–38)	1049,500 (U)	0,175
Lifetime years	6 (0–31)	7.5 (0–28)	1201,500 (U)	0,175
Heroin				
Age at first use	19 (7–40)	17.5 (9–35)	644,500 (U)	0.201
Lifetime years	5.9 (5.99)	6.32 (6.22)	−0.322	0.748
Methadone				
Age at first use	25 (16–47)	25 (6–48)	292.500 (U)	0.297
Lifetime years	1 (0–22)	1 (0–27)	320 (U)	0.313
Cocaine				
Age at first use	20 (12–45)	18.5 (12–40)	3492 (U)	0.031
Lifetime years	3 (0–30)	7 (0–23)	3424 (U)	0.008
Amphetamines				
Age at first use	17.3 (2.43)	16.67 (3.17)	0.444	0.663
Lifetime years	4 (0–7)	2 (0–12)	39.5 (U)	0.83
Cannabis				
Age at first use	17 (11–39)	15 (9–31)	1.544 (U)	0.024
Lifetime years	5 (0–26)	9.50 (0–20)	1546.5 (U)	0.012
Hallucinogens				
Age at first use	17 (14–33)	16.50 (13–24)	40 (U)	0.74
Lifetime years	0 (0–10)	1 (0–10)	35 (U)	0.28

DSH: deliberate self-harm; n: number; SD: standard deviation.
[a] Assessed by means of the Addiction Severity Index-Expanded Version (ASI-X).

after recurrent depression, and was specifically associated with near-lethal DSH in male prisoners, with a notable 15-fold increased risk [44]. DSH related to psychotic disorders was often associated with high lethality [45] due to bizarre types of injuries [46], but also with a lower rate of suicide attempts due to the absence of a clear suicidal intent [41]. Notably, the presence of psychotic symptoms was an exclusion criteria in some studies performed in the prison setting [47,48].

Affective disorders were also independently associated to DSH in our multivariable model. DSH was previously found to be associated with self-reported depressive symptoms [40], but not to a specific diagnosis of major depression, possibly because depressive symptoms were evaluated with self-reported rating questionnaires but not with an established assessment of affective disorders through validated structured diagnostic interviews. Some previous studies did not find a clear association of DSH and major depressive disorder [49]. However, depression was frequently correlated with suicide attempts among inmates [9,44,47,50], and severity of depression was positively associated with the lethality and intent to die of suicide attempts [4,51].

In community psychiatric patients [52], anxiety disorders emerged as a predictor of DSH. Hence, anxiety symptoms were

Table 4
Hierarchical multivariable logistic regression model of socio-demographic and clinical variables associated with DSH in male prison inmates.

Variable	B	Wald	P	OR	95% CI
Step 1					
Age	−0.021	4.014	0.045	0.979	0.960–1.000
Step 2[a]					
Age	−0.013	0.838	0.36	0.988	0.961–1.014
Psychotic disorders	1.829	11.696	**0.001**	6.227	2.183–17.762
Affective disorders	1.049	7.538	**0.006**	2.856	1.350–6.039
Anxiety disorders	0.432	2.048	0.152	1.54	0.853–2.781
Borderline PD	1.792	34.629	$<$ **0.001**	6.004	3.305–10.907
Antisocial PD	−0.246	0.47	0.493	0.782	0.387–1.580
Misuse of multiple substances[b]	0.705	5.305	**0.021**	2.024	1.111–3.687
Lifetime physical abuse	0.319	0.552	0.458	1.375	0.593–3.188
Psychiatric FH[b]	0.751	2.773	0.096	2.118	0.876–5.126

CI: confidence interval; DSH: deliberate self-harm; FH: Family history; OR: odds ratio; PD: personality disorder. Step 1: Chi-square = 4.165, df = 1, $P=0.041$; Step 2: Chi-square = 134.088, df = 8, $P<0.001$. Statistical significance set at $P<0.05$.
[a] Adjusted for age.
[b] Assessed by means of the Addiction Severity Index-Expanded Version (ASI-X).

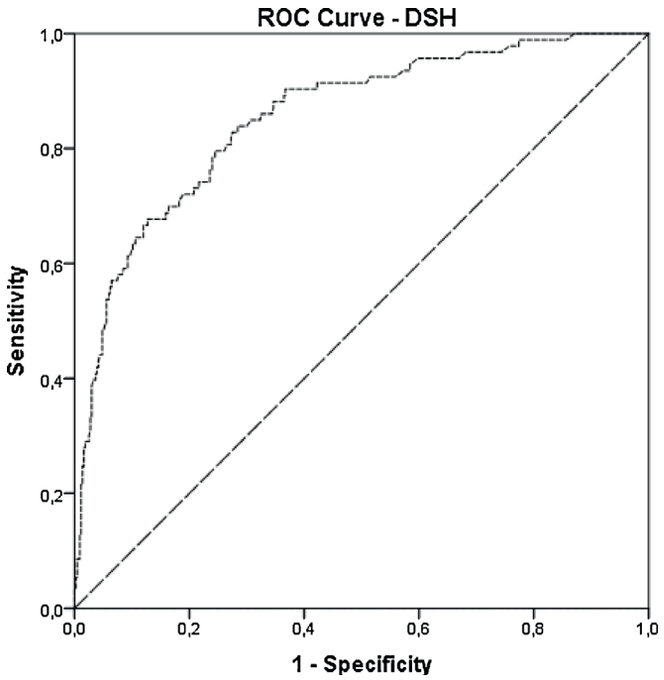

Fig. 1. Deliberate self-harm in male inmates: ROC curve. Receiver operating characteristic (ROC) curve and area under the curve (AUC) for detecting deliberate self-harm (DSH) in male inmates.

usually reported by psychiatric patients with a history of DSH [52,53]. Nevertheless, in correctional settings this association could be limited to younger prison inmates [40].

Considering that psychotic and affective disorders were associated with near-lethal suicide attempts in previous studies [45] and were strong predictors of DSH in our study, greater attention should be paid to an early detection of these Axis I disorders, in order to intercept with a successful treatment plan a possible suffering patient before DSH or suicidal behaviors.

4.2. Misuse of multiple substances

The misuse of multiple substances was strongly associated to DSH in the present study, and this finding is supported by an ever-increasing body of literature. Hence, substance use was postulated as a form of DSH [54]. DSH and substance use disorders were independently associated in male inmates [19,20,55] and also among adolescents serving a sentence in juvenile correctional facilities [40,56]. The association between DSH and misuse of multiple substances seemed more evident in prison populations than in psychiatric outpatient/inpatient samples, where those associations seemed inconsistent across studies [57–60].

The misuse of multiple substances could also be influenced by age. Both DSH and the misuse of multiple substances are strongly associated with younger age [61], and in the present study, an older age had a small protective effect on DSH. A possibility is that this triad may underpin a psychopathological role for impulsivity, which is more elevated in younger age groups, and it is also associated to substance use disorders and DSH in inmate prisoners [36].

4.3. Personality disorders

By definition, borderline PD is strongly related to DSH, as it constitutes a diagnostic criterion for the disorder [62]. So, not surprisingly, it was strongly related with DSH, as previously reported in prison settings [20,40] and also in general population [63] and psychiatric samples [64].

Available evidence on the independent association of antisocial PD and DSH is less consistent thus far. Despite antisocial PD was previously found to be a predictor in both male [40] and mixed [65] samples of offenders, antisocial PD was not independently associated with DSH in our study. A possible explanation is that, as the association between antisocial PD and DSH could generally be better explained in the context of manipulative behaviors rather than a form of environmental coping to handle unbearable emotions [66], it is possible that antisocial inmates in our sample could not properly recall DSH episodes during the assessment [6].

In addition, it should be underlined that in our sample of inmates the prevalence of antisocial PD seemed rather low for a prison population. This could be the consequence of the assessment with diagnostic interviews conducted by clinically trained interviewers and resulting in a significant reduction of the well-known risk of overestimation of PDs in prisoners [6].

4.4. Traumatic experiences and psychiatric family history

Several possible mechanisms, including familiar factors, could influence the associations of Axis II PD and DSH [67]. Traumatic experiences yield an important role in influencing DSH. Previous studies on prison inmates found an association between childhood physical, emotional and sexual abuse and DSH [19,68], but also with other lifetime traumatic experiences such as spousal abuse [69] and witnessing traumas [65]. In our study, lifetime physical abuse was not related to DSH, but it is possible that this effect could be mediated by full-blown psychopathology [11].

Similarly, the presence of parental psychiatric problems did not seem to increase the risk, even though significant differences were identified in the bivariate analyses, as occurred in other studies [11]. The association between parental psychiatric problems and DSH could also be indirectly driven by psychopathology rather than being straightly direct.

4.5. Strengths and limitations

The present study has some limitations that deserve discussion. First and foremost, in this cross-sectional study DSH was assessed through self-report, thus precluding causal inferences. Second, data were drawn from a unique penitentiary institute, and therefore data are not necessarily generalizable to other prisons across different cultures. Furthermore, results were obtained from a purely male sample. Third, the instruments herein used for the evaluation of DSH (e.g. the DSHI) and suicide attempts (specific ASI-X items), are respectively a self-report questionnaire and a semi-structured interview, so data is subject to potential self-report bias. Finally, the diagnostic assessment of antisocial PD in correctional settings is fraught with inherent limitations. Several aspects of this diagnosis overlap with factors associated with criminality [6]. The main strength of this work rests on the inclusion of a relatively large sample, and the use of validated measures, which allowed the proper controlling of potential confounders.

4.6. Preventive strategies and management of deliberate self-harm in inmates

Findings from the present study are not in favor of a linear continuum ranging from DSH to suicide attempts, as they do not show a strong correlation between DSH and suicide attempts. For this reason, it seems unlikely that the two behaviors depict a unique self-aggressive dimension. A consequence would be that these behaviors are associated to similar, yet different populations [6,70], and further studies are required in this direction. Nevertheless, it is of paramount importance to detect DSH and suicidal behaviors in inmates, as it was associated both in our study as in previous literature [71] to higher suicide attempts rate.

As DSH should be considered not as an illness but as a behavior, its management should be largely dependent on the underlying problems [52] such as PD and substances disorders, but according to our data also on psychotic and affective disorders.

The negative impact of DSH on the course of illness and quality of life of patients suffering from it brought to the development of clinical guidelines for the management of DSH in clinical practice [72–74]. Psychological or psychosocial therapies are effective in reducing repetition of DSH, but there is a lack of evidence in determining the effectiveness of specific types of treatment in correctional settings [72–74]. Evidence is also limited for specific pharmacological treatments, unless comorbid psychiatric disorders are present in inmates [72].

Ideally, psychopharmacological treatment and psychological interventions should be provided in correctional settings, and considered in an integrated case-management model.

Prevention and treatment of DSH in inmates can be a strategic therapeutic target. Our results contribute to this objective by suggesting modifiable, treatable clinical correlates to DSH. An improved early detection of DSH could enhance the level of care, allowing for a better and quicker identification and treatment of this behavior, particularly in the presence of psychiatric disorders, and reducing possible complications.

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Disclosure of interest

Dr Verdolini, Dr Attademo, Dr Garinella, Dr del Mar Bonnin, Dr Pauselli, Dr Piselli, Dr Tamantini, Prof Quartesan, Dr Carvalho and Prof Tortorella declare that they have no competing interest.

Dr Murru has served as a consultant, adviser, or speaker for Adamed, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, and Sanofi-Aventis but declares that he has no competing interest.

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Appendix A. Supplementary data

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Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features

Verdolini N, Perugi G, Samalin L, Murru A, Angst J, Azorin J-M, Bowden CL, Mosolov S, Young AH, Barbuti M, Guiso G, Popovic D, Vieta E, Pacchiarotti I. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features.

Objective: To evaluate aggressiveness during a major depressive episode (MDE) and its relationship with bipolar disorder (BD) in a post hoc analysis of the BRIDGE-II-MIX study.
Method: A total of 2811 individuals were enrolled in this multicenter cross-sectional study. MDE patients with (MDE-A, n = 399) and without aggressiveness (MDE-N, n = 2412) were compared through chi-square test or Student's t-test. A stepwise backward logistic regression model was performed.
Results: MDE-A group was more frequently associated with BD ($P < 0.001$), while aggressiveness was negatively correlated with unipolar depression ($P < 0.001$). At the logistic regression, aggressiveness was associated with the age at first depressive episode ($P < 0.001$); the severity of mania ($P = 0.03$); the diagnosis of BD ($P = 0.001$); comorbid borderline personality disorder (BPD) ($P < 0.001$) but not substance abuse ($P = 0.63$); no current psychiatric treatment ($P < 0.001$); psychotic symptoms ($P = 0.007$); the marked social/occupational impairment ($P = 0.002$). The variable most significantly associated with aggressiveness was the presence of DSM-5 mixed features ($P < 0.001$, OR = 3.815). After the exclusion of BPD, the variable of lifetime suicide attempts became significant ($P = 0.013$, OR = 1.405).
Conclusion: Aggressiveness seems to be significantly associated with bipolar spectrum disorders, independently from BPD and substance abuse. Aggressiveness should be considered as a diagnostic criterion for the mixed features specifier and a target of tailored treatment strategy.

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Key words: aggressiveness; bipolar disorder; DSM-5 mixed features specifier; major depressive episode

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Significant outcomes

- In this post hoc analysis of the BRIDGE-II-MIX study, the presence of aggressive behaviours was mainly related with sociodemographic and clinical characteristics associated with bipolarity.
- The most relevant clinical variable associated with aggressiveness during a major depressive episode was the presence of mixed features.
- The identification of aggressive behaviours could be the target of a tailored treatment strategy in this subgroup of bipolar disorder patients.

Limitations

- There is a possible bias due to the fact that the psychiatrists involved in the study were those with a particular interest in bipolar disorder.
- This is a post hoc analysis of the BRIDGE-II-Mix study, whose primary aim was not aggressiveness.
- The retrospective assessment of aggressiveness avoided to explain causality and could possibly lead to self-report bias.

Introduction

Aggressiveness is defined as an overt behaviour involving intent to inflict noxious stimulation or to behave destructively toward another organism or object (1). In psychiatry, it is a behavioural or motor response associated with intent to do harm and it may be self-directed (2).

Several psychiatric disorders, including mood disorders, have been associated with increased rates of aggressiveness and violent behaviours (3). Particularly, bipolar disorder (BD) patients presented increased risk for aggressive behaviours (4, 5). Indeed, aggressiveness has assumed particular importance as a core feature of manic and mixed states (6), independently from psychosis (7), and often emerging as a correlate of comorbid substance abuse and suicidality (8).

In comparison with subjects with no-BD, but suffering from other psychiatric disorders, and healthy controls, BD patients showed in previous studies increased self-reported verbal and physical aggressiveness, particularly during acute episodes and independently from BD subtypes, severity and polarity of the current episode, psychotic symptoms, and current pharmacological treatments (4, 9). In addition, manic patients showed the highest odds ratio for aggressive incidents among psychiatric in-patients (10).

As for trait characteristics of depressive episodes, it has been found that BD-I and BD-II depressed patients had more lifetime aggressiveness/hostility than unipolar depressed patients (11).

Previous studies have shown that comorbidity with other disorders, namely substance and alcohol abuse and borderline personality disorder (BPD), increased the risk of aggressiveness in BD patients (12, 13).

Several factor analyses described the clinical context of aggressiveness in mania. Aggressiveness was associated with paranoia and irritability, loading on the same factor ("irritable aggressiveness") (14). In another factor analysis, aggressiveness loaded on the same factor as irritability, uncooperativeness, impatience, and lack of insight, suggesting the existence of a distinct subtype of mania defined as "aggressive" (7). In a more recent study, the factor analysis revealed five factors, and one of them was termed 'Dysphoria', with positive significant loading for hostility, uncooperativeness, and suspiciousness, representing one of the two classical aspects of manic states (15). In this context, aggressiveness could represent a core feature of manic and mixed episodes of BD and might be a persistent trait in the sense of appearing in the same patients across repeated episodes.

Despite these previous findings, aggressiveness is not currently considered as a DSM diagnostic criterion of mania and consequently is not included in the DSM-5 mixed features in both bipolar and unipolar depressive episodes (16). In fact, only irritable mood represents a major defining characteristic of manic episodes since the first edition of DSM (17) and across the different revisions of the manual up to the last DSM-5. The DSM-5 fails to include the most common symptoms of mixity, including anxiety, agitation, and irritability as criteria for mixed features (18, 19).

Few studies between those mentioned above evaluated possible clinical correlates of aggressiveness during a major depressive episode (MDE)

across mood disorders. These studies were conducted on small samples of patients or derived only from one psychiatric center.

Aims of the study

The aim of the present post hoc analysis was to assess the relationship between bipolar disorder diagnosis or features and the presence of aggressive behaviours during a major depressive episode. We explored the possible clinical and treatment implications of this association.

Material and methods

Sample and assessment

This study is a post hoc analysis of the BRIDGE-II-Mix study. The general methodology of the BRIDGE-II-MIX study was described in detail in previous reports (20–23). The BRIDGE-II-Mix study was a multicenter, international, non-interventional, cross-sectional study. It was conducted between June 2009 and July 2010 in 239 centers in Bulgaria, Egypt, Morocco, the Netherlands, Portugal, Russia, Spain, and Turkey where hospital-based or community psychiatrists were expected to enroll consecutively 10–20 eligible adult patients aged 18 or older consulting for a MDE according to the Diagnostic and Statistical Manual of Mental Disorders-IV edition (DSM-IV) criteria during a 3-month recruitment period.

The selection of the different centers in each country would reflect the psychiatric healthcare provision and the patient care typical of the country's practice and regional diversity. Each center collected anonymous screening logs of the patients. Reasons for non-participation were precoded (refusal to participate, patient unable to complete the questionnaire, and other). Patients presenting with an acute non-psychiatric condition/emergency were excluded.

From the 239 psychiatrists involved in the study, 237 returned their site questionnaire. A total of 2811 patients agreed to participate and provided complete data, representing the full-analysis population. Demographic features were generally similar across countries.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment; hiip://www.wma.net) and the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation (hiip://iea web.org). Good Epidemiologic Practice (GEP)-IEA Guidelines were followed for proper conduct of epidemiologic research, as well as pertinent national, legal and regulatory requirements. Written informed consent was obtained from each patient. In each country, the protocol was approved by the local ethics committee.

Data collection

For each patient, the psychiatrists completed a case report, incorporating inclusion criteria, sociodemographic variables (age, gender, marital status), in-patient or out-patient status, history of psychiatric symptoms (mood symptoms, postpartum depression, suicide attempts), and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the DSM-IV-TR (24) diagnostic criteria for BD, known risk factors for BD (e.g., family history of BD and postpartum depression), previous response to antidepressants, psychiatric comorbidity, current treatment were recorded. The functional status was determined by the investigator using the Global Assessment of Functioning (GAF) (25), and the global illness severity was assessed through the Clinical Global Impression-Bipolar Version (CGI-BP) (26).

The evaluation packet was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. No rating scales requiring calibration with a standard were incorporated. Raters were instructed to follow their usual practice, as training might have altered these practices and been seen as a biasing factor.

The primary objective of the BRIDGE-II-Mix study was to establish the frequency of depressive mixed states by analyzing all the relevant symptoms of either pole. The frequency of depressive mixed states was post hoc defined as (i) the proportion of patients fulfilling the DSM-5 criteria for MDE with mixed features (DSM-5-MXS) (16) or (ii) research-based diagnostic criteria for depressive mixed states (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus three of the following 14 hypomanic symptoms for at least a week: irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, aggression (verbal or physical), racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behaviour, grandiosity, elation, and hypersexuality. The proportion of patients fulfilling the criteria for BD according to the DSM-IV-TR and bipolarity specifier proposed by Angst et al. (27, 28) was also identified.

The objective of the present analysis of the BRIDGE-II-Mix study data was to assess the specific features of patients with (MDE-A) or without (MDE-N) aggressiveness.

An operational clinical definition of aggressiveness has been used, defined by the presence of at least one of the following behaviours during the index MDE: (1) Physical Aggressiveness (PHY): (a) ever threatened or (b) hit people, or (c) got into fights more than most people or (d) become so mad to have broken things; (2) Verbal Aggressiveness (VER): (a) to argue a lot with other people, or (b) to can't help getting into arguments when people disagree, or (c) to get very angry for no good reason with troubles in self-controlling.

Statistical analysis

The chi-square test was used for comparison between groups for categorical variables and Student's *t*-test for continuous variables. The bivariate analysis involved many tests of statistical significance, raising the problem of type I errors. For this reason, we corrected for multiple comparisons and utilized a Bonferroni-corrected threshold for statistical significance, including in the logistic regression only those clinically sound variables under this threshold of 0.004. A stepwise backward logistic regression model was then used to identify the association between aggressiveness and 10 significant variables (BD diagnosis, DSM-5-MXS, severity of mania, comorbid BPD, comorbid substance abuse, lifetime suicide attempts, psychotic features, marked impairment in functioning, no psychiatric treatment, age at first depressive episode). The presence of mixed features in this post hoc analysis was defined according to the DSM-5 mixed specifier (DSM-5-MXS). The stepwise modeling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable from the model and recomputing the revised model, until all remaining variables were at $P < 0.1$. Odds ratios with 95% confidence intervals were used for observed associations. All tolerance values in the regression analyses were >0.2, and all variance inflation factors were <2, thereby indicating that multicollinearity was not a source of bias in the regression models (29). Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All *P* values were two-tailed and statistical significance was set at $P < 0.05$.

Results

Clinical features: MDE-A patients vs. MDE-N patients

From a total sample of 2811 patients, 399 (14.2%) presented verbal or physical aggressiveness (MDE-A group) during the index MDE. The sociodemographic and clinical features are reported in Table 1.

Patients in the MDE-A group were diagnosed more frequently with BD (<0.001), in particular BD-I (<0.001) but not BD-II (0.997), than those in the MDE-N group (see Table 1). The presence of aggressiveness was negatively associated with the diagnosis of unipolar depression ($P < 0.001$). MDE-A group more frequently presented DSM-5-MXS than MDE-N group ($P < 0.001$).

Patients in the MDE-A group showed higher rates of comorbid disorders compared to those in the MDE-N group such as BPD ($P < 0.001$), anxiety disorder ($P < 0.001$), eating disorders ($P = 0.003$), and attention–deficit hyperactivity disorder (ADHD) ($P = 0.011$).

Patients in the MDE-A reported more frequently a current substance abuse ($P = 0.003$) but not a current alcohol abuse ($P = 0.086$) than those in the MDE-N group (see Table 1). In both cases, the alcohol or substance abuse was not in the context of dependence of alcohol (67.2% vs. 61%, $P = 0.022$) or substance (66.9% vs. 61.4%, $P = 0.04$) dependence. Patients in the MDE-A group more frequently reported recurrent alcohol- (2.8% vs. 0.8%, $P = 0.002$) and substance-related (2% vs. 0.2%, $P < 0.001$) legal problems compared to patients in the MDE-N group.

Functioning and severity of patients in the MDE-A group

The severity of depression ($P = 0.044$), mania ($P < 0.001$), and overall BD ($P < 0.001$) were significantly higher in the MDE-A group compared with the MDE-N group. The GAF score was significantly lower in the MDE-A group than in the MDE-N group ($P = 0.015$) (see Table 1).

Patients in the MDE-A group presented with more marked impairment in social/occupational functioning (49.6% vs. 24%, $P < 0.001$) than patients in the MDE-N group.

The presence of psychotic symptoms was more represented in the MDE-A group than in the MDE-N group (15.5% vs. 7%, $P < 0.001$).

Lifetime psychiatric history characteristics of patients in the MDE-A group

Age at first psychiatric symptoms ($P < 0.001$) and age at first depressive episode ($P < 0.001$) were significantly lower in patients in the MDE-A group (see Table 1).

The total number of mood episodes was significantly higher in patients in the MDE-A group ($P = 0.006$).

Table 1. Clinical characteristics: MDE-AGG patients vs. MDE-noAGG patients

Lifetime and current variables (yes listed)	MDE-AGG (n = 399)	MDE-noAGG (n = 2412)	χ^2	P
Sociodemographic characteristics	*n*, %	*n*, %		
Gender, female	276 (14.3)	123 (14.0)	0.013	0.909
Marital status, single	102 (15.2)	297 (13.9)	0.631	0.427
Marital status, married	224 (15.4)	175 (12.9)	3.538	0.60
Marital status, divorced	57 (13.1)	342 (14.4)	0.419	0.518
Marital status, widowed	16 (6.4)	383 (15.0)	12.902	<0.001
Diagnostic features				
DSM-IV-TR BD	96 (24.1)	368 (15.3)	18.617	<0.001
DSM-IV-TR BD-I	71 (17.8)	217 (9.0)	27.868	<0.001
DSM-IV-TR BD-II	25 (6.3)	151 (6.3)	0.000	0.997
DSM-IV-TR MDD	303 (75.9)	2044 (84.7)	18.617	<0.001
DSM-5-MXS	106 (26.6)	106 (4.4)	238.192	<0.001
Current comorbidity				
Borderline PD	81 (20.3)	106 (4.4)	136.936	<0.001
Anxiety disorder	155 (35.8)	648 (26.9)	23.502	<0.001
Panic disorder	56 (14.1)	233 (9.7)	6.686	0.01
Obsessive–compulsive disorder	34 (8.5)	108 (4.5)	10.890	0.001
Generalized anxiety disorder	101 (25.4)	406 (16.9)	16.088	<0.001
Social phobia	30 (7.5)	186 (7.7)	0.001	0.980
Eating disorders	42 (10.7)	155 (6.5)	8.563	0.003
Binge eating syndrome	19 (4.8)	54 (2.3)	7.559	0.006
Night eating syndrome	24 (6.1)	52 (2.2)	17.757	<0.001
Anorexia nervosa	34 (8.6)	105 (4.4)	11.620	0.001
Bulimia nervosa	7 (1.8)	45 (1.9)	0.000	1.000
ADHD	16 (4.1)	45 (1.9)	6.451	0.011
Alcohol abuse	34 (8.5)	147 (6.1)	2.956	0.086
Substance use	22 (5.5)	63 (2.6)	8.867	0.003
Current psychiatric treatment				
No psychiatric treatment	60 (15)	242 (10)	8.427	0.004
Benzodiazepines	159 (39.8)	1128 (46.8)	6.323	0.012
Antidepressants	293 (73.4)	2012 (83.4)	22.443	<0.001
Mood stabilizers	154 (38.6)	644 (26.7)	23.253	<0.001
Antipsychotics	155 (38.8)	809 (33.5)	4.046	0.044
Electroconvulsive treatment	16 (4)	30 (1.2)	14.603	<0.001
Lifetime and current variables	**Mean (SD)**	**Mean (SD)**	***t***	***P***
Age (years)	39.79 (12.635)	44.73 (13.809)	7.130	<0.001
Age at first psychiatric symptoms (years)	27.65 (9.888)	33.35 (13.100)	10.122	<0.001
Age at first depressive episode (years)	29.91 (9.960)	36.13 (12.734)	11.033	<0.001
Severity of the condition				
Total number of previous mood episodes	5.79 (8.019)	4.63 (5.592)	−2.786	0.006
Total number of hospitalizations	1.03 (2.912)	1.77 (3.847)	4.474	<0.001
Total number of lifetime suicide attempts	0.73 (2.872)	0.39 (1.059)	−2.327	0.020
Severity of depression (CGI-BP)	4.59 (1.168)	4.47 (0.941)	−2.024	0.044
Severity of mania (CGI-BP)	1.79 (1.168)	1.25 (0.723)	−8.713	<0.001
Severity of BD (CGI-BP)	2.94 (1.806)	2.24 (1.651)	−6.947	<0.001
GAF	49.30 (14.289)	51.18 (12.578)	2.431	0.015

ADHD, attention–deficit hyperactivity disorder; BD, bipolar disorder; CGI-BP, Clinical Global Impression-Bipolar Version; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders-forth edition, text revised; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-forth edition; DSM-5-MXS, major depressive episode with DSM-5 mixed features; GAF, Global Assessment of Functioning; MDD, major depressive disorder; MDE-AGG, patients with a major depressive episode with physical or verbal aggressiveness; MDE-noAGG, patients with a major depressive episode without physical or verbal aggressiveness *n*, number; PD, personality disorder; SD, standard deviation.

The presence of previous suicide attempts (31.6% vs. 20.8%, $P < 0.001$) was more frequently reported in the MDE-A group.

Patients in the MDE-A group more frequently had a family member requiring treatment (32.1% vs. 18.8%, $P < 0.001$) or a first degree relative with BD (22.1% vs. 14.2%, $P < 0.001$) than those in the MDE-N group.

Current psychiatric treatment

Patients in the MDE-A group were more frequently without any psychiatric treatment than those in the MDE-N group ($P = 0.004$) (see Table 1).

MDE-A patients were more frequently under treatment with antipsychotics ($P = 0.044$), mood stabilizers ($P < 0.001$), or electroconvulsive

treatment (ECT) ($P < 0.001$) than patients in the MDE-N group.

Patients in the MDE-A group were less frequently prescribed with antidepressants (ADs) than those in the MDE-N group (<0.001); however, in those taking ADs, an AD-induced hypomania/mania during the current MDE was more frequently observed in the MDE-A group than in the MDE-N group (23.1% vs. 15.9%, $P < 0.001$).

Clinical variables associated with aggressiveness

After performing a stepwise backward multivariate modeling procedure ($\chi^2(8) = 300.695$, $P < 0.001$), the model explained between 10.6% (COX and Snell R Square) and 18.9% (Nagelkerke R Square) of the variance and statistical significance persisted for age at first depressive episode ($P < 0.001$), negatively correlated with aggressiveness; severity of mania ($P = 0.031$); diagnosis of BD ($P = 0.001$); comorbidity with BPD ($P < 0.001$) but not with substance abuse ($P = 0.633$); absence of current psychiatric treatments ($P < 0.001$); presence of psychotic symptoms ($P = 0.007$); marked impairment in social/occupational functioning ($P = 0.002$) that were positively correlated with aggressiveness. DSM.5-MXS was the variable most significantly associated with aggressiveness ($P < 0.001$, OR = 3.8) (see Fig. 1).

In order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviours, we performed a second stepwise backward multivariate modeling procedure ($\chi^2(8) = 275.677$, $P < 0.001$), excluding the variable of BPD comorbidity. The model explained between 9.7% (COX and Snell R Square) and 17.4% (Nagelkerke R Square) of the variance. DSM-5-MXS still remained the highest significant association with aggressiveness ($P < 0.001$, OR = 3.9). Also, the association with BD diagnosis still remained significant ($P = 0.002$, OR = 1.6), while the presence of lifetime suicide attempts became significant at the logistic regression ($P = 0.013$, OR = 1.4) (see Fig. 2).

Discussion

In this multinational sample of 2811 patients with MDE, a prevalence of aggressive behaviours of 14.2% was found. The detected prevalence is slightly higher than that found in previous large epidemiological studies (30).

Almost one in four BD patients in our study presented physical or verbal aggressiveness during a MDE. This is in line with the results of previous findings supporting the quite frequent association between aggressiveness and BD (11, 30–32).

In general, the presence of aggressiveness during a MDE was associated with a higher severity of manic and depressive episodes. This emerged from both psychometric and clinical assessment and included higher rates of psychiatric comorbidities, more affective episodes, higher frequencies of lack

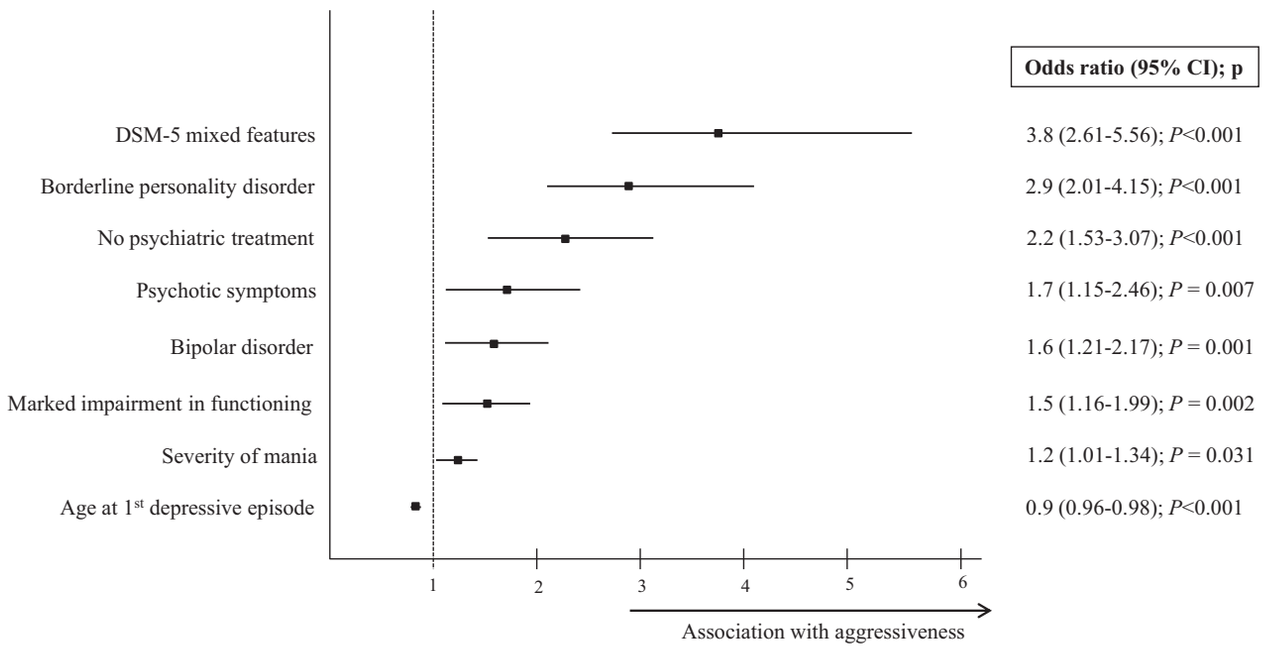

Fig. 1. Logistic regression: significant clinical variables associated with aggressiveness.

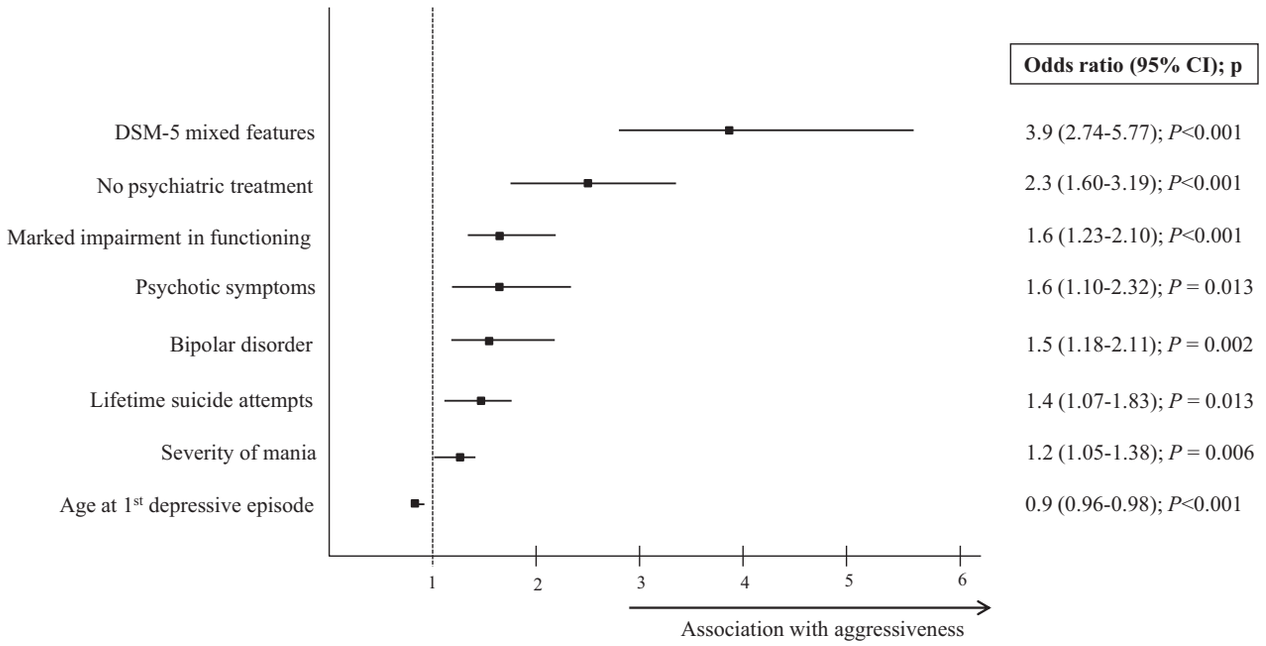

Fig. 2. Logistic regression: significant clinical variables associated with aggressiveness (borderline personality disorder excluded).

of psychiatric treatment, greater impairment in global social/occupational functioning, more frequent psychotic symptoms, and higher rates of previous suicide attempts. Similar findings were reported in previous studies (13, 23, 33), showing that the presence of aggressive behaviours had a significant impact on the clinical outcome of the BD illness, with major implications in terms of management and treatment strategies.

Several findings from the present study seem to support that the presence of aggressive behaviours in the MDE-A group was associated with bipolarity. First, significantly higher frequencies of BD diagnosis were found in depressed patients with aggressiveness, while a diagnosis of unipolar depression was negatively correlated with aggressive behaviours. This is consistent with previous reports of a higher association between aggressiveness and BD depression compared to unipolar depression (11). The MDE-A group showed higher rates of family history for BD as well as younger age at the first depressive episode, which represent the most relevant clinical indicators of unrecognized bipolarity in depressed patients (27, 34–36).

Interestingly, the presence of mixed features during the current MDE was significantly more common in MDE-A patients compared with depressed patients without aggressive behaviours. This is in line with current views on the spectrum of mixed states (37). Hence, several reports showed that the presence of mixed features during a MDE might be considered as a clinical indicator of bipolarity (38–40). The higher rates of mixed features in our depressed patients with aggressive behaviours seem to further support the inclusion of aggressiveness in the BD rubric and within the pool of mixed features during a MDE. This is in accord with the results of a previous study which found that the dimension "Feel angry", as assessed by the Multiple Visual Analog Scales of Bipolarity (MVAS-BP), was the second most frequent (49.5%) bipolar dimension among the mixed depressive patients (41).

As for psychiatric treatment, in the present sample, MDE-A patients had lower rates of AD use compared with patients without aggressiveness. Nevertheless, the MDE-A patients treated with ADs showed significantly higher rates of AD-induced mania/hypomania compared with patients without aggressiveness, which represents another strong indicator of bipolarity (20, 21, 27, 34, 35, 37, 42–45).

As expected, when considering comorbid psychiatric diagnoses, we found that MDE-A patients had higher rates of psychiatric comorbidity, indicating a more severe and difficult-to-treat condition. In particular, the comorbidity with BPD and substance abuse were significantly more reported in depressed patients with aggressiveness. Previous studies found that the presence of comorbid BPD could have an independent predictive value in determining trait aggressiveness in patients with BD (13). It has been supposed that the link between BD, BPD, substance abuse, and

aggressiveness involves the role of impulsivity (13, 46), indicating that aggressive behaviours could be more associated with impulsive-related comorbidities than with bipolar illness itself. Nonetheless, in order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviours, we excluded the variable of BPD comorbidity from the second stepwise multivariate modeling procedure (the variable substance abuse yet resulted to not be significantly correlated with aggressiveness in the first logistic regression). Interestingly, the significance persisted for all the variables considered in the first modeling, with DSM-5 mixed features becoming the most significant variable associated with aggressiveness.

Surprisingly, the presence of lifetime suicide attempts became significant at the logistic regression, when BPD comorbidity was excluded in the second model (see Fig. 2). These results support our hypothesis that aggressiveness could be associated with bipolarity *per se*, independently from comorbid disorders such as BPD and substance abuse.

The role of aggressiveness in suicidal behaviours has been investigated in several studies. Oquendo et al. (47) found higher lifetime aggressiveness in BD patients with a history of suicide attempts compared with BD non-attempters. The same authors (48) reported that aggressive traits besides other clinical factors contribute to predict future suicidal behaviours both in depressed BD and MDD individuals. Moreover, impulsivity was found to be a reliable predictor of suicide risk in BD and MDD patients not as a single trait but only in association with aggressiveness (33, 49, 50). In this context, aggressiveness could be seen as a part of the construct associated with suicidal behaviours in depressed BD and MDD patients. Furthermore, in our study, the presence of DSM-5 mixed features was the variable most significantly associated with aggressiveness. Previous studies found that the presence of DSM-5 mixed features at the index episode was probably the most important risk factor for suicidality (37, 51) and partly contributed to the increased risk of suicide observed in BD-II compared to unipolar depression (52).

Regarding treatment considerations, recent guidelines recommend the need for the early detection of aggressive behaviours in mood disorders (53–55). In our sample, the MDE-A group presented higher rates of psychotic symptoms and more severe mania, together with higher rates of no current pharmacological treatment. Furthermore, the MDE-A group showed higher rates of AD-induced hypomania/mania. Several reports suggest that a prompt therapeutic strategy should be considered to prevent aggressiveness in those patients with higher risk factors, such as severe manic, psychotic symptoms, and lifetime history of self-aggressive behaviours (56, 57). Taken together, these results claim for the need of an "antiaggressive" treatment strategy in this subgroup of BD patients. Moreover, AD monotherapy should be avoided and a combination treatment with mood stabilizers and/or antipsychotics should be considered (58).

The main strengths of the BRIDGE-II-Mix study include the large sample size and the wide range of care settings, both hospital and community, from eight countries across three continents. Furthermore, narrow exclusion criteria increase the generalizability of the findings. The first limitation is the widely varying rates of hospitalized patients across countries, ranging from 1.0% to 57.8%, which reflect economically driven policies on the use of hospitalization-based treatment. A second limitation is that the participating centers were not randomly selected, which may have led to a bias through the inclusion of psychiatrists with a particular interest in bipolar spectrum disorders. This may be seen, however, as a positive point, in the sense that some expertise is needed to detect past hypomania in MDE patients. Indeed, in the present study, aggressiveness in the MDE-A group was assessed retrospectively with high subjectivity of the original rating performed by trained psychiatrists (59). This means that the definition of aggressiveness relies just on retrospectively coded criteria and selected variables already collected in the dataset, rather than *ad hoc* variables fetched using validated ratings. This may introduce a measurement bias, especially considering that the operational definition of aggressiveness adopted is a clinical one.

Moreover, there is a need for additional correlation analyses regarding the relationship between aggressiveness and mixed features, controlling for potential confounders to be included in future longitudinal prospective studies using external validators.

In conclusion, aggressiveness might not only be state-related but also a trait component of bipolarity and a diagnostic indicator of mixicity in patients with MDE. Moreover, the association of aggressiveness and the presence of mixed features in depressed patients could represent an indicator of increased risk for suicidal behaviours. Taken together, these results might have important implications in terms of the reconsideration of aggressiveness for diagnostic criteria for the mixed

features specifier. Finally, the detection of aggressiveness in MDEs could help in establishing a therapeutic strategy aimed at reducing aggressiveness and preventing suicidal tendencies in the perspective of a personalized pharmacological treatment for this subtype of patients.

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Sultans of swing: A reappraisal of the intertwined association between affective lability and mood reactivity in a post-hoc analysis of the BRIDGE-II-MIX study.

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Abstract

Objective: This post-hoc analysis of the BRIDGE-II-MIX study is aimed at evaluating affective lability (AL) as a possible clinical feature of mixed depression and assessing the relationship with atypical depressive features, particularly mood reactivity (MR).

Methods: In the BRIDGE-II-MIX multicenter cross-sectional study, 2,811 individuals suffering from a major depressive episode (MDE) (*DSM-IV-TR* criteria), in the context of bipolar disorder (BD) or major depressive disorder (MDD), were enrolled between June 2009 and July 2010. MDE patients with (MDE-AL, n = 694) and without AL (MDE-noAL, n = 1,883) and with (MDE-MR, n = 1,035) or without MR (MDE-noMR, n = 1,542) were compared through Chi-square test or Student's t-test. Stepwise backward logistic regression models, respectively testing AL and MR as the dependent variable, were performed to differentiate the two clinical constructs.

Results: AL was positively associated with BDI ($P < .001$) and BDII ($P < .001$), with *DSM-5* mixed (DSM-5-MXD) ($P < .001$) and atypical features (DSM-5-AD) ($P < .001$) and negatively associated with MDD ($P < .001$). In the logistic regression models, MR was the variable most significantly associated with AL, and vice versa. AL was positively associated to severity of mania, DSM-5-MXS and negatively correlated with severity of depression whilst MR was better predicted by atypical symptoms such as hyperphagia, hypersomnia and leaden paralysis and correlated both with comorbid anxiety disorders and DSM-5-MXS.

Conclusion: Mixed and atypical depression may lie on the same continuum. MR and AL could represent the underlying matrix, bridging the gap between mixed and atypical depression.

Key words: affective lability, mood reactivity, mixed features, atypical depression, major depressive episode, bipolar spectrum

Introduction

Affective lability (AL) is defined as the predisposition to rapidly reversible and marked shifts in affective states that are extremely sensitive to environmental events with intense behavioral responses[1]. According to the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5), these abrupt switches are characterized by a few hours duration and can represent a response to both pleasant and unpleasant events[2,3].

AL has been used as a synonym of mood lability and emotional lability in consideration of the fluctuation between different mood states, such as anger, depression, anxiety, elation/hypomania, disgruntled mood, with difficulties in controlling the consequences of these oscillations[4–7]. Classically, AL was considered as a trait feature of borderline personality (BPD)[3] and attention deficit hyperactivity disorder (ADHD)[8,9]. Nonetheless, AL has been considered as a state symptom in mood disorders (mainly bipolar disorder II-BDII) and in a percentage of patients with anxiety disorders and post-traumatic stress disorder (PTSD)[6,7,10–12].

The psychopathological construct of AL has been interpreted as a form of ultra-rapid cycling[13]. In BD, it was related to clinical features such as age at onset, axis I comorbidities and number of previous episodes[11,14]. It was also linked to impulse dyscontrol and suicidal behavior in BPD patients[4]. AL assumed a central role as a trait-like clinical feature in mixed episodes, especially in those with depressive polarity[15–17]. Moreover, it represented one of the three most frequent state features in mixed depression, together with agitation and irritability[18].

Despite this, AL was excluded from the DSM-5 “with mixed features” specifier, possibly leaving many cases of mixed depression undiagnosed and subsequently not adequately treated[19,20]. On the contrary, in the DSM-5 mood reactivity (MR) represents a

core criterion for depressive "atypical features" and is defined as a change of mood, but restrictively in response to positive stimuli[3]. Traditionally, atypical depression was associated with an affective temperamental dysregulation[21,22] as part of a common diathesis between depression, BDII and BPD[23,24]. The evidence that patients with depressive mixed states often display atypical features received wide support[19,25–28].

Many experimental studies evaluated AL by means of a number of different assessment tools, with modest clinical agreement[7,29]. AL has been investigated in samples of BD and major depressive disorder (MDD) patients with major flaws in the study methodology, i.e. not providing a clinical evaluation of comorbid BPD[30], avoiding a differentiation between the clinical components of AL related to BPD and those associated with the specific affective disorders[14]. Finally, it has been poorly studied as a state clinical feature in large samples of patients in course of a major depressive episode (MDE). Indeed, several studies focused on the evaluation of this clinical symptom during euthymic periods[5,10,11,14,30,31] with a poor understanding of the framing of AL as a trait or a symptom[8].

As a consequence, this post-hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study was aimed at investigating the psychopathological role of AL in a sample of unipolar and bipolar depressed patients (excluding comorbidity with BPD) as a possible mixed symptom and a clinical correlate of atypical features in depression.

Method

Sample and assessment

The general methodology of the BRIDGE-II-MIX study has been described in previous reports[19,32–36]. Briefly, the BRIDGE-II-MIX study was a multicenter, international, cross-sectional, diagnostic investigation conducted between June 2009 and July 2010 in 239 centers from three different continents. Hospital-based or community psychiatrists consecutively enrolled 10-20 eligible adult patients consulting for a major depressive episode (MDE), diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-IV edition, text revision (DSM-IV-TR)[37] criteria.

Reasons for nonparticipation were pre-coded (refusal to participate, patient unable to complete the questionnaire, other).

Reasons for exclusion were represented by acute non-psychiatric conditions or emergency events.

The full analysis population included 2,811 patients who gave their written informed consent to attend the investigation and provided complete data.

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment; hiip://www.wma.net), the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation (hiip://ieaweb.org) Good Epidemiologic Practice (GEP)–IEA guidelines were followed for proper conduct of epidemiologic research, as well as pertinent national, legal and regulatory requirements. The protocol was authorized in each country by national and local ethics committees.

Data collection

Information about socio-demographic variables, inpatient or outpatient status, history of psychiatric symptoms and previous psychiatric hospitalizations were collected. Features of the MDE, bipolar symptoms, known risk factors for BD, previous response to antidepressants, psychiatric comorbidity, and current treatment were also gathered. Functional status was determined with the Global Assessment of Functioning (GAF)[38] and illness severity was assessed using the Clinical Global Impression-Bipolar Version (CGI-BP)[39].

The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states. After the publication of DSM-5, the frequency of depressive mixed states was retrospectively defined as (i) the proportion of patients fulfilling the DSM-5 criteria for MDE with mixed features (DSM-5-MXS)[3], or (ii) research-based diagnostic criteria for depressive mixed states (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus 3 out of the following 14 hypomanic symptoms (irritable mood, emotional/mood lability, distractibility, psychomotor agitation, impulsivity, verbal or physical aggression, racing thoughts, more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation, hyper-sexuality) for at least one week.

The aim of the present post-hoc analysis of the BRIDGE-II-MIX study was to investigate the psychopathological construct of AL in unipolar and bipolar depression and its clinical correlates, assessing specific features of depressed patients with (MDE-AL) or without (MDE-noAL) AL. An operational clinical definition has been adopted, delineating AL as a state feature represented by marked and rapid shifts between different affective states, in response to positive or negative environmental stimuli and with subsequent influences on behavior. In adapting a definition of AL to the BRIDGE-II-MIX study, the steering

committee of the BRIDGE-II-MIX study decided to combine different previous classifications of AL[1,2,4,40], but chose to consider it not as a trait symptom. In fact, AL was considered as a state feature of mixed depression, as highlighted in the Koukopoulos´ diagnostic criteria for mixed depression[18,41].

The clinical implications of the association between AL and atypical features in depression, particularly MR, were also investigated. AL has been distinguished from MR, defined according to DSM-5 as a variation of mood in depressed patients following only positive stimuli[3].

The presence of mixed features was defined according to the DSM-5 "with mixed features" specifier (DSM-5-MXS).

Patients diagnosed with BPD (n = 187) have been excluded from the analysis in order not to bias the possible correlation between AL and mixed depression due to the trait-like characteristic of AL in BPD[3,4,42]. For the same reason[7], patients presenting ADHD comorbidity (n = 61) have been excluded. The final total sample of the post-hoc analysis was composed of 2,577 patients.

Statistical analysis

Groups were compared using the Chi-square or the Student's t-test according to the types of variables. The bivariate analysis involved many tests of statistical significance, raising the problem of type I error. A Bonferroni-corrected threshold for statistical significance ($P \leq .003$) was then used.

A stepwise backward logistic regression model was used to identify the association between AL and 14 significant variables (DSM-5-MXS, BDII diagnosis, MDD diagnosis, depression "with atypical features" according to DSM-5 (DSM-5-AD),

severity of mania, severity of depression, age at first depressive episode, number of previous affective episodes, comorbid anxiety disorder, hyperphagia, hypersomnia, MR, treatment with mood stabilizers, treatment with antipsychotics). BDI was excluded from the model because violating the assumption of multicollinearity. Subsequently, a stepwise logistic regression model was performed in order to differentiate AL from MR, testing the correlations between MR and the same clinical variables included in the previous model, plus leaden paralysis. DSM-5-AD diagnosis was excluded from the model because violating the assumption of multicollinearity. Finally, two further stepwise logistic regression models were performed in order to assess the associations between AL or MR and the 14 RBDC-MXS symptoms.

The stepwise modeling procedure started with the full model and consisted in eliminating, for each step, the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $P < .1$. Odds ratios (OR) with 95% confidence intervals were assessed for observed associations. All tolerance values in the regression analyses were > 0.2 and all variance inflation factors were < 2, expressing that multicollinearity was not a source of bias in the regression models. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All *P* values were two-tailed and statistical significance was set at $P < .05$.

Results

Diagnostic and clinical correlates of affective lability

Six hundred and ninety-four out of 2,577 patients (26.9%) presented AL (MDE-AL group).

The presence of AL was positively associated with BDI (odds ratio [OR] = 2.1; 95% Confidence Intervals [CI], 1.62-2.79) and BDII (OR = 2.2; 95% CI, 1.58-3.04), and negatively associated with the diagnosis of MDD (OR = 0.4; 95% CI, 0.34-0.54). The high relative percentage of MDD diagnosis and the low relative percentages of BDI and BDII diagnoses in the MDE-AL group depended on the diagnostic distribution of MDD, BDI and BD II in the total sample size (83.5%, 10.2% and 6.3%, respectively). In addition, the MDE-AL group was more frequently diagnosed with DSM-5-MXD (OR = 10.5; 95% CI, 7.10-15.49) and DSM-5-AD (OR = 2.7; 95% CI, 1.92-3.64) (see **Table 1;** bivariate analyses of MR are shown in **Table 2**).

Patients in the MDE-AL group showed higher prevalence of atypical features such as hypersomnia (n = 143, 20.6% versus n = 275, 14.6%, $\chi^2 = 13.000$, OR = 1.5; 95% CI, 1.21-1.90), hyperphagia (n = 126, 18.2% versus n = 234, 12.4%, $\chi^2 = 13.375$, OR = 1.6; 95% CI, 1.23-1.98) and MR (n = 455, 65.6% versus n = 580, 30.8%, $\chi^2 = 253.509$, OR = 4.3; 95% CI, 3.56-5.14), but not leaden paralysis (n = 193, 27.8% versus n = 457, 24.3%, OR = 1.2; 95% CI, 0.99-1.46).

A total of 164 (6.4%) patients were diagnosed with DSM-5-AD. Of these, 103 (62.8%) patients also presented DSM-5-MXS.

Lifetime psychiatric history and severity of patients in the MDE-AL group

The MDE-AL group differed significantly from the MDE-noAL group regarding age at onset of first depressive episode (mean (M)±standard deviation (SD) = 34.37 ±12.368 versus M±SD = 36.34±12.634, t = 3.529, $P < .001$) and total number of previous

mood episodes (M±SD = 5.17±5.389 versus M±SD = 4.36±5.645, t = -3.303, $P = .001$).

Patients in the MDE-AL group presented higher severity of mania (M±SD = 1.69±1.028 versus M±SD = 1.13±0.541, t = -13.052, $P < .001$) evaluated with the CGI-BP and a lower severity of depression (M±SD = 4.40±0.951 versus M±SD = 4.52±0.947, t = 2.868, $P = .004$) compared to those in the MDE-noAL group.

Clinical variables associated with affective lability and mood reactivity

After performing a stepwise backward multiple logistic regression modeling procedure ($\chi^2(5) = 546.632$, $P < .001$) using AL as the dependent variable, the model explained between 20.6% (COX and Snell R Square) and 30.3% (Nagelkerke R Square) of the variance. Statistical significance persisted for the presence of mixed features according to DSM-5 (OR = 3.0; 95% CI, 2.43-3.77); severity of mania (OR = 2.0; 95% CI, 1.71-2.30); MR (OR = 3.7; 95% CI, 2.98-4.57) which were positively associated with AL; severity of depression (OR = 0.9; 95% CI, 0.77-0.97), that showed a negative correlation with AL. The variables most significantly associated with AL were MR and DSM-5-MXS (see **Figure 1 and Table 3**).

To test the differences between AL and MR, a second stepwise backward logistic regression was performed, using MR as the dependent variable. The model ($\chi^2(7) = 317.795$, $P < .001$) explained between 12.6% (COX and Snell R Square) and 17% (Nagelkerke R Square) of the variance. Variables significantly associated with MR were the presence of mixed features according to DSM-5 (OR = 1.5; 95% CI, 1.21-1.76); AL (OR = 3.7; 95% CI, 3.01-4.57); leaden paralysis (OR = 1.6; 95% CI, 1.29-1.92); hyperphagia (OR = 1.4; 95% CI, 1.05-1.77); hypersomnia (OR = 1.3; 95% CI, 1.05-1.76); comorbidity with anxiety disorders (OR = 1.5; 95% CI, 1.2-1.8). The strongest correlation with MR was presented by AL. All the variables were positively correlated (see **Figure 1**

and Table 3).

The RBDC-MXS symptoms significantly associated with AL or MR are shown in the Supplementary Table 1 (see online Supplementary material). Irritable mood, racing thoughts, more talkative/pressure to keep talking, distractibility and impulsivity were directly significantly associated with both AL and MR. Elation was directly significantly associated with AL, verbal or physical aggression was inversely significantly associated with AL whilst risky behavior was inversely associated with MR.

Discussion

In this BRIDGE-II-MIX post-hoc analysis, AL was a common clinical state feature, assessed in one every four patients presenting with a MDE, similar to previous studies[43]. AL was a clinical feature associated with BDI and BDII, as already reported in clinical[5,11] and neuropathology studies[44]. Despite being a common symptom in MDD, in the present sample AL was inversely correlated with unipolar depression when compared with BD. This does not mean that AL represents a bipolar symptom, but that this symptom could act as a possible bridge gap between unipolar depression and BD[5], within the concept of a mood spectrum[45,46].

More than a half of the patients reporting AL were diagnosed with a mixed features specifier, in line with literature[18]. Traditionally, AL in a depressive mixed episode was considered as a risk factor of shifting between MDD and BD[23,47]. Several findings from the present study seem to support that the presence of AL during a MDE was associated with mixity. The association between AL and mixed features was three times higher in the MDE-AL group. AL correlated with a higher severity of co-occurring

hypo/manic symptoms during a MDE whilst it was inversely correlated to severity of depression, as in previous research[43]. Patients in the MDE-AL group were more frequently in treatment with antipsychotic and mood stabilizers and less frequently treated with antidepressants than patients in the MDE-noAL group, according to the recent guidelines on mixed depression[48,49].

Another finding claiming the "mixed" identity of AL was the association with a more severe clinical condition, evaluated through indirect measures of psychopathology, such as a higher total number of previous mood episodes and an earlier age at first depressive episode. Indeed, AL was found to independently predict worse outcomes in BD[16,50–56].

In terms of outcomes, AL hinders the modulation of mood oscillations with consequent behavioral responses. In the present study, AL correlated with dysregulated conducts such as alcohol abuse, as in previous findings[14]. A possible association with suicidal attempts was not reported in this study. Previous findings are conflicting, with studies reporting AL not to increase the risk of suicidal behavior[31,57] and others underlining that the risk of suicidal ideation increases with the level of AL[30,58].

In the present study, MR was the variable most significantly associated with AL, and vice versa. The association did not violate the assumption of independence, thus it is unlikely to consider the two clinical features as two overlapping symptoms. Different factors predicted AL and MR. The construct of AL was positively associated to severity of mania whilst MR was predicted by atypical symptoms such as hyperphagia, hypersomnia and leaden paralysis. This last finding is not surprising in consideration of the diagnostic criteria of the new "atypical features specifier" for depression, namely MR plus two or more atypical symptoms [3]. Furthermore, there were few differences also in

the RBDC-MXS symptoms that predicted AL or MR. Despite few common clinical symptoms associated with both AL and MR (irritable mood, racing thoughts, more talkative/pressure to keep talking, distractibility and impulsivity), AL was associated with both elation and verbal or physical aggression, through a direct association with the former and in inverse association with the latter. On the contrary, the presence of risky behavior was inversely associated with MR.

Mixed depression was seen to correlate with atypical features. In a French national study, severe clinical profile displayed by patients with mixed depression included the presence of atypical features[16] as well as MDE with atypical features was significantly correlated with more depressive mixed states in an Italian study[25]. Almost 50% of patients with atypical depression presented more than two hypomanic symptoms[59]. The presence of a depressive mixed state was found to be the strongest bipolar diagnostic validator predicting atypical depression[60]. Finally, mixed depression overlapped with atypical depression[26]. As a consequence, our findings underlined that the polythetic diagnostic criteria of the new "atypical features specifier" for depression might not be completely reliable and valid because not taking in consideration the longitudinal course of depression, particularly the association with other clinical features such as bipolarity and mixed depression as well as the co-occurrence of anxious symptoms, deemed crucial in atypical depression[61].The different DSM definitions of atypical depression was based on the response to monoamine oxidase inhibitors and emerged by a pattern of linked symptoms followed by studies pursuing diagnostic validity with little research support[61]. In particular, the mandatory criterion of reactive mood could be not completely discriminatory, as it was seen to be significantly associated to other atypical symptoms in BDII but not in unipolar depression[25]. As a consequence, a reformulation of atypical depression within a dimensional framework in the context of both unipolar and bipolar

depression, including certain expressions of anxiety and considering the longitudinal association and stability of atypical symptoms, representing real psychopathological symptoms and not only adaptive homeostatic responses, should be pursued in future research[61].

The notion of mood tone has been extended through a dimensional approach to the construct of emotional reactivity, considering not only the tone but also the intensity and reactivity of mood[43]. A cluster analysis revealed two types of depression, characterized by hypo- or hyper-reactivity. Hypo-reactivity identified the inhibited typical depression, with loss of pleasure, anhedonia and emotional anesthesia. Emotional hyper-reactivity distinguished depressive states with prominent affective symptoms, identifying mixed depression. Emotional hyper-reactivity was not restricted to positive stimuli and might affect all emotions, causing emotional pain[25].

In the hypothetical assumption of a continuum between mood symptoms, Akiskal and Benazzi[60] disclosed that atypical depression could link unipolar depression and BDII. Benazzi challenged the unipolar-bipolar dichotomy, indicating that mixed depression could bridge the gap between the two affective disorders, on the basis of the correlation between intradepressive hypomanic symptoms and depressive symptoms[26]. In another study, Benazzi showed that intradepressive hypomanic symptoms did not present a bimodal distribution, reinforcing the continuity between BDII and MDD depressions[53,62]. Unipolar MDD patients that converted in BDII were robustly distinguished from those who remained unipolar on the basis of AL, intruding into and possibly accentuating during depressive episodes, leading to a braided mixed weaving of trait and state[23].

As a consequence, the findings of this study suggest that mixed depression and atypical depression lie on the same continuum from unipolar melancholic depression to

BDI manic episodes. The underpinning matrix might be the emotional hyperreactivity experienced by the patient. The difference between the two types of depression was represented by the presence of swings due to negative actual or perceived stimuli, within the construct of AL[43]. Indeed, MR and AL are strongly associated in terms of reaction to positive stimuli but are differentiated by the response to negative stressors (see **Figure 2**).

The main strengths of the BRIDGE-II-MIX study include the large sample size and the multicentre international nature of the design.

The first limitation was the widely varying rates of hospitalized patients across countries, which reflected locally driven policies. A second limitation is that the participating centers were not randomly selected, comprising psychiatrists selected because of a particular interest in bipolar spectrum disorders. The definitions of AL and MR relied only on retrospectively coded criteria and selected variables already collected in the dataset, rather than ad hoc variables fetched using validated ratings. This might introduce a measurement bias, especially considering that the operational definitions of AL and MR adopted were clinical. Another limitation was that atypical depression was not an a priori-defined primary outcome. The evaluators did not assess the presence of long-standing interpersonal rejection sensitivity, consequently the investigators established retrospectively a diagnosis of DSM-5-AD that could be underestimated, due to the presence of only three of the four symptoms defining the criterion B according to DSM-5.

For these reasons, additional analyses correlating AL with mixed and atypical features should be undertaken in longitudinal prospective studies, addressing potential confounders.

In conclusion, affective lability seems to represent a simple discriminatory criterion for identifying depressive states with mixed features and should be included in the rubric of mixed features of major depressive episode. The role of affective lability as a mixed symptom in mixed mania could be extrapolated but the authors suggest conducting further research on this specific topic. The intertwined association between affective lability and mood reactivity might bridge the gap between mixed and atypical depression, in the light of a unique continuum between mood states. A better understanding of the presence of mixed and atypical features was needed in order to advocate the therapeutic research on two neglected areas, tailoring specific focused treatment strategies.

Clinical Points

1. Although affective lability has been widely studied as a trait-like clinical symptom of affective disorders, its role as a mixed state feature in depression still remain unclear.
2. Affective lability represents a depressive mixed feature that could help in targeting a tailored treatment strategy as it is positively correlated with the severity of mania, negatively correlated with the severity of depression and is strongly associated with mood reactivity and atypical depression.

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Table 1 *Clinical characteristics: MDE-AL patients versus MDE-noAL patients*

Lifetime and current variables (yes listed)	**MDE-AL (n = 694, 26.9%)**	**MDE-noAL (n = 1883, 73.1%)**	**OR (95% CI)**	***P***
Socio-demographic characteristics	n, %	n, %		
Gender, female	492 (70.9)	1266 (67.2)	1.2 (0.98-1.46)	.085
Marital status, single	157 (22.7)	428 (22.8)	0.1 (.81-1.23)	1.000
Marital status, married	384 (55.5)	985 (52.4)	1.1 (0.95-1.35)	.172
Marital status, divorced	94 (13.6)	289 (15.4)	0.9 (0.67-1.11)	.288
Marital status, widowed	57 (8.2)	177 (9.4)	0.9 (0.63-1.18)	.401
Diagnostic features				
DSM-IV-TR BD-I	102 (14.7)	141 (7.5)	2.1 (1.62-2.79)	< .001
DSM-IV-TR BD-II	68 (9.8)	89 (4.7)	2.2 (1.58-3.04)	< .001
DSM-IV-TR MDD	524 (75.5)	1653 (87.8)	0.4 (0.34-0.54)	< .001
DSM-5-MXS	447 (64.4)	564 (30)	10.5 (7.10-15.49)	< .001
DSM-5-AD	78 (11.2)	86 (4.6)	2.7 (1.92-3.64)	< .001
Current comorbidity				
Anxiety disorder	237 (34.1)	446 (23.7)	1.7 (1.38-2.02)	< .001
Alcohol abuse	53 (7.6)	92 (4.9)	1.6 (1.13-2.28)	.010
Current symptoms				
Hypersomnia	143 (20.6)	275 (14.6)	1.5 (1.21-1.90)	< .001
Hyperphagia	126 (18.2)	234 (12.4)	1.6 (1.23-1.98)	< .001
Mood reactivity	455 (65.6)	580 (30.8)	4.3 (3.56-5.14)	< .001
Leaden paralysis	193 (27.8)	457 (24.3)	1.2 (0.99-1.46)	.074
Current psychiatric treatment				
Mood stabilizers	272 (39.2)	407 (21.6)	2.3 (1.94-2.82)	< .001
Antipsychotics	260 (37.5)	588 (31.2)	1.3 (1.10-1.58)	.003
Antidepressants	548 (79.0)	1565 (83.1)	0.8 (0.61-0.95)	.018
Lifetime and current variables	**Mean** (SD)	**Mean** (SD)	**t**	***P***
Age at first depressive episode (years)	34.37 (12.368)	36.34 (12.634)	3.529	< .001
Severity of the condition				
Total number of previous mood episodes	5.17 (5.389)	4.36 (5.645)	-3.303	.001
Total number of lifetime suicide attempts	0.44 (2.102)	0.32 (0.860)	-1.537	.125
Severity of depression (CGI-BP)	4.40 (0.951)	4.52 (0.947)	2.868	.004
Severity of mania (CGI-BP)	1.69 (1.028)	1.13 (0.541)	-13.052	< .001

AL=affective lability; **BD**=bipolar disorder; **CGI-BP**=Clinical Global Impression-Bipolar Version; **CI**=confidence interval; **DSM-IV-TR**=Diagnostic and Statistical Manual of Mental Disorders-forth edition, text revised; **DSM-5**=Diagnostic and Statistical Manual of Mental Disorders-fifth edition; **DSM-5-AD**=major depressive episode with DSM-5 atypical features; **DSM-5-MXS**=major depressive episode with DSM-5 mixed features; **MDD**=major depressive disorder; **MDE-AL**=patients with a major depressive episode with affective lability; **MDE-noAL**=patients with a major depressive episode without affective lability; **n**=number; **OR**=odds ratio; **SD**=standard deviation

Table 2 *Clinical characteristics: MDE-MR patients versus MDE-noMR patients*

Lifetime and current variables (yes listed)	**MDE-MR (n = 1035, 40.2%)**	**MDE-noMR (n = 1542, 59.8%)**	**OR (95% CI)**	***P***
Socio-demographic characteristics	n, %	n, %		
Gender, female	739 (71.4)	1019 (66.1)	1.3 (1.08-1.52)	.005
Marital status, single	240 (23.2)	345 (22.4)	1.1 (0.87-1.26)	.672
Marital status, married	559 (54.1)	810 (52.6)	1.1 (0.90-1.24)	.501
Marital status, divorced	138 (13.3)	245 (15.9)	0.8 (0.65-1.02)	.082
Marital status, widowed	97 (9.4)	137 (8.9)	1.1 (0.81-1.39)	.730
Diagnostic features				
DSM-IV-TR BD-I	117 (11.3)	126 (8.2)	1.4 (1.10-1.87)	.009
DSM-IV-TR BD-II	71 (6.9)	86 (5.6)	1.3 (0.90-1.73)	.211
DSM-IV-TR MDD	847 (81.8)	1330 (86.3)	0.7 (0.58-0.89)	.003
DSM-5-MXS	517 (50)	494 (32)	3.6 (2.54-5.19)	< .001
DSM-5-AD	164 (15.8)	0 (0)	-	< .001
Current comorbidity				
Anxiety disorder	340 (32.9)	343 (22.2)	1.7 (1.43-2.04)	< .001
Alcohol abuse	67 (6.5)	78 (5.1)	1.2 (0.93-1.82)	.150
Current symptoms				
Hypersomnia	213 (20.6)	205 (13.3)	1.7 (1.37-2.09)	< .001
Hyperphagia	183 (17.7)	177 (11.5)	1.7 (1.32-2.07)	< .001
Affective lability	455 (44)	239 (15.5)	4.3 (3.56-5.14)	< .001
Leaden paralysis	318 (30.7)	332 (21.5)	1.6 (1.35-1.93)	< .001
Current psychiatric treatment				
Mood stabilizers	325 (31.4)	354 (23)	1.5 (1.29-1.83)	< .001
Antipsychotics	362 (35)	486 (31.5)	1.2 (0.99-1.38)	.074
Antidepressants	834 (80.6)	1279 (82.9)	0.9 (0.70-1.05)	.139
Lifetime and current variables	**Mean** (SD)	**Mean** (SD)	**t**	***P***
Age at first depressive episode (years)	35.06 (12.628)	36.31 (12.545)	2.465	.014
Severity of the condition				
Total number of previous mood episodes	4.86 (6.577)	4.39 (4.804)	-1.980	.048
Total number of lifetime suicide attempts	0.38 (1.803)	0.33 (0.845)	-1.060	.289
Severity of depression (CGI-BP)	4.45 (0.942)	4.51 (0.955)	1.441	.150
Severity of mania (CGI-BP)	1.41 (0.855)	1.18 (0.643)	-6.815	< .001

MR=mood reactivity; **BD=**bipolar disorder; **CGI-BP=**Clinical Global Impression-Bipolar Version; **CI=**confidence interval; **DSM-IV-TR=**Diagnostic and Statistical Manual of Mental Disorders-forth edition, text revised; **DSM-5=**Diagnostic and Statistical Manual of Mental Disorders-fifth edition; **DSM-5-AD=**major depressive episode with DSM-5 atypical features; **DSM-5-MXS=**major depressive episode with DSM-5 mixed features; **MDD=**major depressive disorder; **MDE-MR=**patients with a major depressive episode with mood reactivity; **MDE-noMR=**patients with a major depressive episode without mood reactivity; n=number; **n=**number; **OR=**odds ratio; **SD=**standard deviation

Table 3 *Stepwise backward multiple logistic regression model of clinical variables associated with AL or MR in patients with a MDE*

	MDE-AL vs MDE-noAL*			MDE-MR vs MDE-noMR†		
Variables in the equation	**Wald**	**OR (95% CI)**	***P***	**Wald**	**OR (95% CI)**	***P***
Affective lability	-	-	-	151.708	3.7 (3.01-4.57)	< .001
Anxiety disorders	3.109	1.2 (0.98-1.56)	.078	14.247	1.5 (1.20-1.80)	< .001
DSM-5-MXS	97.237	3.0 (2.43-3.77)	< .001	15.325	1.5 (1.21-1.76)	< .001
Hyperphagia	-	-	-	5.585	1.4 (1.05-1.77)	.018
Hypersomnia	-	-	-	5.545	1.3 (1.05-1.71)	.019
Leaden Paralysis	-	-	-	20.011	1.6 (1.29-1.92)	< .001
Mood reactivity	144.213	3.7 (2.98-4.57)	< .001	-	-	-
Severity of depression	6.315	0.9 (0.77-0.97)	.012	3.316	0.9 (0.83-1.01)	.069
Severity of mania	83.139	2.0 (1.71-2.30)	< .001	-	-	-

AL=affective lability; **DSM-5-MXS**=major depressive episode with DSM-5 mixed features; **MDE**=major depressive episode; **MDE-AL**=patients with a major depressive episode with affective lability; **MDE-noAL**=patients with a major depressive episode without affective lability; **MDE-MR**=patients with a major depressive episode with mood reactivity; **MDE-noMR**=patients with a major depressive episode without mood reactivity; **MR=**mood reactivity.

*Chi-square=546.632; df=5; $P < .001$; variables not in the equation: bipolar disorder II, major depressive disorder, depression with atypical features, age at first depressive episode, number of previous affective episodes, hyperphagia, hypersomnia, treatment with mood stabilizers, treatment with antipsychotics.

†Chi-square=317.795; df=7; $P < .001$; variables not in the equation: bipolar disorder II, major depressive disorder, age at first depressive episode, number of previous affective episodes, severity of mania, treatment with mood stabilizers, treatment with antipsychotics.

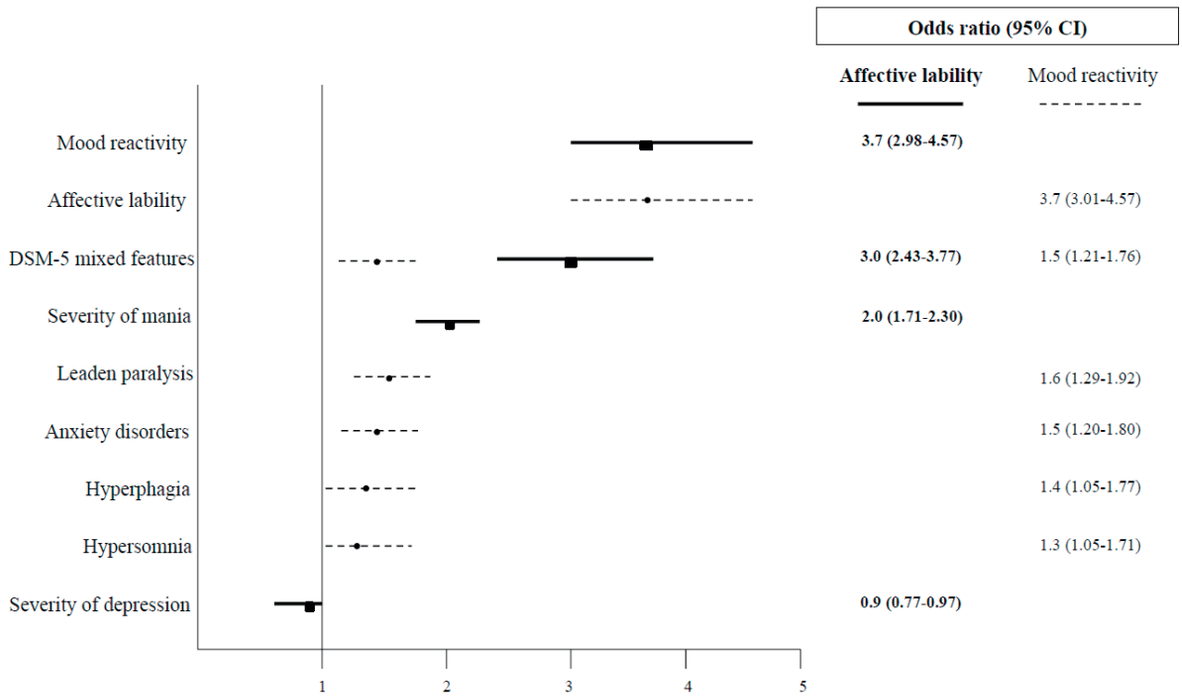

Figure 1 *Logistic regression: Significant clinical variables associated with affective lability and mood reactivity*

Abbreviations: CI=confidence interval

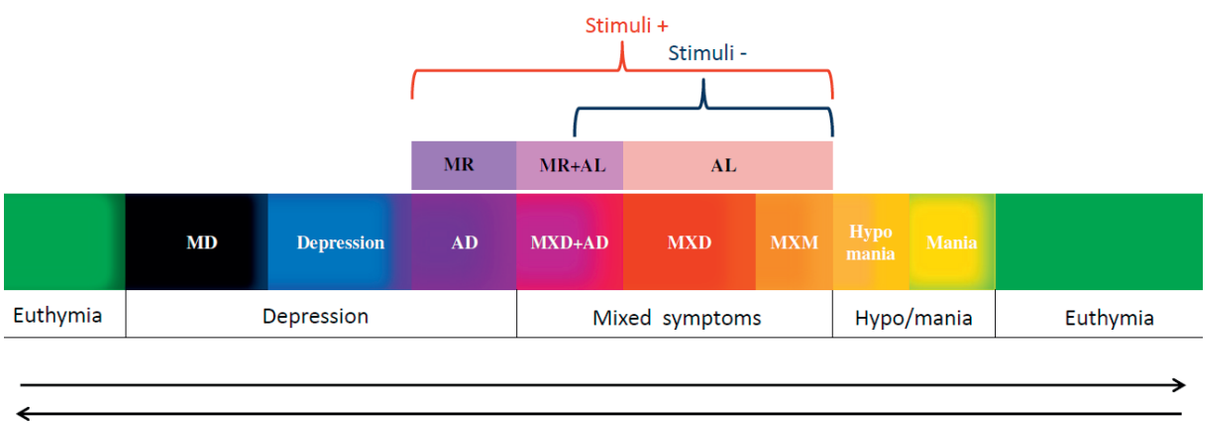

Figure 2 *Affective spectrum revised*

Abbreviations: **AD=**atypical depression; **AL=**affective lability; **MD=**melancholic depression; **MR=**mood reactivity; **MXD=**mixed depression; **MXM=**mixed mania

Note: The figure refers to the dimension of depression-hypomania/mania

SUPPLEMENTARY MATERIAL

Supplementary Table 1 *Stepwise backward multiple logistic regression model of RBDC-MXS hypo/manic symptoms associated with AL or MR*

	MDE-AL vs MDE-noAL*			MDE-MR vs MDE-noMR†		
Variables in the equation	**Wald**	**OR (95% CI)**	***P***	**Wald**	**OR (95% CI)**	***P***
Irritable mood	187.978	5.4	< .001	15.341	1.5	< .001
Racing thoughts	16.279	2.1	< .001	6.203	1.5	.013
More talkative/pressure to keep talking	22.884	2.5	< .001	10.694	1.7	.001
Distractibility	82.459	3.1	< .001	12.382	1.5	< .001
Increased energy	-	-	-	2.805	1.4	.094
Impulsivity	16.314	2.0	< .001	12.655	1.7	< .001
Risky behavior	3.220	0.6	.073	8.153	0.6	.004
Grandiosity	2.958	1.8	.085	-	-	-
Elation	18.572	3.4	< .001	-	-	-
Verbal or physical aggression	3.800	0.7	.051	-	-	-

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Review

Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines

Verdolini N, Hidalgo-Mazzei D, Murru A, Pacchiarotti I, Samalin L, Young AH, Vieta E, Carvalho AF. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines.

Objective: This systematic review provided a critical synthesis and a comprehensive overview of guidelines on the treatment of mixed states.
Method: The MEDLINE/PubMed and EMBASE databases were systematically searched from inception to March 21st, 2018. International guidelines covering the treatment of mixed episodes, manic/hypomanic, or depressive episodes with mixed features were considered for inclusion. A methodological quality assessment was conducted with the Appraisal of Guidelines for Research and Evaluation-AGREE II.
Results: The final selection yielded six articles. Despite their heterogeneity, all guidelines agreed in interrupting an antidepressant monotherapy or adding mood-stabilizing medications. Olanzapine seemed to have the best evidence for acute mixed hypo/manic/depressive states and maintenance treatment. Aripiprazole and paliperidone were possible alternatives for acute hypo/manic mixed states. Lurasidone and ziprasidone were useful in acute mixed depression. Valproate was recommended for the prevention of new mixed episodes while lithium and quetiapine in preventing affective episodes of all polarities. Clozapine and electroconvulsive therapy were effective in refractory mixed episodes. The AGREE II overall assessment rate ranged between 42% and 92%, indicating different quality level of included guidelines.
Conclusion: The unmet needs for the mixed symptoms treatment were associated with diagnostic issues and limitations of previous research, particularly for maintenance treatment.

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Key words: mixed states; mixed features; bipolar disorder; unipolar disorder; guidelines

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Summations

- Olanzapine seemed to be the most effective compound for the treatment of acute mixed hypo/manic or depressive states as well as for the prevention of affective episodes of any polarity, even though the available evidence was still scant.
- Aripiprazole and paliperidone in monotherapy could be effective alternatives in the treatment of acute hypo/manic mixed states while lurasidone and ziprasidone (in combination with treatment as usual) in the treatment of acute depressive manifestations. As for the maintenance treatment, valproate was effective in the prevention of new mixed episodes. Lithium and the combination treatment of quetiapine were useful in preventing affective episodes of all polarities.
- Antidepressant monotherapy should be avoided while clozapine and electroconvulsive therapy were effective options in treatment resistant patients.

Considerations

- Different diagnostic criteria have been used to define manic/hypomanic and depressive presentations (mixed episodes or mixed features).
- All the guidelines included lack of strength in the AGREE II applicability domain. The quality of the *British Association for Psychopharmacology* guidelines was the best, but the *World Federation of Societies of Biological Psychiatry* guidelines represented the most focused guidelines on the treatment of mixed states. The Stahl and colleagues' guidelines were the first ones to address depression with DSM-5 mixed features, but the rigor of development was inconsistent.
- The available evidence on the treatment of mixed patients had been generally extrapolated from *post hoc* or pooled analyses of randomized clinical trials. The findings of this critical systematic review should be kept with caution as the generalizability of these results might be partly suitable for the treatment of mania with mixed features but are less likely applicable to the treatment of depression with mixed features.

Introduction

Bipolar disorder (BD) is a severe chronic mood disorder broadly classified according to the longitudinal course in BD type I (BDI) or type II (BDII) and characterized by episodes of mania, hypomania, and alternating or intertwining episodes of depression with the presence of subthreshold symptoms between the episodes (1). A complex and quite frequent presentation of BD is represented by the occurrence of mixed states, historically defined as the coexistence of depressive and manic symptoms (2).

The identification of mixed features in BD and major depressive disorder (MDD) is an open challenge in psychiatry as an accurate diagnosis is a pre-requisite for the initiation of adequate therapeutic approaches (3–5). The mixed episode was defined by juxtaposed full manic and depressive episodes in the diagnostic and statistical manual of mental disorders-IV-text revision (DSM-IV-TR) (6). A 'with mixed features' specifier (MFS) has been incorporated in the DSM-5 (7); this specifier may be applied to manic episodes in BDI, hypomanic episodes in BDI and BDII, and to major depressive episodes (MDE) experienced in BDI, BDII, BD not otherwise specified (BD-NOS) as well as in MDD (8). As a consequence, hypomanic symptoms could currently denote both MDD or BD and many individuals along the mood disorders spectrum that were previously 'orphans' of a diagnosis could be classified according to a 'mixed-categorical–dimensional' approach (8, 9).

Approximately 30–40% of major affective episodes that occur over the course of BD appear to exhibit mixed features (10–12). Major concerns still exist for the DSM-5 MFS. In fact, it has 100% specificity but only 5.1% sensitivity (5). Specificity at the expense of sensitivity suggests that up to 95% of patients presenting with the MFS according to the DSM-5 are wrongly diagnosed as having 'pure' affective episodes (i.e., without mixed features) (5, 9). The DSM-5 workgroup excluded overlapping symptoms such as distractibility, irritability, and psychomotor agitation, arguing that they may lack the ability to differentiate between manic and depressive states (13), in the choice of a more 'specific' approach at the expenses of the 'sensitivity' of the classification (8, 9). Nevertheless, when criteria that consider overlapping symptoms for the diagnosis of mixed features are used, a more balanced trade-off between sensitivity and specificity was obtained, with a specificity of 87% and a sensitivity as high as 55% (5, 14). In addition, it is not clear which could be the implication on the prevalence of mixed episodes of the DSM-5 MFS in comparison with previous DSM classifications, as literature findings are conflicting. In BD, DMS-5 mixed features rates were found to be threefold higher than DSM-IV-TR mixed episodes in a retrospective naturalistic study (15) while the Bipolar CHOICE, a randomized comparative effectiveness trial, reported that fewer patients suffering from BD met mixed criteria with the DSM-5 nonoverlapping definition compared to the DSM-IV (16). In the multicenter, multinational cross-sectional bipolar disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX study, 7.5% of the entire sample fulfilled DSM-5 criteria for MDE with mixed features, but when a broader definition including overlapping symptoms was applied, the rates of depressive mixed states were as high as 29.1% (17).

The DSM-5 does not provide a clear rationale for not weighing certain depressive symptoms,

such as weight loss or weight gain, decreased or increased appetite, and insomnia or hypersomnia for the establishment of a MFS in the context of mania (or hypomania) even though virtually every symptom of depression may co-occur in acute (hypo)manic episodes (18). Many patients with MDE and mixed features also present with manifestations of anxiety that are not captured by the MFS (18) as well as other clinical features, that is, aggressiveness that have been recently found to be a possible psychopathological indication of an underlying mixed state (19). A recent study identified that a four- or five-symptom cluster composed by the DSM-5 MFS symptoms racing thoughts, increased talkativeness and decreased need for sleep and by the two non-specific symptoms distractibility and irritability, was shown at baseline in a placebo-controlled trial involving patients with MDD with mixed features (20). Hence, it has been hypothesized that the symptoms of the DSM-5 MFS are themselves non-specific (21).

The introduction of a codable diagnostic entity defined according to the MFS should provide a rationale for the selection of distinct therapeutic strategies (9). Nonetheless, no drug treatment has been approved by major regulatory agencies for the management of affective episodes with a MFS (22). The treatment of mixed episodes is an important challenge for psychiatrists as the available evidence is undermined by the methodological limitations of previous RCTs. Generally, the response to pharmacological agents of patients presenting a manic episode with depressive mixed symptoms had been extrapolated from *post hoc* or pooled analyses of RCTs evaluating treatment response in mania (23). In addition, these studies generally did not provide data for the mixed subgroup (22). The evidence for mixed depression is even more scant as patients presenting mixed symptoms are generally excluded by depression RCTs (24). As a consequence, the generalizability of the results of previous RCT may be partly suitable for the treatment of mania with mixed features but are less likely applicable to the treatment of depression with mixed features (25).

The treatment of mixed states represented an unmet need in previous international guidelines of BD. Indeed, clinicians should follow existing guidelines written for the treatment of MDD or BD with few indications for patients presenting with mixed symptoms in spite of the high frequency and clinical significance of mixed states over the course of mood disorders (26).

Only recently, the World Federation of Societies of Biological Psychiatry (WFSBP) published guidelines for the acute and long-term treatment of mixed episodes in BDI (22) and treatment guidelines addressing the DSM-5 MFS during a MDE have also been developed (5). The Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Major Depressive Disorder (27) and the Korean Medication Algorithm Project for Bipolar Disorder: Third Revision (28) specifically addressed the treatment of mixed features. In addition, the available updated editions of the international guidelines for BD reported recommendations for the treatment of mixed episodes and mixed symptoms.

Aims of the study

As mixed features represent a challenge for clinicians at the diagnostic, classification, and pharmacological treatment levels, the aim of this work was to summarize available evidence and to provide a comprehensive review of recently updated guidelines. This work was part of a systematic review protocol of current treatment guidelines for mood disorders, and this particular study focused exclusively on the treatment of mixed states and symptoms. A critical approach has been applied to identify areas of consensus and controversy, to underline the strengths and limitations of available evidence, and also the methodological quality of international guidelines that provided evidence for the management of mixed states in the context of bipolar disorder and major depressive disorder. Finally, unmet needs were identified to provide direction for further research.

Methods

This systematic review followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (29). A study protocol was registered with PROSPERO and published *a priori* (CRD42018078199).

Search strategy

The MEDLINE/PubMed and EMBASE databases were searched up to March 21st, 2018. Detailed search strings are provided in the Supporting Information that accompanies the online version of this article.

This search strategy was augmented through hand-searching of the reference lists of included articles. Duplicate publications were identified and cross-referenced to optimize information. Two independent reviewers (NV and DHM) screened the title/abstracts of retrieved references for

eligibility, evaluated the full-texts of potentially eligible articles, performed the methodological assessment of guidelines, and extracted pre-established relevant information. Disagreements were resolved through consensus, and a third investigator was consulted whenever a consensus could not be achieved (AM).

Eligibility criteria

International guidelines for the treatment of mixed episodes, manic/hypomanic (in BDI, BDII, and BD-NOS), or depressive episodes (in BDI, BDII, BD-NOS, and MDD) with mixed features published in any language were considered for inclusion.

The Institute of Medicine definition of guidelines as 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options' (30) was considered as an operational criteria to define included guidelines.

International guidelines were defined as guidelines performed by: (i) an international organization, representing more than a single country; (ii) a panel of experts from different countries; (iii) a national organization providing that experts from at least three different countries participated in the development of the guideline.

Only guidelines for BD updated from 2011 onwards have been considered in this critical review since guidelines published before those dates have been critically examined elsewhere (31–33). As for guidelines for MDD, only those guidelines updated from 2013 (when the MFS has been introduced) have been considered.

Guidelines were included if they clearly outlined their development and the clinical recommendations' procedures. When available, tables and/or algorithms of medication phases were consulted.

Data extraction

The following information was extracted for each article when available: international organization; publication year; date of the last search; evidence category of treatment options; grading of safety and tolerability.

Treatment recommendations were reported for (i) mixed episodes according to DSM-IV-TR and (ii) mixed features according to DSM-5. When available, data concerning both acute and long-term treatment were described and treatment options were specified for the depressive or manic polarities of mixed episodes or features.

As for efficacy evidence, treatment options were categorized into first-line, second-line, and not recommended treatments in accordance with an adaptation of procedures described elsewhere (31). The category of evidence (CE) describing the level of efficacy was specified for each treatment option in Table S1 of the Supporting Information that accompanies the online version of this article. Specifications on safety and tolerability issues were also extrapolated when available. In general, but not in all the included guidelines, safety and tolerability aspects were integrated with the CE assigned to each compound leading to different recommendation grades (RG). In the purpose of this critical review, we created an operational definition of first- and second-line treatment recommendations, grouping the RG of the different guidelines (see Table S2).

Methodological quality assessment

The methodological quality assessment of included guidelines was carried out with the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool (34). The AGREE II was designed to provide a framework to assess the quality of guidelines judging the methods used for developing the guidelines, the components of the final recommendations, and the factors that were linked to their uptake on the basis of six domains (i.e., scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence).

An electronic group appraisal was created at the My AGREE Plus website (35), and after successfully completing training modules, the two reviewers (NV and DHM) undertook independent appraisals for each of the included guidelines. The scores rated by the two reviewers for the 23 items of the AGREE II, for the six domains, and for the overall quality of the guideline were calculated and scaled according to the AGREE II scoring instructions.

Results

Systematic search results

The initial search returned 7622 hits (Figure S1). Following removal of duplicates, the title/abstracts of 5280 references were screened for eligibility, and 5261 references were excluded. The full texts of 19 references concerning structured treatment algorithms and/or guidelines suggested by official panels were scrutinized in detail for eligibility. Among them, 13 references were

Table 1. Comparison of the included guidelines: evidence of efficacy, acute treatment, first line

First line	Guidelines	Mania/hypomania with mixed features or manic mixed episode	Depression with mixed features or depressive mixed episode
Monotherapy	BAP 3rd edition	Oral SGA (I)	–
	CANMAT/ISBD 2018	SGA: ASN, ARP, OLZ and ZPD (1)	SGA: LUR (2)
	CINP-BD-2017	–	–
	RANZCP Mood Disorders CPG	–	SGA: OLZ, QTP MS: VPA
	Mixed depression guidelines	–	SGA: LUR, ASN, QTP, QTP-XR, ARP and ZPD (1); OLZ and CAR (2) MS: LMT, VPA and Li (2)
	WFSBP Mixed states	SGA: OLZ (A, for ManS), ARP (B, for ManS and DepS) and PLP (B, for ManS)	–
Combination	BAP 3rd edition	CLZ + Li or MS in treatment resistant patients + BDZ	–
	CANMAT/ISBD 2018	SGA + VPA: ASN (2), ARP (2), OLZ (1)	LUR + Li/VPA (1) OFC (2)
	CINP-BD-2017	OLZ + MS (2)	OLZ + MS (2)
	RANZCP Mood Disorders CPG	SGA (ASN, OLZ, ARP, ZPD, RPD) + MS (II)	SGA (OLZ, QTP) or VPA + AD (II) VPA + OLZ (II)
	Mixed depression guidelines	–	MS (Li, LMT, VPA) + SGA Li + VPA Li + VPA + LMT OFC
	WFSBP Mixed states	OLZ + VPA (A for ManS and DepS) QTP + MS (B for DepS)	ZPD + TAU

AD, antidepressants; ARP, aripiprazole; ASN, asenapine; BAP, British Association of Psychopharmacology; BD, bipolar disorder; BDZ, benzodiazepines; CANMAT, Canadian Network for Mood and Anxiety Treatment; CAR, cariprazine; CINP, International College of Neuropsychopharmacology; CLZ, clozapine; CPG, clinical practice guidelines; DepS, depressive symptoms; ISBD, International Society of Bipolar Disorder; ManS, manic symptoms; Li, lithium; LMT, lamotrigine; LUR, lurasidone; OFC, olanzapine+fluoxetine; OLZ, olanzapine; PLP, paliperidone; QTP, quetiapine; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RPD, risperidone; SGA, second generation antipsychotics; TAU, treatment as usual; VPA, valproate; WFSBP, World Federation of Societies of Biological Psychiatry; ZPD, ziprasidone; XR, extended-release.
(I), (1), (A), first category of evidence; (II), (2), (B), second category of evidence.

excluded with reasons (see Table S3). The final selection yielded six articles.

Content results

Evidence of efficacy was summarized in Table 1 (acute treatment, first-line), Table 2 (acute treatment, second-line), Table 3 (maintenance treatment), and Table S4 (not recommended treatment).

Evidence of efficacy

Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. The BAP updated previous guidelines (26) and provided this third revision based on the best new available evidence from RCTs and observational studies employing quasi-experimental designs (36). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (37) was used to grade the recommendations and was preferred to the traditional evidence categories (38) as this approach downgraded non-experimental descriptive studies in favor of any RCT, even of small clinical trials where bias was highly likely. The strength of the evidence was instead rated on the basis of traditional evidence categories (38) and may relate to both RCT and observational findings. Along with the grading of a strategy or individual treatment, the BAP provided recommendations that were not based on systematic evidence but represented an important practical or ethical consensus between the authors that could influence practice (Standard of Care, S).

Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. The CANMAT in collaboration with the ISBD updated the guidelines, and the evidence ratings have been modified from the previous editions to increase rigor (39). A final grading of recommendations into first-, second-, or third-line was listed, and a new hierarchical order of treatments was created for first- and second-line recommendations, considering levels of evidence for efficacy of each treatment, as well as acute and maintenance safety and tolerability and risk of treatment emergent switch. In the sections dedicated to the acute and long-term management of bipolar mania/hypomania and depression, the authors reported about the new mixed feature specifier in the specific section about 'clinical features that help

Table 2. Comparison of the included guidelines: evidence of efficacy, acute treatment, second line

Second line	Guidelines	Mania/hypomania with mixed features or manic mixed episode	Depression with mixed features or depressive mixed episode
Monotherapy	BAP 3rd edition	LMT (IV)	–
	CANMAT/ISBD 2018	ZPD (3) for mixed hypomania	–
	CINP-BD-2017	SGA: ARP, ASN, PLP, RPD, OLZ (3), and ZPD (4) MS: VPA, CBZ (3) OFC (4)	SGA: ARP, ASN, OLZ (3), and ZPD (4) MS: VPA (4) , CBZ (3) OFC (4)
	RANZCP Mood Disorders CPG	–	–
	Mixed depression guidelines	–	MS: CBZ (3)
	WFSBP Mixed states	SGA: ASN (C for DepS), RPD (C), CAR (C for ManS), CLZ (C for ManS), OLZ (C for DepS), ZPD (C for ManS and DepS) FGA MS: VPA (C for ManS), CBZ (C for ManS and DepS)	SGA: LUR, OLZ (C) MS: CBZ (C for DepS)
Combination	BAP 3rd edition	ECT (IV)	–
	CANMAT/ISBD 2018	–	ASN (4)
	CINP-BD-2017	–	–
	RANZCP Mood Disorders CPG	ECT (III)	–
	Mixed depression guidelines	–	CBZ + Li (3) Li + pramipexole (3) Li + ECT (3) MS: (Li, LMT, VAP) or SGA + bupropion or SSRI or MAOI (3)
	WFSBP Mixed states	SGA: QTP (C for ManS), CLZ (C for ManS), MS: OXC (+ Li, C for ManS), GBP (C, for ManS and DepS), TPR (D for ManS) ECT (C for ManS and DepS)	ECT (C)

AD, antidepressants; ARP, aripiprazole; ASN, asenapine; BAP, British Association of Psychopharmacology; BD, bipolar disorder; CANMAT, Canadian Network for Mood and Anxiety Treatment; CBZ, carbamazepine; CAR, cariprazine; CINP, International College of Neuropsychopharmacology; CLZ, clozapine; CPG, clinical practice guidelines; DepS, depressive symptoms; ECT, elettroconvulsive therapy; FGA, first-generation antipschotics; GBP, gabapentin; ISBD, International Society of Bipolar Disorder; ManS, manic symptoms; OXC, oxcarbazepine; Li, lithium; LMT, lamotrigine; LUR, lurasidone; MAOI, monoamine oxidase inhibitor; OFC, olanzapine+fluoxetine; OLZ, olanzapine; PLP, paliperidone; QTP, quetiapine; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RPD, risperidone; SGA, second-generation antipsychotics; SSRI, selective serotonin reuptake inhibitor; TAU, treatment as usual; TPR, topiramate; VPA, valproate; WFSBP, World Federation of Societies of Biological Psychiatry; ZPD, ziprasidone; XR, extended-release.
(III), (3), (C), third category of evidence; (IV), (4), (D), fourth category of evidence.

direct treatment choices'. Unfortunately, the task force did not grade the efficacy of treatments for acute and long-term management of mixed features during bipolar mania and depression but only for hypomania. The authors of this systematic review decided to extrapolate the CE for mixed features from the corresponding bipolar mania and depression recommendations.

The International College of Neuro-Psychopharmacology treatment guidelines for Bipolar disorder in adults (CINP-BD-2017). The CINP recently proposed the first edition of the treatment guidelines for patients with BDI or BDII in primary and secondary care and addressed the treatment of adult patients with mixed features, rapid cycling, and psychotic features but not children, adolescents, or the elderly (40). The authors reviewed data from clinical trials and meta-analyses, reserved the privilege to judge, and use data from open trials, reviews, and opinion letters on an individual basis, according to their research and clinical experience, took into consideration guidelines developed during the last 10 years, and recommendations were stated by consensus through the Delphi method. The workgroup decided to develop a grading method for the evaluation of available data, which is an adaptation of the GRADE. After the grading of data and interventions, the authors created a precise algorithm for experimental reasons and finally establish recommendations.

As for mixed states, the workgroup stated that data suggested that mixed features respond to treatment in a different way than DSM-IV-TR mixed episodes. The workgroup separately provided effects on the manic and the depressive component of mixed episodes of the most important compounds.

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (Mood Disorders CPG). The RANZCP developed the Mood Disorders Clinical Practice Guideline (Mood Disorders CPG) as part of the RANZCP CPG Project 2013–2015 (41). The Mood Disorder CPG is the first Clinical Practice Guideline to address both MDD and BD, coherently with the conceptualization of a mood spectrum. The levels

Table 3. Comparison of the included guidelines: evidence of efficacy, maintenance treatment

Maintenance treatment	Guidelines	Mania/hypomania or depression with mixed features or manicor depressive mixed episode
Monotherapy	BAP 3rd edition	MS: Li (I)
	CANMAT/ISBD 2018	QTP in preventing episodes of any mood episode, of depression and mania, first line
	CINP-BD-2017	SGA: OLZ (1)
	RANZCP Mood Disorders CPG	VPA >> Li; CBZ ?
	Mixed depression guidelines	The same effective acute treatment
	WFSBP Mixed states	1. After an acute mixed episode in preventing episodes of any polarity, first line. Li (B for manic and for any type of episode), OLZ (B), QTP (B, for manic, depressive and any type of episode) 2. After an acute mixed episode in preventing episodes of any polarity, second line. ZPD (C, for manic relapse) 3. After an acute manic or depressed episode in preventing new mixed episodes, first line. VPA (B) 4. After an acute manic or depressed episode in preventing new mixed episodes, second line. Li (D) or OLZ (D)
Combination	BAP 3rd edition	–
	CANMAT/ISBD 2018	QTP + Li/VAP in preventing episodes of any mood episode, of depression and mania, first line.
	CINP-BD-2017	ARP + MS (2)
	RANZCP Mood Disorders CPG	–
	Mixed depression guidelines	AD
	WFSBP Mixed states	1. After an acute mixed episode in preventing episodes of any polarity, first line. QTP + Li or VPA (A for manic, depressive episode and any type of episode) or ECT (C) 2. After an acute mixed episode in preventing episodes of any polarity, second line. RPD (C), ARP + LMT (C, for depressive episodes) 3. After an acute manic or depressed episode in preventing new mixed episodes, first line 4. After an acute manic or depressed episode in preventing new mixed episodes, second line

AD, antidepressants; ARP, aripiprazole; ASN, asenapine; BAP, British Association of Psychopharmacology; BD, bipolar disorder; CANMAT, Canadian Network for Mood and Anxiety Treatment; CBZ, carbamazepine; CINP, International College of Neuropsychopharmacology; CLZ, clozapine; CPG, clinical practice guidelines; ECT, elettroconvulsive therapy; ISBD, International Society of Bipolar Disorder; Li, lithium; LMT, lamotrigine; OLZ, olanzapine; QTP, quetiapine; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RPD, risperidone; SGA, second generation antipsychotics; VPA, valproate; WFSBP, World Federation of Societies of Biological Psychiatry; ZPD, ziprasidone.
(I), (1), (A), first category of evidence; (II), (2), (B), second category of evidence; (III), (3), (C), third category of evidence; (IV), (4), (D), fourth category of evidence.

of evidence were assigned and adapted from the Australian National Health and Medical Research Council (NHMRC) levels of evidence for intervention studies (42). The Mood Disorders CPG gave two types of recommendations: (i) Evidence-based recommendations (EBRs) formulated when evidence from intervention studies was sufficient and consistent to support a recommendation on a given topic. For each EBR, strength of evidence was rated using the NHMRC levels of evidence. (ii) Consensus-based recommendation (CBR), derived through discussion and agreement within the workgroup on specific aspects of mood disorders whose nature and management are incomplete.

As little is known about the diagnosis and treatment of mixed features presentations as defined by DSM-5 (Malhi, 2013, 2014), the authors concluded that treatment guidelines for mixed features rely heavily on clinical experience and consensus recommendations.

Guidelines for the recognition and management of mixed depression. As stated by the workgroup, one of the most important challenges derived by the new DSM-5 MFS is to optimize the treatment for patients with depression exhibiting concomitant subthreshold hypo/manic features (43). With this aim in mind, a panel of experts on mood disorders has been assembled to develop guidelines on the recognition and treatment of mixed depression made in reference to DSM-5.

The World Federation of Societies of biological psychiatry guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. The international taskforce of the WFSBP developed this practice guideline specifically for acute and maintenance pharmacological treatment and prevention of mixed episodes in BD (22). Considering the topic of this critical review, we decided to include this brand-new guideline about mixed episodes and to exclude previous guidelines from the same taskforce about acute mania (23), bipolar depression (44), and maintenance treatment of BD (45).

The authors distinguished the recommendations for the following categories: (i) treatment of acute manic mixed episodes; (ii) treatment of acute depressive mixed episodes; (iii) maintenance treatment after an acute mixed episode in preventing episodes of any polarity; (iv) maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes.

The ranking of evidence was the same used in the development of other guidelines of the WFSBP (46). Categories of evidence (CE) A or B, corresponding to RG 1–3, were defined for treatments that have shown their efficacy in double-blind

placebo-controlled studies. Lower level of evidence was recorded for open studies (CE 'C') or conflicting results (CE 'D') (low RG 4 or 5 respectively). Deviations from the original WFSBP guideline grading system were the role of *post hoc* and subgroup analyses as well as large registry studies. As for *post hoc* analyses, when the study included *a priori* in the analyses plan the *post hoc* analysis and it was sufficiently powered, a CE 'B' was considered. If it was not the case, a lower CE was assigned (CE 'C'). As for registry studies, at least a CE 'C' level was attributed to registry studies (as other retrospective studies) of good quality and minimized risk of bias.

The treatment of unipolar MDE with mixed features according to DSM-5 was not considered in this guideline. When available, the authors considered results from studies in BDII and rapid cycling patients as well as information for efficacy or safety in children or old age.

Safety and tolerability

The CINP-BD-2017 (47) and the WFSBP guidelines (22) graded each medication in terms of safety and tolerability and considered these aspects in RG. The CANMAT-ISBD (39) task-force considered safety and tolerability concerns and risks of treatment emergent switch in mania/hypomania or depression in providing RG providing ratings reached by consensus (see Table S2).

The BAP (36) did not integrate safety and tolerability aspects with CE to provide RG. The Mood Disorder CPG (41) by the RANZCP did not consider safety and tolerability in the development of RG, but the authors provided figures based on expert panel average ratings in which they graphically reported the ratings of tolerability for the different compounds.

Stahl and colleagues (43) reported about safety monitoring in their guidelines for the treatment of mixed depression, but it is not clear whether they integrated these aspects in the RG. They developed a table about the notable side-effects associated with MS and a figure for the relative tolerability of SGA (for sedation, weight gain, extrapyramidal symptoms) (see Table 4).

Quality of the included guidelines

The methodological quality assessment of included guidelines conducted by the two independent reviewers is reported in the Table S5. The quality scores of the specific domains for each guideline obtained by the two appraisers are reported in Table 5. The quality substantially differed among the included guidelines. The AGREE II overall assessment rate ranged between 42% and 92%. The BAP guidelines reached the highest AGREE II overall assessment rate.

Discussion

Summary of the treatment recommendations

The six guidelines included in this systematic critical review provided different recommendations for the treatment of mixed states or features of affective episodes. This could be the consequence of different approaches to rate the quality of available evidence. Four of six guidelines (22, 39, 40, 43) provided some grading of safety and tolerability, with treatment recommendations based on a combination of efficacy and risk/benefit ratio. We discussed each compound according to an operational definition of first- or second-line treatment recommendations as well as each treatment option is provided with the specification of the RG defined according to the original guidelines (see Table S2).

In general, the guidelines recommended starting the treatment with a medication fulfilling the highest criteria for efficacy and tolerability, that is SGAs in combination with lithium or valproate should be reserved for more severe presentations as first-line choice or as a subsequent step when another first-line medication failed. Mood-stabilizing medications generally reached evidence for the long-term treatment. All the guidelines agreed upon avoiding in mixed depression, in both BD and MDD, the use of AD or at least to combine a MS to the ongoing AD treatment.

Mania/hypomania with mixed features or manic mixed episodes. Oral antipsychotics, both dopamine antagonists and partial agonists, were the first-line treatments.

Olanzapine was recommended as first-line choice in the treatment of acute mania/hypomania with mixed features in all eligible guidelines with the exception of the last CANMAT/ISBD guideline (2). In particular, the WFSBP recommended it in monotherapy with RG '2' for manic symptoms but '4' for depressive symptoms during a manic mixed episode in the context of BD. The combination of olanzapine with a MS was recommended as first-line treatment in the RANZCP (II), by the CINP (2) and by the WFSBP (2 for valproate). Olanzapine in monotherapy was graded as '3' by the CINP. Despite the CE for olanzapine was rated 1 in the CANMAT/ISBD guidelines, both for the monotherapy and the combination treatment with

Table 4. Comparison of the included guidelines: grading of compounds according to safety issues and tolerability

	BAP 3rd edition	CANMAT/ISBD 2018*	CINP-BD-2017†	RANZCP Mood Disorders CPG	Mixed depression guidelines	WFSBP MS‡
Grading for ST provided	No	Yes	Yes	No	No	Yes
Integration of ST with CE to provide RG	No	Yes	Yes	No	nk	Yes
Monotherapy						
AD						A –, L 0
Aripiprazole		A = S –, T + L = S –, T +	1			A 0, L +
Asenapine		A = S –, T + L = S –, T +	1			A +, L +
Carbamazepine		A = S ++, T + L = S ++§, T ++	2			A –, L 0
Cariprazine		A = S –, T + L = S –, T –	1			A +, L +
Clozapine			3			–
ECT		A = S +, T ++ L = S +, T ++	2			A –, L –
Escitalopram			1			
FGA						A –, L –
Fluoxetine			1			
Haloperidol		A = S +, T ++ L = S +++, T ++ D +++	2			
Imipramine			2			
Lamotrigine		A = S ++, T – L = S –, T –	2			A +, L +
Lamotrigine (adj)		A = S ++, T + L = S ++, T ++				
Lithium		A = S +, T + L = S ++, T ++	2			A –, L –
Lurasidone		A = S –, T + L = S –, T +	1			A +, L +
Olanzapine		A = S +, T ++ L = S +++, T ++	2			A +, L +
Oxcarbazepine			1			
Paliperidone		A = S –, T + L = S +, T ++	1			A 0, L 0
Paroxetine			1			
Quetiapine		A = S +, T ++ L = S ++, T ++	1			A 0, L –
Risperidone		A = S –, T + L = S +, T ++ D +	1			A 0, L –
Risperidone LAI		A = S –, T + L = S +, T ++				
Risperidone LAI (adj)		A = S +, T ++ L = S +++, T ++				
Sertraline			1			
Topiramate			3			+
Tranylcypromine			2			
Valproate		A = S –, T + L = S ++§, T +	1			A +, L –
Venlafaxine			2			
Ziprasidone		A = S ++, T ++ L = S ++, T +	2			A +, L +
Combination therapies						
Quetiapine + Lithium/Valproate		A = S ++, T ++ L = S +++§, T ++				
Aripiprazole + Lithium/Valproate		A = S +, T + L = S ++§, T ++				
Risperidone + Lithium/Valproate		A = S +, T ++ L = S +++§, T +				
Asenapine + Lithium/Valproate		A = S +, T + L = S ++§, T +				
Olanzapine + Lithium/Valproate		A = S +, T + L = S +++§, T ++				

Table 4. (Continued)

	BAP 3rd edition	CANMAT/ISBD 2018*	CINP-BD-2017†	RANZCP Mood Disorders CPG	Mixed depression guidelines	WFSBP MS‡
Lurasidone + Lithium/Vaproate		A = S +, T ++ L = S ++§, T ++/+				
Ziprasidone + Lithium/Vaproate		A = S ++, T ++ L = S ++§, T +				
Lithium + Valproate		A = S +, T ++ L = S ++, T ++				
SSRIs/bupropion (adj)		A = S −, T + L = S −, T + M/H ++				
Olanzapine-fluoxetine		A = S +, T ++ L = S +++, T + M/H +				

A, acute treatment; AD, antidepressants; BAP, British Association of Psychopharmacology; BD, bipolar disorder; CANMAT, Canadian Network for Mood and Anxiety Treatment; CE, category of evidence; CINP, International College of Neuropsychopharmacology; CPG, clinical practice guidelines; ECT, elettroconvulsive therapy; FGA, first generation antipsychotic; ISBD, International Society of Bipolar Disorder; L, long-term treatment; LAI, long acting injectable; MS, mixed states; nk, not known; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RG, recommendation grades; SSRIs, selective serotonin reuptake inhibitors; ST, safety and tolerability; WFSBP, World Federation of Societies of Biological Psychiatry.

*CANMAT/ISBD 2018 Safety (S) and Tolerability (T) Concerns in Acute (A) and Maintenance (L) treatment and Risks of Treatment Emergent Switch in Mania/Hypomania (M/H) or Depression (D) consensus ratings: − Limited impact on treatment selection; + Minor impact on treatment selection; ++ Moderate impact on treatment selection; +++ Significant impact on treatment selection; nk not known.

†CINP-BD-2017 grading of treatment options according to safety issues and tolerability: from Level 1 (very good tolerability) to Level 3 (poor tolerability). Only most frequently used treatments reported.

‡WFSBP Mixed states Safety & Tolerability (ST) rating for acute (A) and long-term (L) treatment: from '++' (best positive evidence) to '− −' (strong negative evidence); "0" (equally advantages and disadvantages, or unknown).

§Caution in women of child bearing age.

Table 5. Quality scores of the six AGREE II domains and overall assessment

Guidelines	Domain 1 Scope and purpose (%)	Domain 2 Stakeholder involvement (%)	Domain 3 Rigor of development (%)	Domain 4 Clarity of presentation (%)	Domain 5 Applicability (%)	Domain 6 Editorial independence (%)	Overall assessment (%)
BAP 3rd edition	97	67	82	92	40	83	92
CANMAT/ISBD 2018	89	58	60	81	35	71	67
CINP-BD-2017	69	64	66	78	25	96	58
RANZCP Mood Disorders CPG	72	83	64	81	33	96	67
Mixed depression guidelines	72	47	24	67	25	92	42
WFSBP Mixed states	86	50	78	83	33	92	83

BAP, British Association of Psychopharmacology; BD, bipolar disorder; CANMAT, Canadian Network for Mood and Anxiety Treatment; CINP, International College of Neuropsychopharmacology; CPG, clinical practice guidelines; ISBD, International Society of Bipolar Disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, World Federation of Societies of Biological Psychiatry.

valproate, olanzapine was considered as a second-line treatment because of the safety and tolerability concerns. Olanzapine had probably the best positive evidence of all medication for the acute treatment of BDI patients with manic mixed episodes. Its high level of evidence in monotherapy was justified by results from two consecutive short-term RCT (48, 49) and four *post hoc* analyses, two analyzing subgroups of the above mentioned RCT (50, 51), a third *post hoc* analysis also including a Japanese study (52) and a *post hoc* analysis of the first acute three-arm RCT with asenapine vs. placebo or oral olanzapine (53). The evidence of olanzapine as add-on treatment was based on two RCT, one evaluating the combination olanzapine-divalproex vs. divalproex monotherapy (54) and the other one comparing olanzapine + lithium/valproate vs. placebo + lithium/valproate (55), and one *post hoc* analysis of this second RCT (56). The combination of olanzapine with fluoxetine (OFC) was rated as '4' by the CINP (47) for inconclusive data for the manic component of mixed states. Despite this, the CINP graded OFC as the best choice in the presence of a full DSM-IV mixed episode (CINP fourth step recommendation).

Aripiprazole was recommended as a first-line choice in monotherapy by the BAP (I), by the WFSBP (3), for manic and depressive symptoms), by the CANMAT/ISBD (1) and in combination with MS by the RANZCP (II) and by the

CANMAT/ISBD with valproate (1). The CINP rated aripiprazole in monotherapy as '3'. The positive evidence for these recommendations was based on two RCT reported separate data for mixed patients (57, 58), on two RCT with a mixed sample of manic and mixed patients (59, 60), a negative acute study (61) and two underpowered RCTs (62, 63). As for the combination treatment, a RCT tested aripiprazole in combination/augmentation therapy in acute manic and DSM-IV mixed episodes but did not report separate data (64).

Paliperidone in monotherapy was a first-line choice for manic symptoms in acute mixed episodes by the WFSBP (3) on the basis of two different 3-week RCTs, the first one comparing efficacy in BD-I patients, including 171 mixed patients, of extended-release (ER) paliperidone with quetiapine and placebo (65). The second study compared three different dosages of ER-paliperidone (3 mg, 6 mg, and 12 mg) with placebo in patients with DSM-IV criteria for a manic or mixed episode (163 mixed episodes) (66). The CINP rated paliperidone as a second-line choice (3) for acute mixed episodes on the basis of the same studies. On the contrary, paliperidone in combination with lithium or valproate was not found to be superior to lithium or valproate monotherapy in a RCT including patients with a mixed index episode (67).

Other relatively new SGAs, such as *ziprasidone* and *asenapine*, were recommended for mania/hypomania with mixed features or manic mixed episodes but with conflicting RG among the guidelines. *Ziprasidone* was recommended as a first-line choice in combination with MS (II) by the RANZCP and as a second-line choice in monotherapy for manic and depressive symptoms (4) by the WFSBP, by the CINP (4), and the CANMAT/ISBD (2, for mixed mania and hypomania). This seems at odds with the fourth step recommendation in the clinical guidelines for the treatment of acute mania/hypomania in which the authors established that ziprasidone was between the two best choices in the presence of a full DSM-IV mixed episode. The use of ziprasidone in monotherapy was justified by a 3-week RCT (68) and a replication trial by Potkin and colleagues (69). Unfortunately, these studies did not report separated data for manic or mixed patients. A *post hoc* pooled analysis of these two RCT re-examined the data and showed improvement in both manic and depressive symptomatology (70).

Asenapine was a first-line choice in monotherapy according to the CANMAT/ISBD (1) and in combination with a MS (particularly valproate, CANMAT/ISBD 1) according to the RANZCP (II). It was rated as a second-line choice in monotherapy for the acute treatment of depressive symptoms (but not manic symptoms) of manic mixed episodes according to the CINP (3) and the WFSBP (4). The recommendations were based on a 3-week RCT vs. placebo and vs. olanzapine as active comparator (53), on three *post hoc* analyses (71–73) obtained using the pooled data of the previous RCT and an identical designed 3-week RCT (74) and from a 3-week RCT comparing asenapine 5 and 10 mg bid with placebo (108 of 367 mixed patients) (75). Although results were conflicting for the efficacy of asenapine on the manic symptoms of the acute manic mixed state, significant improvement in the Montgomery Asberg Depression Rating Scale (MADRS) with asenapine but not with olanzapine was found, with asenapine differencing from the placebo group more in those patients with higher severity of depression (73). In addition, a further *post hoc* analysis of two acute RCT studies (53, 76) examined a subgroup of 98 patients with a mixed episode, showing significant decreases in MADRS scores greater in the asenapine group than in the placebo group (77). A further study assessed the combination of asenapine with lithium or valproate vs. placebo, but no separate analysis for mixed patients has been supplied (78).

Quetiapine was recommended as a first-line treatment only in combination/augmentation treatment for depressive symptoms (3) and as a second-line treatment for manic symptoms (4) during a manic mixed episode according to the WFSBP. The evidence for these recommendations was based on (i) a RCT in hypomanic patients with mixed features reporting that adjunctive quetiapine is superior to adjunctive placebo in improving overall severity and depressive symptoms, but not (hypo)manic symptoms (79), (ii) a retrospective study of BD patients reporting that the proportion of mixed patients responding to quetiapine was 77% (80), and (iii) a case report of a patient with mixed BD with psychotic features not responding to the combination of valproate, olanzapine, and fluoxetine, who after the replacement of olanzapine by quetiapine improved in the manic and psychotic symptoms (81). There are four positive studies supporting the efficacy of quetiapine up to 800 mg/day for the treatment of acute mania in monotherapy (65, 82–84), but there was some concern about its efficacy against mixed episodes because of the following reasons: mixed patients were excluded (82, 83), a sub-analysis for quetiapine was not provided as it served only as an internal comparator (65) while in the 3-week RCT investigating extended-release quetiapine, quetiapine was not better than placebo for improving manic and depressive symptoms (84). A recent

study (85) evaluated the efficacy of quetiapine extended release vs. placebo as concomitant treatment to mood stabilizers in the control of subthreshold symptoms of BD but did not provide separate analysis for the mixed subgroup of patients.

The efficacy of *cariprazine* has been investigated in placebo-controlled studies (86–88) and in two pooled analyses (89, 90) reporting significant positive results for the mixed patients subgroup. Thus, the RG for cariprazine in monotherapy for the manic symptoms of an acute manic mixed episode is 4 (WFSBP).

Despite the good evidence for acute mania, *risperidone* did not reach high level of evidence in all the guidelines for the treatment of mixed manic states probably because of the risk of switch to depression and the limited number of mixed patients in the trials. The RANZCP recommended it as a first-line treatment only in combination with a MS (II) while both the CINP and the WFSBP recommended risperidone in monotherapy as a second-line treatment (CINP 3; WFSBP 4). Among the four RCT assessing the efficacy of risperidone 1–6 mg/day for the treatment of acute manic and mixed episodes (91–93), one risperidone monotherapy trial including mixed patients ($n = 9$) did not show improvement of manic symptoms vs. placebo (91) as well as the randomized and double-blind head-to-head comparison of risperidone vs. olanzapine (94) showed no significant differences in manic and depressive improvement. As for combination treatment, risperidone was compared with haloperidol or placebo, all in combination with lithium or valproate in mixed patients ($n = 97$), with no significant differences (95).

As for *clozapine*, the WFSBP task-force identified two small studies, a retrospective chart review examining clozapine in dysphoric manic patients as monotherapy or combined with lithium, valproate, or an AD (96) and an open-label study enrolling 10 adolescents with treatment-resistant manic/mixed episodes, prescribed with clozapine alone or in combination with a MS (97). In consideration of the issues existing with safety, the task-force recommended clozapine as a second-line treatment (4) for acute manic mixed episodes in monotherapy or combination therapy (MS only). Similarly, the BAP recommended clozapine in combination with lithium or anticonvulsants as a first-line treatment in treatment-resistant patients.

FGA, in particular *haloperidol*, has been studied in mixed patients mainly as an active comparator for SGA in combination or not with MS (95, 98). No difference was found between olanzapine and haloperidol in monotherapy in terms of rates of symptomatic remission (Young Mania Rating Scale-YMRS scores) while in the comparison with risperidone in combination therapy with a MS (lithium or valproate), haloperidol + MS was not different from improvement observed with placebo + MS, leading to a recommendation grade of 4 for haloperidol in monotherapy for an acute manic mixed episode (WFSBP).

As for MS, only *carbamazepine* in monotherapy was a second-line treatment for both manic and depressive symptoms during a manic mixed episode according to the WFSBP (C) and the CINP (3). The evidence for these recommendations was based on two RCT comparing the acute efficacy of extended-release carbamazepine vs. placebo (99, 100) with improvement for manic (100) or for depressive symptoms (99). To assess the reliability of these results, a combined analysis pooling the data from both trials was conducted ($n = 147$) and demonstrated significant improvement of both manic and depressive symptoms in mixed patients (101). Carbamazepine in acute combination treatment has never been tested in mixed patients.

Valproate in monotherapy was recommended as a second-line treatment according to the CINP (3) and to the WFSBP (4, for manic symptoms). Limited data concerning the efficacy of valproate in acute mixed mania exist even because sometimes subgroup analyses in mixed patients have either not been conducted or properly reported (102, 103). A *post hoc* analysis of a 3-week RCT (104) did not find any preferential effect for divalproex in classic vs. mixed manic patients (105). A small case series tested valproate in intravenous infusion in a very few sample of severely manic, mixed, or bipolar depressed patients (two manic, two mixed, one mixed with rapid cycling, two depressed) with improvement for the two mixed patients (106). No evidence exists for valproate in combination therapy for acute mixed states.

Lamotrigine in monotherapy has been recommended as a second-line treatment by the BAP (IV) probably on the basis of a possible extension to mixed patients of recommendation for manic patients. Nonetheless, no randomized controlled studies in manic mixed patients or subgroup analyses of studies in acute mania with lamotrigine have been reported.

Topiramate was rated as 5 (second-line) in monotherapy by the WFSBP. Topiramate has been tested in four RCTs in acute mania with negative results (107); hence, none of these RCT supplied a subgroup analysis for patients with mixed states. Evidence for topiramate in the treatment of acute mixed mania derived from one retrospective chart review (108), two open studies that used

topiramate as adjunctive therapy in patients refractory to other treatments (109, 110) and a retrospective study evaluating adjunctive topiramate in adolescents (111), reporting partial improvement in manic mixed patients.

Oxcarbazepine and *gabapentin* have been evaluated by the WFSBP and estimated as a second-line treatment in combination therapy (4). As for *oxcabazepine*, mixed patients with an unsatisfactory clinical response to lithium have been administered with add-on oxcarbazepine with good clinical response in five of six mixed patients (112). *Gabapentin* has been tested in monotherapy in a 8-weeks RCT in dysphoric mania (113) with superiority of gabapentin to carbamazepine in mania ratings and to lamotrigine in depression ratings as well as important shortcomings in design and reporting limited the reliability of the results. Gabapentin has been tested in five open-label studies as adjunctive treatment (114–118) with improvement in manic (114, 116, 117) or in depressive symptoms (115, 117, 118).

Lithium lacked of specific evidence for the treatment of acute manic mixed episodes. No difference in treatment efficacy between lithium and placebo was found in a retrospective analysis (105) of a randomized, double-blind study on depressive mania (104). Lithium has also been studied as an add-on treatment of different SGA vs. placebo, but there was no placebo comparison for the lithium treatment (55, 56, 67).

Electroconvulsive therapy (ECT) was considered as a second-line treatment (BAP IV, RANZCP III, WFSBP 4) for both depressive and manic symptoms of a manic mixed episode. The evidence for ECT was based on a case series suggest that ECT is effective in the treatment of acute mixed episodes (119–121), on a retrospective study on 20 manic-depressive mixed patients (122) and other observational studies (123–125). Even though there was no RCT evaluating the efficacy of ECT relative to other treatments in mixed affective states, ECT has been found to have reasonable evidence for its safe and effective use in manic mixed patients, particularly in those patients refractory to pharmacotherapy.

Finally, the treatments that the guidelines advised to avoid were AD monotherapy, lithium in monotherapy (CINP 5), antipsychotics in monotherapy, particularly asenapine for manic symptoms (evidence from *post hoc* analysis is negative for asenapine monotherapy to be effective against acute manic symptoms, WFSBP category E, CINP 5), paliperidone for depressive symptoms (WFSBP category E, CINP 5), quetiapine for both manic and depressive symptoms (WFSBP category E, CINP 5) and combination treatment of FGA (haloperidol, WFSBP category E, CINP 5), SGA (risperidone, WFSBP category E, CINP 5; paliperidone, WFSBP category E), or other treatment, that is, celecoxib (CINP 5).

Depression with mixed features or depressive mixed episodes. Even though depression with mixed features or depressive mixed episodes is already well-known conditions, they are relatively new diagnostic entities and only recently research on their specific treatment has been conducted and recommendation guidelines have been developed.

There are currently no psychotropic agents approved by FDA and EMA for the treatment of depression with mixed features. No MS is actually approved for use in depression of any kind except lamotrigine (43). In general, AD treatment in monotherapy should be avoided (39, 43).

SGAs are the only psychotropic agents that have been specifically tested for the treatment of depression with mixed features, but not all of them have demonstrated efficacy in bipolar depression. As a consequence, caution is needed when extrapolating recommendations from studies in bipolar depression for depression with mixed features (unipolar or bipolar).

Ziprasidone in monotherapy for acute depressive mixed episode was rated as a first-line treatment in the Stahl et al. guidelines (1) and by the WFSBP in combination with treatment as usual (3) but as a second-line treatment according to the CINP (4). The evidence for these recommendations was based on a 6-week, randomized, placebo-controlled trial on patients suffering from BDII or MDD during a MDE (126). Ziprasidone was added to the TAU and compared to placebo. Mixed BDII and MDD patients on ziprasidone presented higher response and remission rates, with more benefit in BDII than in MDD, and reduction in depressive symptoms but not in manic ones. A *post hoc* analysis of this study was conducted to assess other predictors of response, but no significant effect was found (126).

Olanzapine was rated as a first-line treatment both in monotherapy (RANZCP I, Stahl et al. guidelines 2) and in combination with MS (CINP 2, RANZCP II with valproate, Stahl et al. guidelines 2) or AD (RANZCP II, Stahl et al. guidelines 2 first-line with fluoxetine). Olanzapine monotherapy (WFSBP 4, CINP 3) or the combination olanzapine+fluoxetine (CINP 4, CANMAT/ISBD 2) was rated as a second-line treatment according to WFSBP, the CINP, and the CANMAT/ISBD. The evidence was conflicting and was based on a *post hoc* analysis (127) of a 8-week RCT on BD-I

patients during a depressive episode treated with placebo, olanzapine, or OFC (128). Compared to placebo, both olanzapine and OFC were efficacious treatments of bipolar depression with mixed features, with OFC being the most efficacious treatment. A pooled analysis (52) of this study, together with a second RCT on BDI patients with depression (129), was conducted. Olanzapine was significantly better than placebo in reducing depressive symptoms, irrespectively of the presence of concurrent manic symptoms.

Lurasidone was considered a first-line treatment in monotherapy or in combination by Stahl and colleagues and by the CANMAT/ISBD (1), and as a second-line treatment in monotherapy according to the WFSBP (4). Lurasidone was evaluated in the treatment of bipolar mixed depression with a placebo-controlled monotherapy RCT (130), a placebo-controlled combination RCT (131), and a second controlled combination treatment RCT enrolling MDD patients with mixed features in which lurasidone did not separate from placebo (132). A *post hoc* analysis of the monotherapy RCT was conducted on patients with mixed manic features (133), and treatment with lurasidone was associated with significantly greater reductions in MADRS scores with possible capabilities of lurasidone to prevent treatment emergent affective switch (TEAS). Lurasidone was the only compound to have been investigated for the treatment of MDE with MFS in the context of MDD. A randomized, double-blind, placebo-controlled study (134) and three *post hoc* analyses of the same RCT have been conducted specifically in MDD patients with mixed features. The first *post hoc* analysis (135) evaluated the efficacy of lurasidone in treating MDD with mixed features including irritability, with significant improvement at week 6 of MADRS score in both patients with and without irritability and in specific YMRS items (irritability and disruptive aggressiveness). The second *post hoc* analysis (136) evaluated the efficacy of lurasidone in treating patients with MDD with mixed features and mild and moderate-to-severe levels of anxiety, with significant changes in 6 weeks in MADRS total score for patients with both mild or moderate-to-severe anxiety and changes in HAM–A total score. The third *post hoc* analysis (137) found lurasidone to be effective in treating postmenopausal MDD patients with mixed features.

Even though quetiapine (even in the extended-release formulation), asenapine, aripiprazole, and cariprazine were considered a first-line treatment according to the RANZCP (quetiapine) and to the Stahl and colleagues' guidelines (1) in monotherapy and in combination with an AD (RANXCP II for quetiapine) or a MS (Stahl and colleagues' guidelines), and a second-line treatment according to the CINP (aripiprazole, asenapine CINP 3) and to the CANMAT/ISBD (3), the WFSBP did not find any suitable study on quetiapine, asenapine, aripiprazole, and cariprazine in acute depressive mixed episodes to rate the evidence.

The RANZCP and the Stahl and colleagues' guidelines proposed MS, particularly *valproate*, *lamotrigine,* and *lithium*, alone or in combination, as possible first-line treatment for acute depressive mixed states. *Carbamazepine* was rated as a second-line treatment by the CINP (3), by the Stahl and colleagues' guidelines, and by the WFSBP (4, monotherapy for depressive symptoms). Nonetheless, the WFSBP did not find any suitable study to rate the evidence for lithium, lamotrigine, and valproate. As for carbamazepine, no RCT exists on the treatment for acute depressive mixed states but a case series (138) of carbamazepine monotherapy in bipolar depression ($n = 9$) reported improvement of Hamilton Depression Rating Scale (HAMD) depressive symptoms.

ECT was recommended as a second-line treatment in combination with MS (WFSBP 4, Stahl and colleagues' guidelines 3) on the basis of subanalyses of observational studies. The Agitated-Irritable Mixed-Depression group in the study by Medda and colleagues (121) was found to have the greatest improvement from ECT (139).

Other recommended second-line treatments by Stahl and colleagues were the combination of MS or SGA with bupropion, SSRI, or MAOI.

Finally, *paliperidone* (CINP), *AD* in monotherapy (WFSBP, Stahl and colleagues' guidelines), *topiramate* (Sthal and colleagues guidelines), *risperidone, haloperidol,* and *celecoxib* in combination with MS (CINP), *carbamazepine + olanzapine, or risperidone* (Stahl and colleagues' guidelines) are not recommended treatments in acute depressive mixed states.

Maintenance treatment. MS and SGA were rated as efficacious treatment in the long-term management of mixed states.

Lithium, *valproate,* and *olanzapine* were the treatments that were considered as effective in the prevention of a new mixed episode after an acute manic or depressed index episode, with scant and conflicting evidence. Olanzapine and lithium were rated as a second-line treatment in preventing mixed recurrence according to the WFSBP (5) while the BAP rated lithium as a first-line treatment against mixed relapse. *Lithium* (WFSBP 5, BAP I) and *valproate* (WFSBP 3) were significantly associated with a reduced rate of admissions

because of a mixed episode in a big observational Swedish registry study (140). In a re-analysis (141) of an head-to head comparison RCT olanzapine vs. lithium (142), olanzapine had a significantly lower risk of symptomatic mixed episode relapse/recurrence than lithium. Valproate was the only compound rated as a first-line treatment in the prevention of a new mixed episode on the basis of the results of a meta-analysis (143) that includes a 20-month maintenance RCT comparing valproate and lithium without no placebo-arm (144) showing no statistical difference between valproate and lithium in preventing a mixed episode. The study was difficult to rate because it was evaluated *post hoc* in the meta-analysis and lithium might be not the ideal standard comparator. Negative evidence (E) was reported for aripiprazole (after a manic index episode), carbamazepine, lamotrigine, quetiapine in preventing a new mixed episode.

In the prevention of episodes of any polarity after a mixed index episode, *lithium* in monotherapy or in combination was considered a first-line treatment (BAP I, WFSBP 3) on the basis of the results of retrospective studies (145–148), maintenance RCT (149), and subanalysis of maintenance RCT (150). Nonetheless, valproate was found to be even more effective than lithium (RANZCP) in the prevention of new affective episodes in a *post hoc* analysis (151) on dysphoric mania ($n = 123$) of a 12-month maintenance study comparing valproate, lithium, and placebo (152). These results were at odds with those of an observational cohort study (146) with linkage of nationwide registers in which the overall rate of hospital admissions was significantly increased for valproate compared with lithium in patients with a mixed index episode. Because of this conflicting evidence, valproate was rated as E (negative evidence) according to the WFSBP and consequently not recommended in the prevention of episodes of any polarity. *Carbamazepine* was poorly studied as a maintenance treatment for patients with a mixed states, and the available evidence was difficult to rate because of limitations in the study design. In fact, the efficacy of carbamazepine extended-release as maintenance treatment was evaluated in bipolar patients during a manic or mixed episode but the data of the separate analysis for the mixed subgroup were only reported for depressive symptoms. Carbamazepine treatment maintained the significant decrease of depressive symptoms, but the evidence is not confirmative in the absence of reported numbers for relapses (153).

Olanzapine in monotherapy was recommended as a first-line treatment (CINP 2, WFSBP 3) in the prevention of any type of affective episodes after an acute mixed episode on the basis of a RCT for maintenance treatment comparing olanzapine vs. placebo (154) and its *post hoc* analysis (155). In fact, olanzapine-treated patients showed significantly lower rates of symptomatic relapse of any kind. No definite data are available for the combination with lithium or valproate as the only RCT conducted on olanzapine + MS did not report separate results for mixed patients (156). Even though the evidence was quite good, the second-line recommendation by the WFSBP was mainly because of profound concerns about weight gain and long-term metabolic effects of olanzapine in the long-term.

Quetiapine was considered as a first-line treatment both in monotherapy (WFSBP 3, for manic and for any type of episode prevention; CANMAT/ISBD 1) and in combination with lithium or valproate (WFSBP 2, CANMAT/ISBD 1, for manic, depressive, and any type of episode prevention). The evidence for these recommendations was based on a large relapse and recurrence prevention RCT (147) with a wide mixed patients subgroup ($n = 223$), on two identically designed RCT comparing quetiapine vs. placebo + lithium or valproate (157, 158), and a *post hoc* analysis of the mixed patients included in the two previous RCT that confirmed the efficacy of quetiapine in the long-term treatment (159).

As for *ziprasidone*, it was a second-line treatment for manic relapse in monotherapy (WFSBP 4) on the basis of a monotherapy (68) and a combination RCT (160).

Aripiprazole was recommended as a first-line strategy in the prevention of episodes of any polarity in combination treatment with MS (CINP 2). The WFSBP task-force rated aripiprazole as a second-line strategy for depressive recurrence in combination with lamotrigine (WFSBP 4) but reported negative evidence (E) for aripiprazole + MS (lithium or valproate) in the prevention of any episode. The evidence for these recommendations is based on a *post hoc* analysis (161) of a 52-week maintenance combination study of aripiprazole + MS vs. placebo (162) that found no significant advantage of aripiprazole for the group of mixed patients for time to any relapse, a small maintenance RCT, with no separate outcomes reported for mixed patients (163) and a *post hoc* interaction analysis of a 52-week RCT testing lamotrigine + aripiprazole vs. lamotrigine + placebo (164) showing that time to relapse to a depressive episode was significantly longer with the aripiprazole combination compared with the placebo. Data on the maintenance treatment of aripiprazole in monotherapy are not available.

Risperidone was recommended as a second-line treatment (WFSBP 4) in combination/augmentation therapy after a mixed index episode in preventing episodes of any polarity on the basis of two open-label studies in which risperidone added to lithium or valproate supplied evidence for acute efficacy maintained long-term (6 months) (165) and presented significant improvement of both manic and depressive symptoms over 24 weeks (166).

Even though little is known about the impact of acute *ECT* on the long-term outcome of bipolar patients, the WFSBP task-force recommends ECT as a second-line maintenance treatment in combination with a MS (WFSBP 4) on the basis of a case series (167), a prospective naturalistic study (168) and a naturalistic study on rapid-cycling patients unresponsive to prophylactic MS (169).

As for *lurasidone*, it was not possible to rate the evidence for the long-term treatment because in the three studies aimed at investigating the efficacy of lurasidone vs. placebo including mixed patients (170–172), no separate outcome has been reported for this group. A recent *post hoc* analysis evaluating remission and recovery associated with lurasidone in the treatment of MDD with mixed features (173) reported patients treated with lurasidone significantly achieved recovery compared to placebo after 6 weeks of treatment, but this study was not included in the considered guidelines.

The evidence for long-term treatment of AD was scant, and The International Society for Bipolar Disorders (ISBD) task-force discouraged the use of AD use in BD because of safety reasons (174). Stahl and colleagues underlined that a small minority of patients presenting a depressive episode with mixed features could improve with a long-term treatment that includes an AD, but only as an adjunct to MS.

Comparison of the different guidelines

As a general rule, all the guidelines included were created without any financial support from pharmaceutical companies and experts of the task-force were selected according to their expertise. Guidelines have been developed by multidisciplinary teams involving experts from different countries to facilitate their applicability around the world.

The BAP guidelines were at their third revision and the CANMAT guidelines at their 4th update, while the other guidelines included in this critical review were at their first edition.

The BAP guidelines, the RANZCP Mood Disorders CPG, the CINP-BD-2017, and the CANMAT guidelines were primarily aimed at providing recommendations for the treatment of BD or mood disorders in general while the WFSBP guidelines and the Stahl and colleagues' guidelines focused on mixed states or mixed features. The WFSBP had their primary scope on the acute and long-term treatment of manic or depressive mixed episodes in BDI disorder as categorized in DSM-IV and DSM-5 while the Stahl and colleagues' guidelines were developed to help in the recognition and management of a MDE with mixed features in the context of BD or MDD in reference to DSM-5 criteria. Stahl and colleagues' guidelines did not report separated treatment strategies for BD and MDD with MFS but simply referred to depression with mixed features or mixed depression.

Different aims corresponded to different methods. As a consequence, the guidelines differed in their methodology.

As for the literature search methodology, the articles included in each guideline varied according to the specific purpose of the different task-forces. The methodology of the BAP guidelines did not allow for a systematic review of all possible data from primary sources and publications identified up to December 2015. Similarly, the Stahl and colleagues' guidelines as well as the CANMAT/ISBD update 2018 did not provide a time limitation or information about the literature search. The RANZCP task-force did not report the time limitation of the literature search but assessed that the same search was repeated regularly between April 2013 and October 2015. The CINP guidelines have been developed following the PRISMA method, and a systematic search was conducted up to March 25, 2016. Finally, the WFSBP task-force conducted the original search on May 29, 2013, and it was updated on March 12, 2017.

The methodology of the definition of category of evidence and the recommendation grades varied across the included guidelines. The BAP guidelines were the most elaborated and used the GRADE approach to justify the quality standard of recommendations, including both RCT and observational studies to provide more objective and highly clinically relevant recommendations. On the contrary, the process used to gather and synthesize the evidence and the methods to formulate the recommendations in the Stahl and colleagues' guidelines, which were more clinical-expertise oriented than evidence-base oriented, was not well stated, as confirmed by the low-quality score of the AGREE II domain 3.

The first main distinction across guidelines came from the different weight given to *post hoc* analyses, as they play a prominent role in studies

including mixed patients. According to the WFSBP, when a *post hoc* analysis has been included *a priori* in the analyses plan and is sufficiently powered, a CE 'B' could be considered. On the contrary, the CINP college rated *post hoc* analyses as level 3 of the efficacy grading with discrepancies in the recommendation grades between the guidelines. No specific grading for *post hoc* analyses was provided by the other guidelines.

In addition, both the BAP and the WFSBP task forces decided to accept registry observational studies in their evidence categories to take in consideration the valuable information about the 'real-world' effectiveness and acceptance of treatment modalities that these studies could provide, with different grades of efficacy on the basis of the quality of the studies. The CANMAT/ISBD guidelines included health system administrative data but rated them as CE 3.

Another point is the importance given to meta-analyses. All the guidelines, WFSBP and CINP guidelines excluded, define the presence of positive results from meta-analyses as full evidence for the efficacy of a determined compound (not clear in the Stahl and colleagues' guidelines). Particularly, the CANMAT/ISBD task force differentiated the evidence from meta-analysis on the basis of the narrow or wide confidence intervals (CE 1 or 2 respectively). On the contrary, the WFSBP taskforce did not use the results of meta-analyses as evidence of the same level of the results from single RCT fulfilling inclusion criteria. Meta-analyses were only used in the case of existing negative studies to grade the evidence in the case of studies showing non-superiority to placebo or inferiority to comparator treatment. The members of the CINP college included meta-analyses in the evidence they graded but considered them as a second level of the efficacy grading, prioritizing good research-based evidence supported by at least 2 placebo-controlled studies of sufficient magnitude and good quality.

Clinical messages

According to the guidelines included in this critical review, the acute treatment of both depressive and manic/hypomanic mixed episodes is based on SGA. Lithium and valproate as well as SGA were found to be efficacious in the prevention of new affective episodes. The choice between the different compounds should be made on the basis of clinical issues that arise from these recommendations.

Particularly, recommendation grades (RG) for each compound have been generally derived from safety and tolerability aspects integrated with CE, with few exceptions. Indeed, the BAP, the Mood CPG, and the Sthal and colleagues' guidelines did not report a grading for safety and tolerability.

SGA were the psychotropic agents that have been generally considered as first-line choice in the treatment of acute mania/hypomania or depression with mixed features in all the guidelines. The compounds identified as SGA differed widely between them, mainly in terms of safety and long-term tolerability (175), particularly in the maintenance treatment, resulting in a downgrading of the RG, especially when making a distinction between RG 1 and 2 (i.e., olanzapine).

Another important clinical aspect in guiding the choice of maintenance therapy should be the polarity index of the different compounds (176). SGAs such as risperidone, aripiprazole, ziprasidone, olanzapine, quetiapine, and other compounds such as lithium have a polarity index superior to 1 which means that they are better preventing mania than depression. Only lamotrigine and lurasidone have a polarity index under 1 (and are, thus, better suited for patients with depressive predominant polarity) (177). These general considerations can get even more complicated when it comes to mixed states for the presence of intertwined opposite symptoms that may change the antimanic or depressive prophylactic efficacy. Pharmacotherapy of mixed states is challenging because antipsychotics used to treat manic symptoms, and AD could potentially deteriorate symptoms of the opposite polarity (13). According to the polarity index (177), lamotrigine and lurasidone might have a depressive preventive efficacy in BD maintenance treatment, but currently, the evidence is still lacking for the long-term treatment of mixed episodes. Only lithium, olanzapine, and quetiapine in monotherapy had robust evidence for the prevention of new depressive episodes in the guidelines included in this critical review. As a consequence, the prevention of depressive recurrence is still a challenging point, mainly because of the lack of evidence for the preventing effect of SGA, MS, and antiepileptic compounds.

The scarcity of researched treatment options is frequently associated with a clinical management that often relies on AD (178). The International Society for Bipolar Disorders (ISBD) Task-force Report on AD use in Bipolar Disorders (174) recommends avoiding AD use in BD patients with a history of past mania, hypomania, or mixed episodes emerging during previous AD treatment and that should be avoided in patients with high mood instability or with a history of rapid cycling. Despite this, there is still a wide use of AD in the real-world clinical psychiatry (179–181) despite the

weak evidence for the efficacy and safety of AD in BD. The EMBLEM study reported that more AD maintenance use was seen in patients with mixed episodes (179). The two main consequences in the use of AD in patients with mixed features are the risk of switching in mania and the risk of suicide. A recent *post hoc* analysis of the BRIDGE-II-MIX study (182) underlined that AD-induced hypomania/mania patients with MDD reported higher rates of treatment resistance, mood lability, and irritability following treatment with AD and were mainly represented in the groups of depressed patients with mixed features and among BD patients. As for the risk of suicide, several studies found an association of lifetime mixed episodes, higher rates of AD use, and increased risk of suicide behaviors (183–185). It is for this reason that the ISBD task-force recommended that AD in BD patients should be prescribed only as an adjunct to mood-stabilizing medications (174). As underlined by Stahl and colleagues, AD may protect from depressive recurrences in a small minority of patients with mixed features, both in bipolar and in unipolar patients (43, 186), especially if prescribed in combination with antimanic agents.

The idea is that MDE with mixed features should be viewed differently from unipolar MDE without mixed features in terms of natural history, clinical outcome, and treatment (5). Mixed features in MDD have been seen to be related to high recurrence (187) and other detrimental clinical correlates, such as higher risk of suicide (188), obesity (189), and borderline personality disorders comorbidity (190) in recent BRDGE-II-Mix *post hoc* analyses. Furthermore, nearly a quarter of patients suffering from MDD may convert to BD (191). According to the findings of two recent meta-analyses (191, 192), the transition from MDD to BD was predicted by clinical features such as family history of BD, earlier age of onset of depression, the presence of psychotic symptoms (191, 192), the number of depressive episodes, the resistance to AD, the severity of depression, the prevalence of chronic depression (192) and, interestingly, subthreshold manic symptoms during a MDE (191). Hence, the MFS may serve a clinically relevant role as a 'warning sign' for bipolarity, in spite of its limitations.

The fact that certain antipsychotics or MS should be given as first-line in the acute and long-term treatment of mixed MDE rather than AD monotherapy should lead to a paradigm shift in the 'safe' and 'comfortable' use of AD, preferring the more 'dangerous' and 'uncomfortable' compounds such as SGA and MS (193). Indeed, psychiatrists are called to choose between over-diagnosis of MDE with MFS better treated with SGA or missing the diagnosis of mixed symptoms and treating the patient with AD with consequent treatment resistance of harmful side-effects (suicide, switches into hypo/mania) (194). In line with this aspect, the most important virtue of the DSM-5 MFS could be the higher sensitivity than the DSM-IV-TR mixed episodes classification in the identification of the orthogonal aspects of suicidality (i.e., suicidal ideation, suicide attempts) (2). As mixed depressive episodes are three times more common in BDII compared to MDD, the possibility to apply the MFS even to BDII would allow a more accurate identification of suicidal tendencies (2, 9).

Finally, there is growing evidence suggesting that mixed symptoms commonly contribute to poor treatment response with implications of potentially less satisfactory response to treatment (195–197) (Level IV BAP). Clozapine in combination treatment with MS was found to be superior to TAU in treatment-resistant patients during a mixed manic episode. Even though ECT is often a neglected treatment option carrying the burden of unfavorable media portrayal and wrong general beliefs and thus frequently used as a last-resort-treatment for severe bipolar patients (178), it has been found to have reasonable evidence for its safe and effective use in manic mixed patients, particularly in those patients refractory to pharmacotherapy.

Methodological limitations

This critical review has limitations, mainly depending on the methodological issues of the included guidelines.

The guidelines included in this critical overview reported on the treatment of manic/hypomanic and depressive episodes with mixed features or mixed states, using different diagnostic criteria (DSM-IV or DSM-5) to define mixed symptoms.

All the guidelines included in this critical review lack of strength in the applicability domain, which evaluate the resource implications of applying the guideline, the barriers, and facilitators to implementation and the strategies to improve uptake (34). The guidelines included, except from the BAP guidelines, did not report about monitoring or auditing criteria; consequently, it will be impossible to rate improved outcomes for patients treated in accordance with these guidelines. Ideally, guidelines should evaluate the role of specific pharmacological interventions in the treatment of mixed states considering efficacy and real-world effectiveness (31) but the guidelines included did not report

about facilitators and barriers to their application or on the resource implications of the applicability of their recommendations.

Another common methodological flaw of the studies included in the guidelines considering treatment for mixed states was that the response of mixed patients to pharmacological agents had been extrapolated from *post hoc* or pooled analyses of RCT that have enrolled both pure and mixed manic patients, assuming a comparable response to treatment for both subgroups of patients (22).

Given the several criticisms arisen toward the different classifications of mixed states and mixed features in the different editions of the DSM, many researchers tried to provide alternative definitions and to adopt different criteria for diagnosis mixed presentations (198–201). As there is not a consensus regarding the definition of mixed states and because of the major concerns about the DSM-5 MFS, it is not surprising that there is a paucity of evidence examining treatment outcomes and mixed features have been assessed *post hoc* and with a cross-sectional design in the most recent literature (13). Indeed, only few of the RCTs included in the guidelines considered the DSM-5 MFS as the primary outcome of treatments for bipolar hypomanic, manic, and depressive episodes.

Another further major flaw of the literature is that mixed depressive patients are not usually reported in depression RCT (24). Furthermore, the evidence about the treatment of MDD with MFS is still scant and limited to lurasidone (134–137, 173). Accordingly, the guidelines included in this systematic review did not differentiate the treatment for MDE with MFS in the context of BD or MDD (43).

One of the most important limitations of guidelines is their excessive reliance on evidence-based data resulting from RCT, which bring important limits in their design such as poor generalizability of the results and the sponsor bias. Interestingly, only the BAP guidelines considered observational studies and independent trials. These studies have methodological limitations and lower internal validity than RCTs, but they are much more generalizable and may have less sponsor bias (36, 202). Indeed, a recent systematic review assessing the effectiveness of maintenance treatment of lithium vs. other mood stabilizers highlighted that RCTs are affected by methodological limitations, specifically in the case of comparative maintenance trials (202).

Few methodological limitations of the systematic review itself were worthy to be mentioned. In the attempt to be as rigorous as possible, the authors decided to consider as eligible only international guidelines resulting in only six guidelines meeting all the inclusion criteria, with the exclusion of national guidelines. Despite this, the scientific value derived by the international teams with experts from different countries of the included guidelines could insure their applicability around the world and not only on a national basis. Finally, as the quality methodology of the included guidelines was assessed with the AGREE II tool, the authors of this systematic review could not completely exclude that the findings may be influenced by the interpretation and ranking of the evidence by the two reviewers (NV and DHM). Nonetheless, the two reviewers successfully completed the training modules of the AGREE II tool and undertook independent appraisals for each of the included guidelines, warranting the rigor of the methodology of this systematic critical review and the reliability of its findings.

Future perspectives

From a diagnostic point of view, a dimensional approach defining the most parsimonious clinical model aimed at understanding the specificity of the relationship of mixed features within the context of bipolar vs. unipolar disorders is needed. The clinical presentations could be best characterized along a number of domains, in which cognition and energy play critical roles in mixed presentations in terms of attention, memory, motivation, drive, and behavioral activity that should be better understood and rated. Mood could also be assessed, with a focus on specific symptoms rather than symptom clusters or diagnostic syndromes, with a differentiation between spontaneous mixed states and those induced by treatment (13). Clinical mixed presentations should also be differentiated by other course and comorbid specifiers, such as anxious distress or atypical symptoms. In addition, clinicians should assess the clinical aspects of mixed presentations not only evaluating the single affective mixed episode but also trying to understand the longitudinal course of affective disorders presenting with mixed components.

A better understanding of the neurobiology of mixed states will be necessary to develop more effective treatments (203). Indeed, it is not completely clear which are the clinical characteristics of patients experiencing mixed features that can firmly predict treatment response or side-effects. Genetic and neurobiological research could help identifying new compounds, profiles of response, and safety/tolerability concerns in mixed patients in the perspective of a personalized pharmacological treatment for the different subtypes of mixed states.

Future research should try to overcome the limitations of the current inadequate amount of data on mixed states treatment (25). One of the most important problems in recommending treatments in mixed states is the lack of evidence for many compounds that could be possibly used in the acute and long-term treatment of mixed states (i.e., RCT on long-term treatment with asenapine, lurasidone, or lamotrigine in monotherapy for mixed patients). Clinical well-designed adequately powered double-blind placebo-controlled studies assessing the efficacy, safety, and tolerability of psychotropic agents in mania, hypomania, or depression with mixed features are needed. Compounds that are already known to be effective (i.e., olanzapine) as well as controversial options (i.e., carbamazepine, lamotrigine) deserve a better understanding. In addition, large observational studies are needed because of the possibility to identify 'real-world' clinical variables associated with the treatment of mixed states.

A specific focus should be the long-term treatment as it represents an often ignored but fundamental topic in the treatment of the mixed presentations. Particularly, many treatment options, including 'old' well-known medications such as carbamazepine, lamotrigine, or even relatively 'new' compounds such as asenapine, lurasidone, and paliperidone, have not been studied in depth in mixed patients the long-term.

As psychotherapies and psychoeducation are important and well documented techniques for improving compliance and resilience against mood changes in the treatment of bipolar disorder, their integrative role and established component of treatment should be better investigated in mixed affective presentations. Indeed, psychotherapeutic trials showed efficacy in bipolar depressive symptoms and in maintenance treatment, as add-on treatment to medication in both cases, but no psychotherapy has yet provided an alternative strategy for management of patients in acute manic phases (36). To the best of our knowledge, no study reported on psychotherapy in acute mixed patients so far. Only one study has been published on recurrence prevention of mixed episodes, with adjunctive psychoeducation that was found to be effective in delaying the time to a new mixed episode (204).

In conclusion, treatment guidelines are a useful tool to guide the management of acute and long-term treatment of affective mixed clinical presentations together with professional knowledge and clinical judgment, in the attempt to orientate clinical practice toward evidence base. In mixed states, despite their heterogeneity, all guidelines agree with interrupting an ongoing AD monotherapy and adding mood-stabilizing medications. Olanzapine might have the best evidence for the treatment of acute mixed hypo/manic or depressive states as well as maintenance treatment of mixed presentations in preventing new mixed episodes or affective episodes of any polarity. Aripiprazole and paliperidone in monotherapy seemed to be effective alternatives in the treatment of acute hypo/manic mixed states while lurasidone and ziprasidone (in combination) revealed as promising SGA substitutes in the treatment of acute depressive manifestations without the adverse effects load of olanzapine. As for the maintenance treatment, valproate was recommended in the prevention of new mixed episodes while lithium as well as combination treatment of quetiapine was rated as effective in preventing affective episodes of all polarities. Finally, clozapine and especially ECT are options to consider in treatment-resistant presentations. These findings should be kept with caution as the available evidence is still scant. For example, to support the superiority of olanzapine, large comparative RCTs should be conducted assessing its efficacy vs. other compounds and not only vs. placebo.

The problem of which guideline is better is a difficult one. The included guidelines showed high scientific standards and good methodologies with some differences between the guidelines mentioned in this critical review that could orientate the clinicians in the choice of which guideline to follow. According to methodological robustness, the quality of the BAP guidelines was undoubtedly the best, reflected by the highest AGREE II overall assessment rate among the included guidelines. Nonetheless, the treatment of mixed states could not be longer derived from the treatment of manic or depressive episodes in the context of bipolar disorder because of the new DSM-5 mixed features specifier which is also applicable to unipolar depression. In this sense, the WFSBP Guidelines for the Biological Treatment of Bipolar Disorders: Acute and Long-term Treatment of Mixed states in Bipolar Disorder represented the most focused guidelines on the treatment of mixed states, with the added value of a similarly good global quality. Conversely, the Stahl and colleagues' guidelines were the first one to address depression with DSM-5 mixed features, although concern was raised for the rigor of development and the overall assessment rate. The CANMAT/ISBD guidelines, finally, are the most recent and up-to-date. In clinical practice, treatment guidelines are a suitable framework to start thinking on the management strategy for a particular patient, but decisions need

always to be individualized in the growing context of personalized medicine.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Detailed search strategy.
Figure S1. PRISMA flow-chart.
Table S1. Grading of the categories of evidence.
Table S2. Operational definition of recommendation grades.
Table S3. List of excluded studies, with reasons.
Table S4. Comparison of the included guidelines: evidence of efficacy, not recommended treatments.
Table S5. Methodological quality assessment by the two independent reviewers.

DISCUSSION

General aspects

Bipolar disorder is a severe psychiatric disorder unfortunately associated with serious psychosocial consequences (Ballester et al., 2012; Látalová, 2009). Despite being less prevalent than depressive disorders, BD is a quite disabling illness particularly due to its severe outcomes such as increased risk for self-harming behaviors and legal problems (Ferrari et al., 2016).

Aggression is linked to violent crime and suicide in psychiatric and forensic populations (Sahlin et al., 2017). According to literature, the impulsive subtype of aggression is the most frequently motivating CB in BD, especially occurring during manic episodes (Siever, 2008). At the same time, impulsive aggression in mood disorders may be a reliable suicide risk marker as it seems specifically related to suicidal behaviors (Perroud et al., 2011). In addition, the combined risk of suicidality and criminality in BD was found to be substantially elevated (Webb et al., 2014).

These aggressive behaviors are clinically important due to the danger for the patient and others. They increase the burden of disease in general and also contribute to stigmatization (Látalová, 2009).

The present chapter presents and discusses the key findings of this doctoral thesis, particularly the clinical implications of hetero- and self-aggression in BD and their mutual association. The limitations of the studies are also discussed along with the unmet needs and the future implications for research on the topic.

Clinical implications of hetero-aggression in BD

Criminal behavior as a proxy of hetero-aggression and violence in BD was the focus of **Study I**. In the meta-analysis, that is to the best of our knowledge the first one providing a comprehensive quantitative assessment of the topic, the prevalence of VCB in BD individuals was lower than previous epidemiological studies, reporting rates ranging from 11% (Swanson et al., 1990) up to 25.34% (Pulay et al., 2008).

BD was not significantly associated with VCB compared to both general population controls or to patients with any psychiatric disorder. Interestingly, an increased risk for VCB in BD emerged when BD patients were compared to individuals suffering from depressive disorders. On the contrary, BD was less associated with VCB when BD was compared to psychotic disorders. This findings were in line with literature, with OR for incarceration as high as 1.34 in BD patients compared with MDD patients in an USA sample (Hawthorne et al., 2012) whilst in a Swedish case-control study, schizophrenia was a stronger predictor of violence than BD (Sariaslan et al., 2015). The first NESARC wave (2001-2002) (Pulay et al., 2008) returned similar information, with an OR for VCB in BD of 3.72 in BD-I and of 1.73 in MDD. Similar results are observed in European studies. In the Dunedin cohort study (Arseneault et al., 2000) the risks for court-convictions and/or self-reported violence were 2.1 in MDD, 3.5 in BD and 5.4 schizophrenia. The risk for re-offending VCB seemed to keep the same progression among diagnoses (2.06 in schizophrenia, 1.96 in BD and 1.41 in MDD) (Chang et al., 2015).

Some discrepancies had also been reported in literature for the comparison between depressive and bipolar disorder. In fact, the Swedish population studies reported a three-fold increase in the risk for VCB in MDD (Fazel et al., 2015) that was a little bit higher than the risk in BD (OR=2.6) (Fazel et al., 2010). Nonetheless, schizophrenia continued to be the psychiatric condition most frequently associated with VCB (OR=6.3) (Fazel and Grann, 2006).

In the meta-analysis (**Study I**), BD was significantly associated with VCB in cross-sectional surveys, in USA samples and in those studies assessing VCB through self-report information but in meta-regression analyses, no moderators have been identified to explain the association.

Neither comorbid disorders nor socio-demographic factors significantly moderated the risk of BD individuals to commit VCB. This is at odds with previous literature. For example, male sex, despite being a well-known risk factor for VCB in the general population (Sher and Rice, 2015) and in psychotic samples (Fazel et al., 2009), did not significantly moderate the association between BD and VCB. In previous literature, male BD patients more frequently reported a criminal history (Matejkowski et al., 2014) and presented higher risks for legal involvement (Christopher et al., 2012;

Friedman et al., 2005; Graz et al., 2009; McCabe et al., 2013; Webb et al., 2014) with a significant increased 6-fold rate of violent crimes than female BD patients, when absolute rates are taken into account (Graz et al., 2009). Nonetheless, female BD patients still have an increased risk of being charged with a legal offense than women in the general population, with a stronger increase compared to the one presented by male BD patients compared to men in the general populations (Fazel et al., 2010; Fazel and Grann, 2006; Friedman et al., 2005; McDermott et al., 2007; Quanbeck et al., 2004). Legal outcomes in female patients seem worse when taking into account a major risk factor for criminal acts such as SUD, and the effect is stronger than in male patients (Friedman et al., 2005; Robertson et al., 2014). Similarly, other studies reported that female inmates were significantly more likely than men to exhibit drug dependence and being arrested due to substance-related charges (McDermott et al., 2007). This underlines that the gender distribution of risk in BD patients might depend on different effects explained by multiple co-variables that might not strictly depend on the underlying psychiatric condition, namely BD.

Similarly, a strong relation between SUD and violence is often assumed (Fazel et al., 2009). In clinical practice this should represent a major concern, as it is well established that BD presents the highest lifetime prevalence rate of comorbid substance abuse among axis I disorders (Grande et al., 2016), with esteemed rates of 60.7% (Regier et al., 1990) up to more than 80% in poorly adherent patients (Murru et al., 2013). In **Study I,** SUD did not represent a moderator for the association between BD and VCB. This was probably related to the heterogeneity in the assessment of SUD across the included studies, with only few of them (Abram and Teplin, 1991; Alnıak et al., 2015; Shaffer et al., 2007) that separated recent from past SUD. Indeed, in the study by Alniak and colleagues (Alnıak et al., 2015) the rate of lifetime SUD (59%) was higher than the current rate (39%), but in the logistic regression model only patients with a current SUD were classified as violent (OR=2.881).

Nonetheless, it has been found that in BD, specific genetic influences unrelated to SUD and not associated with familiar factors (i.e. familiar criminal history), explained a fifth of the correlation with violent criminality (Sariaslan et al., 2015), meaning that intrinsic BD factors might explain the occurrence of VCB in BD patients. Indeed, in a case-linkage study (Daff and Thomas, 2014) analyzing the association between BD and criminal offense with a particular focus on comorbid SUD, the odds of violent

offending remained 2.49 times higher than in controls when BD patients with a comorbid SUD have been excluded.

In previous studies, legal involvement was more likely reported by patients during manic or mixed states (Quanbeck et al., 2005) and characterized by impulsive symptoms (Christopher et al., 2012). Indeed, impulsive aggression might more frequently occur in manic episodes (Siever, 2008). In a study conducted on a sample of 219 BD type I patients (190 in mania group, 29 in depression group) sentenced to compulsory psychiatric treatment after committing homicide (Yoon et al., 2012), planned homicides were mainly related to the depressive phases as well as altruistic motivation for homicide and presence of psychotic symptoms whilst the manic state was most frequently associated with affective impulsivity. A recent article (Alnıak et al., 2015) found increased levels of impulsivity in BD patients with criminal history and past incarcerations. Despite specific manic symptoms with a high impulsive component such as social indiscretions and reckless driving predicted criminal involvement in previous studies (Christopher et al., 2012; McCabe et al., 2013), in **Study I** mania was not a significant moderator of the association between VCB and BD probably because of the high heterogeneity of included studies.

Clinical implications of self-aggression in inmates suffering from mood disorders

In **Study II**, whose aim was to determine the prevalence of DSH in prisoners and to study clinical variables (i.e. mood disorders and BD) specifically related to this behavior, a history of DSH was not uncommon in the correctional setting, with a prevalence as high as 17.7% consistent with previous studies in which lifetime DSH in adult offenders ranged between 15% (Fotiadou et al., 2006) to 35% (Sakelliadis et al., 2010) in male prisoners. In male inmates, the percentages of lifetime SA reported in literature are quite similar, ranging between 12.9% (Mandelli et al., 2011) and14.5% (Sarchiapone et al., 2009).

DSH was associated with specific clinical variables in the prison population. Mood and psychotic but not anxiety disorders were predictors of DSH. It was independently associated with BPD but not antisocial PD. The misuse of multiple substances was

significantly related to DSH but no association was found with both lifetime physical abuse and psychiatric problems in the parents.

In particular, mood disorders were independently associated to DSH which was previously found to be associated with self-reported depressive symptoms (Mohino Justes et al., 2004) but not to a specific diagnosis of major depression, possibly due to limitations of previous literature. In fact, depressive symptoms have been frequently evaluated in forensic settings by means of self-reported rating questionnaires but not with an established assessment of mood disorders through validated structured diagnostic interviews (Mohino Justes et al., 2004).

Depression was found to be frequently correlated with SA among inmates (Fazel et al., 2008; Mandelli et al., 2011; Rivlin et al., 2010; Sarchiapone et al., 2009), and severity of depression was positively associated with the lethality and intent to die of suicide attempts (Kempton and Forehand, 1992; Lohner and Konrad, 2006). In consideration of the association between mood disorders and near-lethal SA in previous studies (Wool and Dooley, 1987) or DSH in **Study II**, greater attention should be paid to an early detection of these Axis I disorders, in order to intercept with a successful treatment plan a possible suffering patient before DSH or suicidal behaviors.

To the best of our knowledge this is the first study reporting the prevalence of inmates diagnosed with BD and presenting with DSH. One previous study aimed at evaluating the prevalence of severe mental illness and DSH in prison (Fotiadou et al., 2006), detected a total prevalence of BD as high as 7.5% in the total sample of inmates but did not report separated percentages of DSH among the inmates diagnosed with BD. Another study (Mohino Justes et al., 2004) assessed the differences in the rates of bipolar manic symptomatology (but not diagnosis) but found no difference between those who self-harmed and those who did not.

Clinical implications of the association between hetero- and self-aggression in bipolar disorder and mixed symptoms

Since the main objective of this doctoral thesis was to evaluate the psychiatric correlates of self- or hetero-aggression in the context of BD, particularly in those patients suffering from mood episodes with mixed features of the opposite pole, we think that the findings of **Study III** represent the best synthesis of this research line.

In this study, a multinational sample of 2,811 patients presenting a MDE have been evaluated and a prevalence as high as 14.2% of aggressive behaviors have been reported. More patients among those reporting hetero-aggression suffered from BD than MDD and among those with BD, almost one in five patients presented physical or verbal aggression during a MDE.

Several findings from **Study III** seem to support that the presence of aggressive behaviors during a MDE was associated with bipolarity such as the higher rates of family history of BD as well as a younger age at the first depressive episode, which represent the most relevant clinical indicators of unrecognized bipolarity in depressed patients (Angst et al., 2012, 2011, 2010; Benazzi and Akiskal, 2008).

Furthermore, the presence of aggression during a MDE was associated with a higher severity of manic and depressive episodes as assessed through both psychometric and clinical assessment and included higher rates of psychiatric comorbidities, more mood episodes, higher frequencies of lack of psychiatric treatment, greater impairment in global social/occupational functioning, more frequent psychotic symptoms and, particularly, higher rates of previous SA. Similar findings were reported in previous studies (Garno et al., 2008; Perroud et al., 2011; Popovic et al., 2015), showing that the presence of aggressive behaviors had a significant impact on the clinical outcome of the BD illness, with major implications in terms of management, prognosis and treatment strategies.

Interestingly, the presence of mixed features during the current MDE was significantly more common in those patients reporting aggression, in line with the results of a previous study which found that the dimension “Feel angry”, as assessed by the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) was the second most frequent bipolar dimension among the mixed depressive patients (Azorin et al., 2012). Previous studies found that the presence of DSM-5 mixed features at the index episode was also the most important risk factor for suicidality (Reinares et al., 2015; Solé et al., 2017).

Not surprisingly, the comorbidity with BPD and SUD increased the risk of aggression in depressed patients, as underlined in previous studies reporting that the presence of comorbid BPD could have an independent predictive value in determining trait aggression in patients with BD (Garno et al., 2008). It is worth noting that in the

present study aggression was not considered as a trait identifier but as a state mixed symptom in the context of an affective depressive episode, allowing for a possible differentiation from those aggressive traits associated to BPD.

In previous literature, the link between BD, BPD and SUD and aggression has been attributed to impulsivity (Garno et al., 2008; Swann et al., 2010). Impulsivity is also a key factor in self-directed aggression, meaning all forms of self-harm and suicidal behavior (Jiménez et al., 2016). In BD, it is unclear whether impulsivity is a marker of the bipolar illness itself or rather the result of neural damage due to repeated mood episodes or comorbid drug use (Bauer et al., 2015), but there seems to be a strong genetic component (Jiménez et al., 2014).

Nonetheless, in order to control for the possible bias of impulsivity-mediated components influencing the association between bipolarity and aggressive behaviors, we excluded the variable of BPD comorbidity from the second stepwise multivariate modeling procedure (the variable substance abuse yet resulted to not be significantly correlated with aggression in the first logistic regression).

Surprisingly, the presence of lifetime SA became significant when BPD comorbidity was excluded in the second model supporting our hypothesis of the association between hetero-aggression and self-aggressive behaviors. Indeed, the role of aggression in suicidal behaviors has been investigated in several studies. Higher levels of lifetime aggression have been found in BD patients with a history of SA compared with BD non-attempters (Oquendo et al., 2000) and aggressive traits, among other clinical factors, contribute to predict future suicidal behaviors both in depressed BD and MDD individuals (Oquendo et al., 2004).

Interestingly, the underpinning role played by impulsivity for suicidal tendencies in BD seemed to be mediated by aggression. In the previous study by Oquendo and colleagues (Oquendo et al., 2000), whilst levels of aggression differed among those BD patients with versus those without SA, attempters did not differ from non-attempters on lifetime impulsivity. Indeed, aggression was found to be a reliable predictor of suicide risk in BD and MDD patients not as a single trait but only in association with aggression (Carli et al., 2010; Mann et al., 2009; Perroud et al., 2011).

In another study aimed at evaluating the clinical implications of a history of previous VCB in BD patients (Swann et al., 2011), a criminal history was associated with more history of SA and manic predominant polarity. These patients presented increased impulsivity reflected by impaired response inhibition but not by questionnaires.

The link between suicidality and criminality has also been identified in a retrospective case-control study comparing a national Swedish BD cohort with a general population sample and unaffected siblings (Webb et al., 2014). In the BD sample, suicidality was more likely to be lethal and criminality more likely to be violent than in the general population. Unaffected siblings presented significantly higher risk for each adverse outcome than the general population, underlining a genetic derived component of aggression. Important predictors of subsequent criminality in BD patients were a personal history of attempted suicide or previous crime and parental factors such as parental suicide or violent/nonviolent crime. Interestingly, in both BD patients and unaffected siblings the risk of suicidality was greater than the risk of criminality.

Nonetheless, in **Study I** suicidal behaviors did not represent a significant moderator of the association between VCB and BD, probably due to the fact that only few of the articles included in the meta-analysis evaluated the presence of a history of SA (Webb et al., 2014).

In consideration of the association between mood disorders and DSH in **Study II** and between DSH and the risk of conviction for a violent offense in previous studies (Sahlin et al., 2017), we consider of paramount importance assessing both risk of violence and the risk of suicide and DSH among BD patients, both in the general population or in forensic settings.

As for the symptomatological presentations of co-existing mixed symptoms and other specific clinical features, in **Study IV** we assessed the psychopathological link between AL and MR and the clinical implications of the association with other mixed symptoms, particularly verbal or physical hetero-aggression. Surprisingly, verbal or physical aggression were inversely significantly associated with AL whilst risky behavior was inversely associated with MR. The presence of neither AL nor MR was related with the total number of lifetime SA. On the contrary, irritable mood and impulsivity were directly significantly associated with both AL and MR. It could be speculated that AL could be related with self- and hetero-aggression only through the

mediation of the underpinning role played by impulsivity and not directly. For example, in a cross-sectional study examining the association between impulsivity-like traits, emotional lability and physically aggressive behaviors among college students (Dvorak et al., 2013), the association between emotional lability and the likelihood of aggressive behaviors was moderated by two impulsivity-like traits: high negative urgency and low positive urgency. Nonetheless, this speculation should be tested in clinical research assessing AL, aggression and impulsivity not only as a trait but also as a state feature.

In conclusion, hetero- and self-aggression could represent a specific psychopathological dimension in both BD and MDD patients. Indeed, it could be speculated that their diathesis for acting on feelings of anger or suicidal ideation is suggested by a higher level of lifetime aggression and a pattern of repeated SA (Oquendo et al., 2000).

Treatment

On the basis of the findings of the studies included in the present doctoral thesis, we would like to underline the importance of ensuring an early diagnosis and a proper treatment and follow-up of BD patients in order to improve prognosis and avoid both self-harming behaviors and criminal involvement. Evidence-based treatments for BD exert an overall control over all symptoms dimensions, also encompassing the aggressive symptom dimension (Grunze et al., 2013; Nivoli et al., 2012, 2011).

Most of the symptoms related to an increased risk for criminal behavior or suicidal behaviors can be managed with proper evidence-based treatments, as shown in **Study V**, so that it is of key importance that adherence to treatment is especially enforced. Indeed, in the study including institutionalized inmates diagnosed with BD-I during a 7-month period in a U.S. correctional facility (Quanbeck et al., 2004), the majority of BD inmates (74.2%) were in a manic (n=35) or mixed (n=14) acute phase of illness at the time of arrest. Among those arrested during a manic episode, 60% were hospitalized within the month prior to arrest. Of these, 31.4% were discharged from an inpatient setting within the week prior to arrest. At the moment of arrest, only 21.2% of the inmates were attending follow-up visits at the community psychiatric services.

Also in **Study III**, those depressed patients presenting aggressive behaviors had lower rates of psychopharmacological treatment.

In **Study IV**, specific treatment strategies for aggression and suicidal behavior in mixed depressive episode have been reported. The fact that AD monotherapy could worsen suicidal tendencies or increase irritability/aggression in BD patients underlines the need for certain antipsychotics or mood stabilizers as first-line in the acute and long-term treatment of mixed MDE (Stahl et al., 2017, 2014).

Limitations

Study I has limitations. First, the considerable methodological heterogeneity across the included studies. Second, the exploratory nature of the meta-analysis has to be taken into account and negative findings should be carefully considered. Also, the generalizability of the findings should be limited due to the absence of studies proceeding from Asia, Africa and South America. Furthermore, a third of the included studies were cross-sectional, precluding causal inferences and limiting the deduction of the directionality between BD and VCB. Finally, excluding the risk of publication bias is not possible. Nonetheless, to the best of our knowledge, it was the first meta-analysis providing a comprehensive quantitative assessment of VCB and its components in individuals with BD.

In **Study II,** DSH was assessed through self-report, thus precluding causal inferences, data were drawn from a unique penitentiary institute and obtained from a purely male sample precluding generalizability to other prisons across different cultures or to female inmates. The instruments used for the evaluation of DSH (e.g. the DSHI) and SA (specific ASI-X items) were respectively a self-report questionnaire and a semi-structured interview, so data could be subject to potential self-report bias. Finally, the diagnostic assessment of antisocial PD in correctional settings was fraught with inherent limitations due to the possible overlapping of this diagnosis with factors associated with criminality (Fazel et al., 2016). The main strength of this work rests on the inclusion of a relatively large sample and on the use of validated measures which allowed the proper controlling of potential confounders in a specific setting that has been poorly investigated.

In the multicentric BRIDGE-II-MIX studies (**Study III and IV**), the first limitation was that the participating centers were not randomly selected, which may have led to a bias through the inclusion of psychiatrists with a particular interest in bipolar spectrum disorders. This may be seen, however, as a positive point, in the sense that some expertise is needed to detect past hypomania in MDE patients. Furthermore, rates of hetero-aggression, history of suicidal behavior, AL and MR were collected retrospectively, meaning that the definition of aggression, AL and MR relied just on retrospectively coded criteria and selected variables already collected in the dataset, rather than ad-hoc variables fetched using validated ratings. Nonetheless, one of the main strengths of the BRIDGE-II-MIX study is the inclusion of a large sample size and a wide range of care settings from eight countries across three continents.

Study V has limitations mainly depending on the methodological issues of the included guidelines. Indeed, the guidelines included in this critical overview reported on the treatment of manic/hypomanic and depressive episodes with mixed features or mixed states, using different diagnostic criteria (DSM-IV or DSM-5) to define mixed symptoms. Another common methodological flaw of the studies included in the guidelines considering treatment for mixed states was that the response of mixed patients to pharmacological agents had been extrapolated from post-hoc or pooled analyses of RCT that have enrolled both pure and mixed manic patients, assuming a comparable response to treatment for both subgroups of patients. In addition, since the quality methodology of the included guidelines was assessed with the AGREE II tool, the authors of this systematic review could not completely exclude that the findings may be influenced by the interpretation and ranking of the evidence by the two reviewers. Nonetheless, the two reviewers successfully completed the training modules of the AGREE II tool and undertook independent appraisals for each of the included guidelines, warranting the rigor of the methodology of this systematic critical review and the reliability of its findings. Finally, the authors decided to consider as eligible only international guidelines resulting in only six guidelines meeting all the inclusion criteria, with the exclusion of national guidelines. Despite this, the scientific value derived by the international teams with experts from different countries of the included guidelines could ensure their applicability around the world and not only on a national basis.

Worldwide, suicidality and criminality, with few exceptions, share common etiopathogenetic substrates and genetic background or could be triggered by similar internal/external events (Fountoulakis and Gonda, 2017).

Possible additional correlates for both VCB and suicidal tendencies should be considered in a political perspective. For example, the higher rates of suicide and homicide in the U.S. in comparison with other Countries could be explained with the differences in accessing firearms with important implications in terms of law enforcement and general public (Appelbaum, 2006; Mann et al., 2005).

Other studies explained the association between suicide and homicide in function of latitude and longitude (Van Lange et al., 2017; Voracek and Formann, 2004) or with genetic theories, such as the Finno-Ugric theory, suggesting a higher risk for suicide and homicide in a group of nations in central and north-east Europe of assumed similar ancestry, with common genetic factors explaining both the manifestations (Fountoulakis and Gonda, 2018).

Studies investigating subjects suffering from BD or presenting with impairment of impulse control, suicidal behavior or aggression have found similar results addressing the impaired central serotonergic activity (Schaffer et al., 2015). Recently, genetic influences unrelated to SUD were found to explain a fifth of the correlation with VCB in BD (Sariaslan et al., 2015), but implications for these findings are still to be ascertained. In the past, molecular components of the serotonergic system involved in either metabolism/turnover or receptor signaling have been identified as involved in aggression (Siever, 2008) so that their role as candidates for impulsive aggression in BD have been hypothesized, for example for the low expression variant of the monoamine oxidase A (MAOA) gene (Meyer-Lindenberg et al., 2006). Similarly, the frequency of a variant of the same MAOA gene has been found to be higher in men who attempted violently to their life (Courtet et al., 2005). A clinical explanation of this genetic basis was found in a sample of individuals who committed suicide (Dumais et al., 2005). The psychological autopsy found that violent method of suicide was associated with higher levels of lifetime aggression and impulsivity even after controlling for age, sex, substance disorders and major psychopathology (Dumais et al., 2005).

Endophenotypes, originally described as internal phenotypes mediating on the path between genes and the diseases that they moderate, have been investigated in suicidology in the attempt to aid the functional characterization of susceptibility genes implicated in the vulnerability to suicidal behavior. These represent heritable markers, state independent trait identifier with longitudinal stability representing less complex clues to genetic underpinnings of psychiatric diagnoses and behaviors (Kendler and Neale, 2010). Endophenotypes associated with vulnerability to suicidal behavior include impulsive/aggressive personality traits, disadvantageous decision making and serotonin dysfunction (Courtet et al., 2011). Similarly, the significant heterogeneity of the association between VCB and BD could be explained with the phenotypic variability of BD (ALDA, 2004) that should be studied at a genetic level, possibly through a mendelian randomization experiment (Burgess et al., 2015). Indeed, a common behavioral impulsive-aggressive endophenotype has been hypothesized (Turecki, 2005) but it is not yet known at which level trait identifiers could moderate state symptoms and clinical manifestations of BD.

It has been further speculated that impulsive-aggressive behaviors might be mediated by familiar lability to suicide and that stressful life events (Lopez-Castroman et al., 2014) as well as comorbid disorders (i.e. BPD and SUD) might play a role (Turecki, 2005). This impulsive-aggressive behavioral endophenotype resulted to be independent from the role of associated axis I psychopathology in previous literature (Perroud et al., 2011; Turecki, 2005) but this seemed not to be applicable to DSH in inmates as reported in **Study II.** Furthermore, it might explain only a relative component of violent criminality in BD since in **Study I** impulsivity was not a moderator of VCB in BD and we think that more complex neural, psychological and cognitive mechanisms might change aggression into violent criminality. Similarly, comorbid SUD and BPD might be entailed but not fully explain the association between self- and hetero-aggression in mood disorders as we underlined in **Study III**. In **Study IV**, an inverse association between aggression and AL, seen as mixed features of depressive episodes, was identified. Impulsivity, an important component in mixed mood presentations, was seen to correlate with both AL and self- and hetero-aggressive behaviors (Michaelis et al., 2004; Perroud et al., 2011), suggesting that these clinical variables could be integrated into models where interacting mixed features could represent both risk or protective factors for specific behavioral

outcomes. Nonetheless, it is still complicated to identify correctly the boundaries between the state or trait nature of these clinical features, particularly in the case of comorbid disorders.

Neuroimaging could further help in understanding the alterations associated with self- and hetero-aggression, which generally involve the dysfunction of prefrontal cortex in both suicide and violence, particularly the efficacy of orbital frontal/cingulated cortical processing involved in modulating and often suppressing the emergence of aggressive behaviors primarily by acting on serotonin 5-HT2 receptors in these regions (Courtet et al., 2011; Rosell and Siever, 2015; Siever, 2008). The same areas appeared to be altered in BD (Strakowski et al., 2012) but a consensus is still lacking for the neuroimaging aspects defining self- and hetero-aggression in BD. Disadvantageous decision making as well as the capability to recognize facial expression and to empathize with others' feelings have been studied in functional magnetic resonance imaging studies and seemed to play a role that should be further investigated (Demirel et al., 2014; Jollant et al., 2005).

Another hypothetical explanation for violence and aggression in BD was based on the phenomenon of "kindling" occurring when circuits subjected to repeated stimulation become sensitized to future stimulation, as in epilepsy and in the contexts of repeated episodes of bipolar illness (Rosell and Siever, 2015). The regions that are implicated in kindling are regions of the limbic cortex which might be implicated in impulsive aggression and responsive to the beneficial effects of anticonvulsants and lithium (Rosell and Siever, 2015).

Future perspectives and final remarks

In **Study I** the comparison between the included studies was difficult because of differences in the VCB classification systems with consequent high heterogeneity of the results of the meta-analysis. As a consequence, the identification of a worldwide accepted operational definition of VCB is needed.

Furthermore, well-defined and generalized risk-assessment indicators and outcomes of VCB, early identification of potential offenders and effectiveness of interventions are still lacking and represent possible subjects of future research. Similarly, clinical

variables already known to be important in both VCB and self-aggressive behavior should be tested, not only in psychiatric settings but also in forensic environment. For example, the model that resulted in **Study II** could be useful in predicting DSH in inmates and its efficacy should be further tested.

In terms of public health perspective, research focus should be switched from relative to absolute risk measured, i.e. population-attributable risk (PAF). Identifying the percentage of VCB that can be ascribed to BD would help reducing stigmatization (Varshney et al., 2016). Indeed, a recent umbrella review of meta-analyses of risk factors for interpersonal violence found that the highest PAFs for violence were substance misuse, being victim of violence in childhood and PD whilst BD and schizophrenia represented the lowest PAFs for violence (Fazel et al., 2018).

In addition, it is important to keep in mind that the most common victims of aggression in the context of BD are the patients themselves. This is worthy to note not only because BD is the mood disorder with the highest suicide rate (Vieta et al., 2018) but also because the association between BD and VCB should also be considered on the likelihood of BD patients to be victims of crimes. Violent victimization among psychiatric patients was observed more frequently than VCB (Choe et al., 2008). As patients victims of violence are more likely to engage in VCB and in suicidal behaviors (Latalova et al., 2014), avoidance of this potential, dangerous loop is warranted.

In terms of treatment, recent guidelines recommend the need for the early detection of aggressive behaviors in mood disorders (Garriga et al., 2016; Goodwin et al., 2016; Stahl et al., 2014) and for the management of DSH in clinical practice (Carter et al., 2016; Kendall et al., 2011; National Collaborating Centre for Mental Health, 2004).

Several reports suggest that a prompt therapeutic strategy should be considered to prevent aggression in those patients with higher risk factors, such as severe manic, psychotic symptoms and lifetime history of self-aggressive behaviors (Sahlin et al., 2017; Verdolini et al., 2017). The tendency towards manic relapses should be properly addressed (Samalin et al., 2016) as well as the depressive polarity to avoid self-injuries representing predictors of both criminality and suicide in BD (Sahlin et al., 2017; Verdolini et al., 2017; Webb et al., 2014). Taken together, these results claim for the need of an “anti-aggressive” treatment strategy in this subgroup of BD patients. Even

though AD could target the underlying serotonin dysfunction, AD monotherapy should be avoided and a combination treatment with mood stabilizers and/or antipsychotics, chosen on the basis of their pharmacodynamics and neurotransmitter profile, should be considered (Vieta, 2014).

Aggressive behaviors should be assessed in RCT and adequately researched as a specific treatment outcome of antipsychotics and mood stabilizers.

Clinical mixed presentations should also be differentiated by other course and comorbid specifiers, such as anxious distress, atypical symptoms or substance related disorders. In the light of the results of this doctoral thesis, the clinical aspects of mixed presentations should be assessed not only evaluating the single affective mixed episode but also trying to understand the longitudinal course of mood disorders presenting with mixed components.

Since psychotherapies and psycho-education are important and well documented techniques for improving compliance and resilience against mood changes in the treatment of BD, their integrative role and established component of treatment should be better investigated in aggressive clinical presentations.

Genetic and neurobiological research could help identifying new compounds, profiles of response and safety/tolerability concerns in BD patients presenting self- or hetero-aggressive behaviors in the perspective of a personalized pharmacological treatment. Indeed, the Research Domain Criteria (RDoC) approach to classification included among the others the dimensionally defined construct named “Frustrative Nonreward” which behavioral focus is on aggression. Cross-cutting mechanisms related to BD that might involve this and other constructs could help in better understanding the “aggressive” dimension of BD.

CONCLUSIONS

By means of this doctoral thesis, the PhD candidate and the research group contributed to a better understanding of the aggressive dimension in the context of BD, adding acknowledge to a line of research that, despite the obvious practical importance, has attracted relatively little attention in the literature.

The main conclusions obtained in the present doctoral thesis are:

1. One every fourteen patients suffering from bipolar disorder reported violent criminal behavior. Nonetheless, the association with violent criminality was not significant in comparison with the general population. Even though the association with violent criminality was not significant when patients suffering from bipolar disorder were compared with patients suffering from any other psychiatric disorder, the chance of committing violent criminal behavior was smaller in patients with bipolar disorder than in those suffering from psychotic disorders but higher in comparison with patients with depressive disorders. In meta-regression analyses, no significant moderators emerged. The identification of potential moderators of the association between bipolar disorder and violence should be the focus of further research.

2. Mood disorders as well as psychoses, borderline personality disorder and poly-drug use were the most relevant clinical predictors of deliberate self-harm in prison. Traumatic experiences and psychiatric family history were not directly related to deliberate self-harm, probably due to the mediation of the association represented by underpinning psychopathology. Consequently, the assessment of deliberate self-harm in psychiatric settings is important as it is both a strong indicator of clinically relevant psychiatric disorders and is associated with suicide attempts.

3. In the sample of affective patients evaluated during a major depressive episode, the presence of aggressive behaviors was mainly related with socio-demographic and clinical characteristics associated with bipolarity. The most relevant clinical variable associated with aggression was the presence of mixed features. After controlling for the possible confounding bias of impulsivity-mediated components

associated to the comorbidity with borderline personality disorder, a 1.4-fold increase of the risk for aggressive behaviors associated with the presence of lifetime suicide attempts has been observed.

4. In patients suffering from mixed depression, affective lability represents a depressive mixed feature that could help in targeting a tailored treatment strategy as it is positively correlated with the severity of mania, negatively correlated with the severity of depression and is strongly associated with mood reactivity and atypical depression. No correlation between affective lability and the total number of lifetime suicide attempts was found. Verbal or physical hetero-aggression during the index major depressive episode was inversely associated with the presence of affective lability.

5. Ensuring an early diagnosis, a proper treatment and follow-up for BD patients aimed at improving prognosis and avoiding both self-harming behaviors and criminal involvement is of paramount importance. The identification of self- and hetero-aggressive behaviors represents the target of a tailored treatment strategy in the subgroup of bipolar disorder patients characterized by a shared psychopathological "aggressive" dimension.

In conclusion, the self- and hetero-aggressive components of bipolar disorder have been investigated in this doctoral thesis, leading to a better and broader knowledge on the topic, both in psychiatric and in correctional settings. A sub-group of patients within those suffering from bipolar disorder have been identified, presenting specific clinical characteristics such as a mixed symptomatology and a possible worst prognostic course of illness, representing the goal of a tailored treatment focused particularly on the aggressive dimension of bipolar disorder.

RESUM EN CATALÀ

AUTO I HETEROAGGRESSIÓ:
Implicacions clíniques en Trastorn Bipolar i Estats Mixtos

INTRODUCCIÓ

El Trastorn Bipolar (BD per les sigles en anglès), és un trastorn de la personalitat caracteritzat per l'alternança o enllaç d'episodis de mania, hipomania y episodis depressius amb la presència de símptomes subclínics entre episodis (Grande et al., 2016). Aquesta presentació de BD es defineix per la coexistència de tres o més símptomes de depressió durant un episodi hipo/maníac, o pel contrari, de hipo/mania durant un episodi de depressió major (Solé et al., 2017).

El pronòstic és àmpliament variable i depèn de les característiques clíniques del BD (presencia de símptomes psicòtics, clicladors ràpids, nombre d'episodis, polaritat predominant) i de les comorbiditats psiquiàtriques (trastorns relacionats amb l'abús de substàncies i trastorns de la personalitat) o mèdiques (desordres metabòlics o cardiovasculars). Aproximadament el 30-40% dels episodis afectius majors que tenen lloc durant el transcurs d'un BD presenten característiques mixtes, el que suggereix l'existència d'un subgrup d'individus amb una malaltia de major complexitat i amb una taxa més elevada de comorbiditats psiquiàtriques i mèdiques (McIntyre et al., 2015).

L'agressió es defineix com un clar comportament relacionat amb un intent d'infligir un estímul nociu o un comportament destructiu cap a un altre organisme o objecte. En psiquiatria es considerada una resposta comportamental que pot ser autodirigida (Moyer, 1976). El concepte de "violència" implica, generalment, una agressió cap a humans i es considera tant la base del comportament criminal com la raó per la qual s'estigmatitzen les malalties mentals.

Les pitjors manifestacions de BD estan representades, per una banda per comportaments autoagressius anomenats autolesions deliberades (DSH per les sigles en anglès) com els intents de suïcidi o el suïcidi completat, i per l'altra, comportaments heteroagressius com els crims violents i no violents (Goodwin et al., 2016).

En el BD, el risc de criminalitat no és tan evident com ho pot ser el risc de suïcidi però els actes ofensius són inclús més comuns i s'associen amb un risc absolut més elevant. El risc de violència és més elevat en individus que s'autolesionen, i particularment en pacients amb BD (Sahlin et al., 2017). El suïcidi en BD està independentment associat amb variables clíniques, especialment amb els episodis DSH al llarg de la vida i amb la criminalitat (Webb et al., 2014), remarcant el possible paper neurobiològic de l'agressió en casos de BD amb un mal pronòstic. De fet, l'agressió es considera una característica central de gran importància en els estats maníacs i mixtos, independentment de la psicosi, i sovint pot aparèixer correlacionada amb l'abús de substàncies i el suïcidi (Maj et al., 2003). (Maj et al., 2003). Tot i això, encara no s'ha inclòs com un criteri diagnòstic específic per a la mania o les característiques mixtes en el Manual Diagnòstic i Estadístic dels Trastorns Mentals (DSM per les sigles en anglès) (American Psychiatric Association., 2013).

L'agressió s'associa amb crims violents i amb suïcidi en poblacions psiquiàtriques i forenses (Sahlin et al., 2017). D'acord amb la literatura, les agressions de subtipus impulsives són les que més freqüentment motiven el comportament criminal en el BD, especialment si tenen lloc durant episodis maníacs (Siever, 2008). En la mateixa línia, les agressions impulsives en els trastorns de la personalitat poden esdevenir un marcador fiable per al risc de suïcidi que podria estar especialment relacionat amb els comportaments suïcides (Perroud et al., 2011). A més a més, s'ha vist que el risc combinat de suïcidi i criminalitat en BD és especialment elevat (Webb et al., 2014).

Millorar la comprensió dels factors clínics associats tant al risc de presentar un comportament criminal com al risc de conductes autodestructives entre individus que pateixen BD hauria de ser un objectiu d'especial rellevància. Descriure els predictors clínics que sorgeixen durant el curs del BD, especialment quan hi ha una història prèvia de comportaments autodestructius o criminals, podria ajudar a millorar la gestió del risc d'auto i heteroagressió, i per tant, el pronòstic de la malaltia (Webb et al., 2014).

Com a conseqüència, és necessari millorar la recerca relacionada amb el comportament auto i heteroagressiu en el BD per a poder identificar subgrups de pacients, especialment els que pateixen de MFS, ja que presenten un pitjor pronòstic i podrien beneficiar-se d'un tractament personalitzat.

Amb l'objectiu de comprendre millor l'auto i heteroagressió en el BD, especialment en el subgrup de pacients que presenten característiques mixtes, proposem una nova línia d'estudi centrada en la identificació de les característiques clíniques específiques desencadenants dels comportaments agressius en el BD.

El primer pas ha sigut estudiar el comportament criminal com un marcador d'heteroagressió i violència en el BD. Per això es va avaluar quantitativament aquesta associació entre el comportament criminal i el BD tenint en compte diferents factors moduladors (per exemple, característiques clíniques i trastorns comòrbids), utilitzant una aproximació de metaanàlisi i metaregressió. Es va investigar sobre el risc de presentar un comportament criminal en el BD en comparació amb altres trastorns psiquiàtrics com depressió major (MDD per les sigles en anglès), esquizofrènia i altres psicosis, trastorns relacionats amb el consum d'alcohol o drogues, i trastorns de la personalitat. A data d'avui, aquesta és la primera revisió sistematitzada i la primera metaanàlisi amb una anàlisi quantitatiu del comportament criminal i violent, així com els seus components en pacients amb BD (**Estudi I**).

El segon pas va ser determinar la prevalença de DSH en població penitenciaria, ja que està menys estudiada, intentant establir l'associació entre el BD i les DSH en aquest àmbit (**Estudi II**). A més a més, es va intentar relacionar aquests resultats amb un tercer estudi (**Estudi III**) en el qual es realitzar una anàlisi post-hoc del estudi "Trastorns Bipolars: Estudi Multicèntric per a la millora en el Diagnòstic, Guia i Educació (BRIDGE)-II-MIX". Aquest estudi pretenia avaluar l'agressivitat com una característica mixta durant un episodi de depressió major i la seva relació amb el trastorn bipolar (BD) i altres variables clíniques com la història de vida i els intents de suïcidi.

L'**Estudi IV** va tenir com a objectiu establir el paper psicopatològic de la labilitat afectiva com a un possible símptoma mixt i un correlat clínic de les característiques atípiques de la depressió. Amb aquest objectiu es va realitzar una anàlisi post-hoc de l'estudi BRIDGE-II-MIX centrat en la rellevància clínica de l'associació interrelacionada de la labilitat afectiva i la reactivitat de l'estat d'ànim i la seva correlació amb altres símptomes mixtos, particularment l'heteroagressió física o verbal.

Per últim en un cinquè i, en base als resultats d'aquests quatre estudis que han permès establir les possibles implicacions clíniques i de tractament de l'agressió en els estats mixtos del BD, es va decidir abordar la necessitat de millorar les indicacions clíniques actuals per al tractament dels estats mixtos. Per això, s'ha desenvolupat el protocol PROSPERO per tal de procedir amb una revisió crítica sistematitzada de les evidències existents i una guia resum per al tractament dels estats mixtos aportant consells per a la gestió i el tractament específic dels aquests símptomes i característiques clíniques associades com la auto i heteroagressió en la pràctica clínica diària (**Estudi V**).

OBJECTIUS I HIPÒTESIS

Objectiu

L'objectiu principal d'aquesta tesi doctoral ha sigut el avaluar els correlats psiquiàtrics de l'auto i heteroagressivitat en el trastorn bipolar i, especialment, en aquells pacients que presenten episodis afectius amb característiques mixtes del pol contrari.

Objectius primaris

1. Establir la prevalença del comportament criminal considerat com un marcador d'heteroagressió i violència en el trastorn bipolar, així com els moderadors d'una possible associació entre el trastorn bipolar i el comportament criminal (**Estudi I**).

2. Determinar la prevalença de les autolesions deliberades en presos, així com estudiar les variables clíniques (per exemple, el diagnòstic de trastorn afectiu i trastorn bipolar) relacionades específicament amb la presència d'aquestes autolesions deliberades en presos (**Estudi II**).

3. Abordar la relació entre la presència de comportaments agressius durant el transcurs d'un episodi de depressió major amb característiques mixtes en el contexts del trastorn bipolar, tenint en compte característiques clíniques com els intents de suïcidi previs (**Estudi III**).

4. Investigar la relació psicopatològica entre la labilitat afectiva i la reactivitat del estat d'ànim, així com les implicacions clíniques d'aquesta associació amb altres símptomes mixtos particularment l'heteroagressió verbal o física (**Estudi IV**).

5. Agrupar aquestes evidències disponibles en un compendi crític, oferint una revisió exhaustiva de les pautes més recents en el tractament dels estats i símptomes mixtos, incloent aspectes clínics més complexes com l'auto i l'heteroagressió (**Estudi V**).

Objectius secundaris

1. Investigar el risc de presentar u comportament criminal en el trastorns bipolar en comparació amb altres trastorns psiquiàtrics com la depressió major, la esquizofrènia o altres psicosis, trastorns relacionats amb el consum d'alcohol o drogues i trastorns de la personalitat (**Estudi I**)

2. Avaluar les variables clíniques diferents dels trastorns afectius que poden predir la presència de autolesions deliberades en població penitenciària (**Estudi II**).

3. Identificar si la presència de conductes agressives pot esdevenir un indicador clínic de diagnòstic en els pacients amb depressió bipolar mixtos (**Estudi III**).

Hipótesis

1. Els trastorns psiquiàtrics s'han estudiat com possibles factors de risc de comportaments criminals violents amb un major risc d'heteroagressió i violència en poblacions psiquiàtriques. Estudis previs han intentat agrupar aquestes evidències de l'associació entre la violència i el trastorn bipolar amb resultats contradictoris i limitacions metodològiques. *Hipotetitzem que els pacients amb un trastorn bipolar presentaran una major prevalença de comportament criminal en comparació amb la població general, presentant un patró identificable de possibles factors de risc com la presència de símptomes maníacs, trastorns relacionats amb l'abús de substàncies comòrbids* **(Estudi I)**.

2. *Hipotetitzem que el risc de violència en trastorn bipolar serà més elevat en relació a altres condicions psiquiàtriques com l'ansietat i els trastorns depressius. Pel contrari, el risc de violència en trastorn bipolar serà menor en comparació amb l'esquizofrènia o altres trastorns psicòtics* **(Estudi I)**.

3. Igual que en la població general i en altres cohorts psiquiàtriques, *els comportaments autoagressius com l'autolesió deliberada, no es distribuiran de forma*

homogènia en les poblacions de reclusos, mostrant una associació amb factors sociodemogràfics i clínics concrets com els trastorns de l'estat d'ànim i de la personalitat **(Estudi II)**.

4. Com que l'hetero i l'autoagressió semblen estar relacionades amb comportaments disfuncionals, *postulem que els pacients amb trastorns del comportament podran presentar taxes més elevades d'heteroagressió associades amb comportaments autoagressius com història prèvia d'intents de suïcidi* **(Estudi III)**.

5. *Hipotetitzem que els comportaments heteroagressius es presentaran de forma diferencial en pacients amb trastorns afectius depenent de la fase específica de la malaltia. Concretament, en episodis maníacs o en pacients que presenten un episodi depressiu amb característiques mixtos del pol oposat. Aquests pacients presentaran un major risc que els pacients amb un trastorn depressiu, independentment dels trastorns comòrbids com el trastorn límit de la personalitat (BPD per les sigles en anglès) o els trastorns relacionats amb l'abús de substàncies (SUD per les sigles en anglès)* (**Estudi I** i **III**).

6. Altres característiques clíniques d'un episodi mixt, com la labilitat afectiva, poden estar correlacionades amb l'auto i heteroagressió. De manera especial, la labilitat afectiva pot disminuir els costosos recursos de control d'impulsos que regulen la intensitat de les fluctuacions emocionals. *Postulem que els pacients depressius mixtos que presenten emocions làbils seran més vulnerables a patir comportaments auto i heteroagressius* (**Estudi IV**).

7. *Establint un bon tractament farmacològic i psicològic, personalitzat del comportament agressiu dels trastorns bipolars, que garanteixi una bona gestió i seguiment en els pacients externs de les unitats de salut mental, permetrà avançar en els esforços dirigits a la reducció del risc d'agressió en els trastorns bipolar* (**Estudi I, II, III** i **V**).

MATERIALS I MÈTODES

Estudi I: *Comportament criminal en els trastorns bipolars*

Disseny del estudi: revisió sistematitzada i metaanàlisis

Criteris d'inclusió: es van incloure els articles originals revisats pel sistema de revisió per parelles publicats en qualsevol llengua si complien els següents criteris: estudis observacionals; més del 95% de la mostra de participants amb més de 18 anys, avaluació de CB o de comportament violent (mitjançant instruments d'autoavaluació en entrevistes epidemiològiques a gran escala); un diagnòstic de BD establert d'acord el ICD i/o els criteris del DSM, estudis que presentaven dades de prevalença de VCB en BD o de l'associació entre VCB i BD.

Anàlisi estadístic: una metaanàlisi d'efectes aleatoris va estimar la prevalença de VCB en BD. La mida del efecte (ES per les sigles en anglès) per a les mesures d'associació es va estimar com una OR i un IC del 95%. Els estimadors es van calcular per separat considerant la població general com a controls sense trastorns psiquiàtrics, o controls de qualsevol altre trastorn psiquiàtric que no fos BD. L'heterogeneïtat entre els estudis es va avaluar amb la Q de Cochran (Bowden et al., 2011). Las anàlisis de metaregressió es van realitzar quan estaven disponibles les dades d'almenys cinc conjunts de dades independents. Totes las anàlisis es van realitzar amb el programa STATA MP versió 14.0 ("Stata MP software version 14.0, Stata Corp, College Station, TX, USA," 2018) utilitzant el paquet metan. El nivell alfa de significació estadística es va establir en .05.

Estudi II: *Autolesió deliberada en presos*

Disseny del estudi: estudi transversal

Mida de la mostra: la mostra incloïa 526 reclusos, dels quals 93 (17.7%) van informar d'almenys un comportament DSH al llarg de la vida.

Criteris d'inclusió/exclusió i procediments del estudi: es van considerar com a possibles candidats els presos homes majors de 18 anys una avaluació psiquiàtrica completa. Els entrevistadors es van entrenar específicament per poder discriminar entre un intent de suïcidi (SA) i DSH.

Anàlisi estadístic: es va derivar una variable dicotòmica de DSH quan els presos contestaven afirmativament en alguns dels primers 16 ítems de la escala DSHI. Es van realitzar una anàlisi bivariant mitjançant Chi-quadrat, T-test de mostres independents o

test de Mann-Whitney en funció del tipus de distribució de la variable. Mitjançant correlacions parcials es va poder avaluar la relació entre el nombre de SA i el nombre d'episodis de DSH a la vida després d'ajustar per la variable edat. Finalment es va realitzar una anàlisi de regressió logística jeràrquica. La fiabilitat del model per detectar DSH en presos es va explorar amb una anàlisi receiver operating characteristic (ROC).

***Estudi III**: anàlisis post-hoc de l'agressió en l'estudi BRIDGE-II-MIX*

Disseny de l'estudi: anàlisi post-hoc de l'agressió en l'estudi BRIDGE-II-MIX. Es tracta d'un estudi multicèntric, internacional, no intervencionista i transversal per determinar la prevalença d'estats mixtos depressius.

Mida de mostra: Un total de 2.811 pacients amb MDE van acordar participar en l'estudi i representen la població total amb la qual es van realitzar els anàlisis. D'entre aquests pacients, 399 (14.2%) van presentar agressions verbals o físiques durant l'índex MDE.

Criteri d'inclusió/exclusió i metodologia del estudi: per a l'estudi BRIDGE-II-MIX, es van incloure pacients adults de 18 anys o més que van demanar consulta per la presència d'un MDE durant els tres mesos que va durar el reclutament. Per a la anàlisi post-hoc es va utilitzar una definició operacional i clínica d'agressió, definida per la presencia de al menys un dels següents comportaments durant l'índex MDE: 1. Agressió Física (PHY per les sigles en anglès): a. amenaçar alguna vegada, o b. colpejar persones, o c. ficar-se en baralles més que la majoria de persones, o d. enfadar-se tant com per trencar objectes. 2. Agressió Verbal (VER per les sigles en anglès): a. barallar-se molt amb altres persones, o b. no poder evitar discutir quan les persones estan en desacord, o c. enfadar-se molt sense cap raó específica amb dificultats d'autocontrol.

Anàlisis estadístics: es van utilitzar els tests Chi-quadrat i Student T-test per a la comparació entre grups en funció del tipus de variable. Per explorar l'associació entre variables clíniques i conductes agressives, i es va construir un model de regressió logística múltiple amb un procediment de modelació per pasos (stepwise backward logistic regression).

***Estudi IV**: Anàlisi post-hoc de l'estudi BRIDGE-II-MIX sobre l'associació entrellaçada entre la labilitat afectiva i la reactivitat de l'estat d'ànim*

Disseny del estudi: es va realitzar una anàlisi post-hoc del estudi BRIDGE-II-MIX investigant la construcció psicopatològica de la labilitat afectiva (AL per les seves sigles en anglès) en depressió unipolar i bipolar i els seus correlats clínics, avaluant les característiques específiques dels pacients "amb" o MDE-AL o pacients "sense" o MDE-no AL. Les implicacions clíniques de l'associació entre AL i les característiques atípiques de la depressió, especialment la reactivitat de l'estat d'ànim (MR) també es va avaluar.

Mida de la mostra: la mostra definitiva per la anàlisi post-hoc estava composada per 2577 pacients, dels quals 697 pacients (26.9%) presentaven AL (grup MDE-AL) i 1035 (40.2%) presentava MR (grup MDE-MR).

Procediments del estudi: La definició clínica operacional que es va adoptar definia AL com un estat caracteritzat per canvis marcats i ràpids entre diferents estats afectius en resposta a estímuls ambientals positius o negatius, i amb posteriors influències sobre el comportament. AL es va diferenciar de MR, d'acord amb la definició del DSM-5, com una variació del estat anímic en pacients depressius després d'estímuls únicament positius (American Psychiatric Association., 2013).

Anàlisi estadístic: es va utilitzar el test de Chi-quadrat i Student T-test per la comparació entre grups de variables categòriques i contínues respectivament. Un model de regressió logística per pasos a la inversa es va utilitzar per identificar l'associació entre AL i variables significatives resultants dels anàlisis bivariants. Posteriorment, es va utilitzar un model de regressió logística per diferenciar MR respecte AL. Per últim, amb l'objectiu de avaluar l'associació entre AL o MR i els 14 símptomes mixtos dels criteris diagnòstics de depressió basats en la recerca, es van utilitzar dos models de regressió logística més.

***Estudi V**: Revisió sistemàtica i valoració qualitativa de les guies clíniques sobre estats mixtos en trastorno bipolar i depressió major*

Disseny del estudi: revisió sistematitzada de la literatura amb avaluació metodològica i qualitativa de les pautes incloses.

Procediments de l'estudi: el protocol del estudi es va registrar amb PROSPERO i va ser publicat prèviament (CRD42018078199). Els procediments sistematitzats van seguir l'informe *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (Moher et al., 2009).

Estratègies de búsqueda i criteris d'inclusió: es va realitzar una cerca de guies per al tractament d'episodis mixtos, maníacs/hipomaníacs (en BDI, BDII i BD-NOS) o d'episodis depressius (en BDI, BDII, BD-NOS i MDD) amb característiques mixtes publicades en qualsevol llengua en les bases de dades de MEDLINE/PubMed i EMBASE fins al 21 de març de 2018.

Procediments del estudi: es van extreure les recomanacions de tractament, tant dels tractaments aguts com crònics, i es van especificar les opcions per a les polaritats depressives o maníaques dels episodis o característiques mixtos.

La qualitat de les guies incloses es van avaluar metodològicament mitjançant l'eina Appraisal of Guidelines for Research and Evaluation (AGREE) II (Brouwers et al., 2010), dissenyada per a proveir un marc avaluador de la qualitat de les guies.

En l'**Estudi II, III i IV** tots els valors *p* eren bilaterals i el nivell de significació estadística es va establir en $p<0.05$. Las anàlisis estadístiques es van realitzar utilitzant el *Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS*, versió 23.0 per a Windows Inc., Chicago, IL, USA)

RESULTATS

S'han inclòs dotze articles en la metaanàlisi avaluant VCB en el BD (**Estudi I**) amb dades de 9,020,778 participants, dels quals 58,475 eren pacients amb BD, 8,962,303 eren controls de la població general i 231,587 eren pacients amb un antre trastorn psiquiàtric. Els participants que presentaven VCB eren un total de 91,387.

La prevalença de VCB en individus amb BD era de 7,1% (95% IC, 3.0-16.5; k=4). L'associació entre BD i VCB no era significativa OR=2.784; 95% IC, 0.687–11.287, p=.152). En las anàlisis de metraregressió, l'associació entre BD i VCB era significativa únicament en els estudis transversals (k=4), estudis en els que la VCB es va avaluarmitjançant mesures autoinformades, i en estudis realitzats en els Estats Units d'Amèrica (EUA). No es van obtenir efectes moderadors significatius.

Per que respecta a les autolesions, en el **Estudi II** el 17.7% del total de la mostra de presos van reconèixer haver patit al menys un comportament DSH a la vida.

Els pacients que presentaven un comportament DSH al llarg de la vida van ser diagnosticats de manera més freqüent amb un diagnosi d'Axis I, a excepció dels trastorns d'adaptació. En relació als trastorns afectius, es va veure que del total de presos amb DSH el 28% presentaven a aquest tipus de diagnòstics (6.5% presentaven BD, 16.1% trastorns depressius i 5.4% trastorns afectius no especificats).

En el model jeràrquic de regressió múltiple, el DSH es va associar de manera independent amb la presència d'un trastorn psicòtic vigent (aOR=6.227, p=0.001), el BPD (aOR=6.004, p<0.001), les desordres afectius (aOR=2.856, p=0.006) i amb l'abús de múltiples substàncies (aOR=2.024, p=0.021).

Respecte a la mostra de pacients amb un diagnòstic de MDE, el 14,2% del total de la mostra presentava agressivitat verbal o física durant l'índex MDE (**Estudi III**). Els pacients que presentaven aquesta agressivitat verbal o física en el moment de l'avaluació psiquiàtrica eren diagnosticats de manera més freqüent amb BD, en concret de BD-I no de BD-II, mentre que la presencia d'agressivitat s'associava negativament amb el diagnòstic de depressió unipolar (p<0.001). L'índex de MDE presentava de manera més habitual característiques mixtes en aquells pacients amb agressivitat verbal o física.

En el model de regressió, una presentació depressiva mixta era la variable clínica que s'associava de manera més marcada amb l'agressivitat (OR=3.8). Les altres variables clíniques associades amb l'agressivitat eren la severitat de la mania, el diagnòstic de BD, la comorbiditat amb el BPD però no amb el d'abús de substàncies, la presència d'un tractament psiquiàtric vigent, la presència de simptomatologia psicòtica i un

marcat deteriorament en el funcionament social /ocupacional. L'edat de debut del primer episodi depressiu es va associar significativament amb l'agressivitat però, amb un patró negatiu. En el model de regressió logística, la presencia d'intents de suïcidi al llarg de la vida es va associar amb la bipolaritat per si mateixa, independentment dels trastorns dels trastorns comòrbids com el PD límit o l'abús de substàncies.

En l'**Estudi IV**, la mateixa població de pacients patint un MDE vigent es va estudiar per determinar la rellevància clínica de l'associació interrelacionada entre AL i MR, i la seva correlació amb altres símptomes mixtos, especialment la heteroagressió verbal o física. L'estat d'ànim irritable, taquipsíquia, logorrea, pèrdua d'atenció i impulsivitat es van associar de manera directa i significativa tant amb AL com amb MR. Mentre que l'eufòria es va associar de manera directa amb AL, i l'agressió verbal o física es va associar de manera inversa amb AL, la presència d'un comportament de risc es va relacionar de manera inversa amb MR.

De la mateixa manera que les estratègies de tractament, l'**Estudi V** va remarcar l'associació entre la presència d'episodis mixtos al llarg de la vida, les taxes més elevades d'ús d'AD i l'increment en el risc de comportaments suïcides (Baldessarini et al., 2012b; Pacchiarotti et al., 2011; Valentí et al., 2011). Per aquesta raó, només els pacients amb BD amb tractament AD haurien de tenir una prescripció complementària de fàrmacs estabilitzadors del estat anímic (Pacchiarotti et al., 2013a). Pel que respecta a l'agressió en un episodi depressiu mixt, la lurasidona va ser l'únic component que es va investigar per al tractament de MDE amb MFS en el context de MDD amb resultats prometedors en termes d'eficàcia, seguretat i tolerància.

DISCUSSIÓ

L'**Estudi I** es va centrar en el comportament criminal com a marcador de la heteroaggressió i violència en BD. La metaanàlisi presentada en aquesta tesi, que a data d'avui ens consta com la primera en proporcionar un avaluació quantitativa exhaustiva d'aquest tema, evidencia que la prevalença de VCB en individus amb BD era més baixa que l'estimada en estudis epidemiològics anteriors que presentaven taxes que anaven del 11% (Swanson et al., 1990) fins al 25,34% (Pulay et al., 2008).

El BD no estava associat significativament amb VCB en comparació, tant amb la població control general com, amb els pacients amb altres trastorns psiquiàtrics. De manera interessant, vam observar que hi havia un increment del risc en pacients amb BD i VCB quan els pacients amb BD es comparaven amb individus amb un trastorn depressiu. Per una altra banda, el BD estava menys associat amb VCB quan es comparava el grup de BD amb el grup amb trastorns psicòtics. Aquests resultats segueixen la mateixa línia que la resta d'estudis, amb una OR per al empresonament d'un 1.34 en pacients amb BD en comparació amb pacients amb MDD d'una mostra dels EUA (Hawthorne et al., 2012) mentre que en un estudi cas-control suec, l'esquizofrènia era un predictor de violència més robust que el BD (Sariaslan et al., 2015). Els primers resultats del estudi NERSAC (2001-2002) (Pulay et al., 2008) van ser similars, amb OR per BD-I amb VCB de 3.72 I de 1.73 per a MDD. Els resultats d'estudis europeus estan també en la mateixa línia. En la cohort de Dunedin (Arseneault et al., 2000) el risc d'una sentència condemnatòria i/o d'una violència autoreportada eren de 2.1 en MDD, de 3.5 en BD i de 5.4 en esquizofrènia. El risc de reincidir amb VCB sembla que es manté en la mateixa progressió entre diagnòstics (2.06 en esquizofrènia, 1.96 en BD i 1.41 en MDD) (Chang et al., 2015).

En estudis previs, la implicació legal es reportava més freqüentment per pacients durant un estat mixte o maníac (Quanbeck et al., 2005) caracteritzat per la presència de símptomes impulsius (Christopher et al., 2012). De fet, l'agressió impulsiva pot tenir lloc de manera més freqüent en episodis maníacs (Siever, 2008). Tot i que els símptomes maníacs específics amb un elevat component impulsiu, com les indiscrecions socials i la conducció temerària, predeien la implicació criminal en els estudis previs (Christopher et al., 2012; McCabe et al., 2013), en l'Estudi I la mania no es podia considerar un modulador significatiu de l'associació entre VCB i BD, segurament com a conseqüència de la elevada heterogeneïtat dels estudis inclosos.

En l'**Estudi II**, que te com a objectiu establir la prevalença de DSH en presos i estudiar les variables clíniques (com per exemple, els trastorns afectius i el BD), específicament relacionat amb aquest comportament, no era poc comuna la presència d'una història prèvia de DSH en l'àmbit penitenciari amb una prevalença del 17.7%, d'acord amb estudis previs en els quals la presència de DSH en delinqüents adults variava entre 15% (Fotiadou et al., 2006) i el 35% (Sakelliadis et al., 2010) en presos homes. En

aquest grup, el percentatge d'intent de suïcidi descrit en la literatura era bastant similar, variant entre el 12.9% (Mandelli et al., 2011) i el 14.5% (Sarchiapone et al., 2009).

El DSH es va associar amb variables clíniques específiques de la població de presos. Els desordres afectius i psicòtics, però no d'ansietat, funcionaven com a predictors de DSH. Particularment, els trastorns afectius s'associaven de manera independent amb el DSH, el qual prèviament s'havia associat amb la simptomatologia depressiva autoinformada (Mohino Justes et al., 2004), però no a un diagnòstic específic de depressió major, segurament com a conseqüència de les limitacions dels estudis previs. De fet, els símptomes depressius han estat avaluats en l'àmbit forense mitjançant qualificacions obtingudes a partir de qüestionaris autoinformats, no mitjançant avaluacions estandarditzades per als trastorns afectius amb entrevistes diagnòstiques estructurades (Mohino Justes et al., 2004).

La depressió es va correlacionar de manera freqüent amb els intents de suïcidi entre els presos (Fazel et al., 2008; Mandelli et al., 2011; Rivlin et al., 2010; Sarchiapone et al., 2009), i la severitat de la depressió s'associava de manera positiva amb el grau de letalitat del intent de suïcidi (Kempton and Forehand, 1992; Lohner and Konrad, 2006). Tenint en compte l'associació entre els trastorns afectius i els intents de suïcidi quasi-letals descrits en estudis previs (Wool and Dooley, 1987), així com de DSH en l'**Estudi II**, s'haurien de posar més esforços per detectar de manera precoç aquests trastorns del Axis I amb l'objectiu de proporcionar un pla de tractament efectiu als pacients abans de patir DSH o un intent de suïcidi.

L'objectiu d'aquesta tesis doctoral ha estat avaluar els correlats psiquiàtrics de l'auto i heteroagressió en el context del BD, especialment en aquells pacients que pateixen episodis afectius amb característiques mixtes del pol contrari. És per aquesta raó que els resultats de l'**Estudi III** esdevenen la millor síntesi d'aquesta línia de recerca.

Els resultats de l'Estudi III semblen donar suport a la idea de que la presència de comportaments agressius durant un MDE s'associa amb la bipolaritat, com en el cas de taxes elevades d'història familiar amb BD, així com l'aparició d'un episodi depressiu en edats joves. Aquestes característiques representen indicadors clínics molt rellevants en el cas de una bipolaritat no reconeguda en pacients depressius (Angst et al., 2012, 2011, 2010; Benazzi and Akiskal, 2008).

A més a més, la presència d'agressió durant un MDE es va associar amb una major severitat del episodi maníac o depressiu quan es valoraven mitjançant avaluacions psicomètriques i clíniques, i incloïen unes taxes més elevades de comorbiditats psiquiàtriques, més episodis afectius, freqüències més elevades de falta de tractament psiquiàtric, un major deteriorament en el funcionament global social/ocupacional, una major freqüència de símptomes psicòtics i especialment, taxes més elevades d'intents de suïcidi previs. Estudis previs ja havien reportat resultats similars (Garno et al., 2008; Perroud et al., 2011; Popovic et al., 2015), evidenciant l'impacte significatiu de la presència de comportaments agressius sobre el resultat clínic del BD, amb majors implicacions en termes d'estratègies de gestió, pronòstic i tractament.

No és d'estranyar que la comorbiditat entre BPD i SUD incrementés el risc d'agressió en pacients depressius. En estudis previs aquesta relació entre BD, BPD i SUD i l'agressió s'havia atribut a la impulsivitat (Garno et al., 2008; Swann et al., 2010). La impulsivitat esdevé un factor clau en l'agressió autodirigida, incloent totes aquelles formes d'autolesió o comportaments suïcides (Jiménez et al., 2016). No obstant, per tal de controlar el possible biaix dels components mediats per aquesta impulsivitat que poguessin influenciar en aquesta associació entre la bipolaritat i els comportaments agressius, la comorbiditat amb BPD es va excloure en el segon model de regressió múltiple (la variable d'abús de substàncies, així i tot, va resultar no correlacionar significativament amb l'agressió en la primera regressió logística).

Sorprenentment, la presència de SA al llarg de la vida va esdevenir significatiu quan es va excloure la comorbiditat de BPD en el segon model, donant suport a la nostra hipòtesi sobre l'associació entre els comportaments d'heteroagressió i autoagressió. De fet, el paper de l'agressió en els comportaments suïcides s'ha investigat en diferents estudis, evidenciant que els nivells més elevats d'agressió estan presents en pacients amb BD amb una història prèvia d'intents de suïcidi en comparació amb els pacients sense història prèvia (Oquendo et al., 2000). A més, sembla que els trets agressius, entre d'altres factors clínics, contribueixen a la predicció de futurs comportaments suïcides tant en pacients amb BD depressiu i pacients amb MDD (Oquendo et al., 2004).

En relació a les presentacions sistematològiques relatives a la coexistència de símptomes mixtos i altres característiques clíniques específiques, en l'**Estudi IV** es va

estudiar la relació psicopatològica entre AL i MR i les implicacions clíniques de l'associació amb altres símptomes mixtos, especialment l'heteroagressió verbal o física. De manera sorprenent, l'agressió verbal o física estava inversament associada de manera significativa amb AL, malgrat que el comportament de risc estava inversament associat amb MR. Ni la presència de AL ni de MR es va relacionar amb el nombre total de intents de suïcidi al llarg de la vida. De manera contrària, l'actitud irritable i la impulsivitat es van associar de manera directa tant amb AL com amb MR. Per tant, seria fàcil especular que AL podria estar relacionat amb l'auto i heteroagressió únicament amb el paper mediador subjacent de la impulsivitat i no de manera directa.

En base als resultats dels estudis inclosos en la present tesi doctoral, ens agradaria destacar la importància d'assegurar un diagnòstic precoç i un tractament i seguiment adequat dels pacients amb BD amb l'objectiu de millorar el pronòstic i evitar tant els comportaments autodestructius com les implicacions criminals que poden tenir. Els tractaments per al BD basats en evidències garanteixen un control general de totes les dimensions simptomatològiques a més d'englobar el component agressiu dels símptomes. (Grunze et al., 2013; Nivoli et al., 2012, 2011). La majoria dels símptomes relacionats amb el increment de risc de presentar un comportament criminal o suïcida es poden gestionar gràcies a tractaments adients basats en l'evidència, com es reflexa en l'**Estudi V**, per la qual cosa, és fonamental que l'adherència al tractament estigui especialment reforçada.

LIMITACIONS

L'**Estudi I** presenta limitacions relacionades amb la gran heterogeneïtat metodològica entre els estudis inclosos. Un terç dels estudis inclosos eren transversals, impossibilitant les inferències causals i limitant la deducció de la direccionalitat entre el BD i la VCB. En l'**Estudi II**, el DSH es va avaluar a través d'informes autoinformats impossibilitant, de nou, les generació d'inferències causals. A més, s'ha de tenir en compte que les dades es van obtenir d'una única institució penitenciària amb una única mostra d'homes, impossibilitant l'extrapolació a altres presos, altres cultures o a dones. En l'estudi multicèntric BRIDGE-II-MIX (**Estudi III** i **IV**), els centres participants no estaven seleccionats de manera aleatòria. A més a més, les taxes d'heteroagressió, la història prèvia de comportament suïcida, o labilitat afectiva i la reactivitat de l'estat

anímic es van recollir de manera retrospectiva. Per últim, en l'**Estudi V** té limitacions principalment relacionades amb els problemes metodològics de les guies clíniques incloses.

CONCLUSIONS

Mitjançant la realització d'aquesta tesi doctoral, la doctoranda i el grup de recerca han contribuït a una millor comprensió de la dimensió agressiva en el context del BD aportant coneixement a una línia de recerca que, malgrat la seva rellevància en la practica clínica diària, no ha atret la suficient atenció en la recerca.

Les principals conclusions obtingudes de la present tesi doctoral són:

1. Un de cada catorze pacients que pateixen de trastorn bipolar presenten un comportament criminal violent. Tot i això, l'associació amb el comportament criminal no va esdevenir significativa en relació a la població general. Encara que l'associació amb violència criminal no fos significativa quan els pacients presentaven un trastorn bipolar en comparació amb pacients amb algun altre trastorn psiquiàtric, la probabilitat de patir un comportament criminal violent era menor en pacients amb un trastorn bipolar que en aquells que patien trastorns psicòtics, però era més elevada en relació amb pacients amb trastorns depressius. En las anàlisis de metaregressió no es van trobar moduladors significatius. El focus de la recerca hauria d'estar centrat en la identificació de moduladors potencials de l'associació entre trastorn bipolar i violència.

2. Els trastorns afectius, així com les psicosis, un diagnòstic de trastorn límit de la personalitat i un trastorn per ús de múltiples substàncies van esdevenir els predictors més rellevants a l'hora de predir les autolesions deliberades en població penitenciària. Les experiències traumàtiques i la presència d'una història familiar psiquiàtrica no es van relacionar de manera directa amb conductes d'autolesió deliberades, probablement com a conseqüència del paper modulador associat de la presència subjacent de psicopatologia. Conseqüentment, l'avaluació d'autolesions deliberades és important en les avaluacions psiquiàtriques ja que es pot considerar un indicador rellevant de la presència d'un trastorn psiquiàtric i intents de suïcidi.

3. En la mostra de pacients afectius avaluats durant un episodi de depressió major la presència de comportaments agressius es va relacionar principalment amb característiques sociodemogràfiques i clíniques associades a la bipolaritat. La variable clínica associada amb l'agressió de manera més rellevant va ser la presència de característiques mixtes. Després de controlar per el possible biaix de confusió dels components mediats per la impulsivitat associats a la comorbiditat amb un trastorn de personalitat límit, es va trobar que el risc de conducta agressiva associat amb la presència de suïcidi al llarg de la vida s'incrementava 1.4 vegades.

4. En pacients amb una depressió mixta, la labilitat afectiva representa una característica depressiva mixta que pot ajudar en l'assignació d'una estratègia de tractament personalitzada ja que es correlaciona positivament amb la severitat de la mania i amb la presència de reactivitat de l'estat d'ànim i depressió atípica i, negativament, amb la severitat de la depressió i positivament. No es va trobar una correlació entre la labilitat afectiva i el nombre total d'intents de suïcidi al llarg de la vida. L'heteroagressió verbal o física durant el major índex d'un episodi depressiu estava inversament associat amb la presència de labilitat afectiva.

5. Garantir un diagnòstic precoç, un tractament adient i un seguiment per als pacients amb BD orientat cap a una millora del pronòstic i evitant la presència tant de comportaments autodestructius com de conducta criminal és de vital importància. La identificació de comportaments auto i heteroagressius esdevé l'objectiu de les estratègies de tractament personalitzades en el subgrup de pacients amb trastorn bipolar caracteritzats per dimensions psicopatològiques "agressives" compartides.

LIST OF ABBREVIATIONS

ADHD Attention Deficit Hyperactivity Disorder

AGREE II Appraisal of Guidelines for Research and Evaluation

AL Affective Lability

ASI-X Addiction Severity Index-Expanded Version

AUC area under the curve

BD Bipolar Disorder

BDI BD type I

BDII BD type II

BD-NOS BD not otherwise specified

BPD Borderline Personality Disorder

BRIDGE-II-MIX Bipolar Disorders: Improving Diagnosis, Guidance and Education multicentric study

Cal-VAT California State Hospital Violence Assessment and Treatment

CE category of evidence

CGI-BP Clinical Global Impression-Bipolar Version

CI Confidence Interval

DSH Deliberate Self-Harm

DSHI Deliberate Self-Harm Inventory

DSM Diagnostic and Statistical Manual of Mental Disorders

ECA Epidemiological Catchment Area

GAF Global Assessment of Functioning

ICD International Classification of Diseases

JCR Journal Citation Reports

MADRS Montgomery–Åsberg Depression Rating Scale

MAOA monoamine oxidase A

MDD major depressive disorder

MDE major depressive episode

MDE-A major depressive episode with aggression

MDE-N major depressive episode without aggression

MFS Mixed Features Specifier

MR Mood Reactivity

MS Mixed States

MVAS-BP Multiple Visual Analog Scales of Bipolarity

NCS National Comorbidity Survey

NESARC National Epidemiologic Survey on Alcohol and Related Conditions

OR Odds Ratio

PAF Population-attributable Risk

PD Personality Disorder

PHY Physical Aggression

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT Randomized Controlled Trial

RDoC Research Domain Criteria

RG Recommendation Grades

ROC Receiver Operating Characteristic Analysis

SA Suicide Attempt

SCID-I Structured Clinical Interview for DSM-IV Axis I Disorders

SCID-II Structured Clinical Interview for DSM-IV Axis II Disorders

SD Standard Deviation

SUD Substance Use Disorder

US United States of America

VCB Violent Criminal Behavior

VER Verbal Aggression

YMRS Young Mania Rating Scale

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Yoon, J.H., Kim, J.H., Choi, S.S., Lyu, M.K., Kwon, J.H., Jang, Y.I., Park, G.T., 2012. Homicide and bipolar I disorder: A 22-year study. Forensic Sci. Int. 217, 113–118. hiips://doi.org/10.1016/j.forsciint.2011.10.037

Young, M.H., Justice, J. V, Erdberg, P., 2006. Risk of harm: inmates who harm themselves while in prison psychiatric treatment. J. Forensic Sci. 51, 156–62. hiips://doi.org/10.1111/j.1556-4029.2005.00023.x

CURRICULUM VITAE

Norma Verdolini

MD, Psychiatrist

Researcher in Clinical Neurosciences

Bipolar Disorders Unit, Department of Psychiatry and Psychology, Institute of Neurosciences (ICN), Hospital Clínic de Barcelona, Catalonia, Spain

FIDMAG Germanes Hospitalàries Research Foundation, Sant Boi de Llobregat, Barcelona, Catalonia, Spain

CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Barcelona, Catalonia, Spain

Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, Santa Maria della Misericordia Hospital, University of Perugia, Italy

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nverdolini@clinic.cat, *nverdolini@fidmag.com*, *norma.verdolini@gmail.com*

June 14th 1985

EDUCATION

2016-2018	**PhD in Clinical Neurosciences** School of Medicine, University of Barcelona (Spain) Research project: "SELF- AND HETERO-AGGRESSION: Clinical Implications in Bipolar Disorder and Mixed States" *Supervisors: Eduard Vieta Pascual and Isabella Pacchiarotti*
2011-2016	**School of Specialization in Psychiatry** School of Psychiatry, University of Perugia (Italy)
2004-2010	**B.A. Medicine** School of Medicine, University of Perugia (Italy)

TEACHING EXPERIENCE

From 2015	**Collaborator Teacher** in the Bachelor of Medicine from the University of Perugia to teach in the subject entitled "Psychiatry" *Perugia, Italy*

March 2015	**Invited talker** in the Bachelor of Medicine at the Clare College, University of Cambridge, *Cambridge, UK*

RESEARCH TRAINING

2015 Sep – 2016 May	**Training stay** at the Bipolar Disorders Program - Hospital Clinic - Barcelona (Spain) *Stay supervisor: Eduard Vieta*
2014 Aug-Dec	**Training stay** at the SEPT (South Essex Partnership University NHS Foundation Trust), in collaboration with the University of Cambridge, Clare College *Stay supervisors: Mark Agius*

PROFESSIONAL AFFILIATIONS

From 2018	Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM *Instituto de Salud Carlos III, Ministry of Economy and Competitivity*
From 2017	Psychiatric Associations *Sociedad Española de Psiquiatría Biológica (Spain)* *Societá Italiana di Psichiatria (Italy)*
From 2016	Official Association of Doctors in Barcelona ("Col·legi Oficial de Metges de Barcelona")
From 2014	Official Association of Doctors in UK ("General Medical Council (UK)"
From 2011	Official Association of Doctors in Italy ("Association of Doctor-Surgeons and Dentists of the Province of Macerata, Italy)

RELEVANT PEER-REVIEWED JOURNAL ARTICLES

2018

- Sultans of swing: A reappraisal of the intertwined association between affective lability and mood reactivity in a post-hoc analysis of the BRIDGE-II-MIX study**.**
Verdolini N, Menculini G, Perugi G, Murru A, Samalin L, Angst J, Azorin J-M, Bowden CL, Mosolov S, Young AH, Barbuti M, Popovic D, Vieta E, Pacchiarotti I, for the BRIDGE-II-Mix Study Group
J Clin Psychiatry, in press. Accepted for publication on 2018 10 Aug.

research article, IF: 4.247, Q1, citations 0

- Depressive mood and circadian rhythms disturbances as outcomes of seasonal affective disorder treatment: A systematic review.
Menculini G, **Verdolini N**, Murru A, Pacchiarotti I, Volpe U, Cervino A, Steardo L, Moretti P, Vieta E, Tortorella A.
J Affect Disord. 2018 Dec 1;241:608-626. doi: 10.1016/j.jad.2018.08.071. Epub 2018 Aug 15. Review. PMID:30172213

review, IF: 3.786, Q2, citations 0

- Violent criminal behavior in the context of bipolar disorder: Systematic review and meta-analysis.
Verdolini N, Pacchiarotti I, Köhler CA, Reinares M, Samalin L, Colom F, Tortorella A, Stubbs B, Carvalho AF, Vieta E, Murru A.
J Affect Disord. 2018 Oct 15;239:161-170. doi: 10.1016/j.jad.2018.06.050. Epub 2018 Jul 5. Review. PMID:30014956

review, first author, IF: 3.786, Q2, citations 0

- Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines.
Verdolini N, Hidalgo-Mazzei D, Murru A, Pacchiarotti I, Samalin L, Young AH, Vieta E, Carvalho AF.
Acta Psychiatr Scand. 2018 May 13. doi: 10.1111/acps.12896. [Epub ahead of print] Review. PMID:29756288

review, first author, IF: 4.984, Q1, citations 0

- Predictors of Client Satisfaction with Outpatient Mental Health Clinic Services in Italy and New York.
Pauselli L, Galletti C, **Verdolini N**, Paolini E, Gallucci D, Balducci PM, Bernardini F, Kogan JH, Shim R, Moretti P, Compton MT.
Community Ment Health J. 2018 Jul;54(5):562-570. doi: 10.1007/s10597-017-0196-6. Epub 2017 Nov 17. PMID:29147978

research article, IF: 1.159, Q3, citations 0

2017

- Effects of music on seizure frequency in institutionalized subjects with severe/profound intellectual disability and drug-resistant epilepsy.

D'Alessandro P, Giuglietti M, Baglioni A, **Verdolini N**, Murgia N, Piccirilli M, Elisei S.
Psychiatr Danub. 2017 Sep;29(Suppl 3):399-404.
research article, IF: 1.341, Q3, citations 1

- Oral versus long-acting injectable antipsychotics: hospitalisation rate of psychotic patients discharged from an Italian Psychiatric Unit.
Sicilia V, Del Bello V, **Verdolini N**, Tortorella A, Moretti P.
Psychiatr Danub. 2017 Sep;29(Suppl 3):333-340. PMID:28953786
research article, IF: 1.341, Q3, citations 0

- Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features.
Verdolini N, Perugi G, Samalin L, Murru A, Angst J, Azorin JM, Bowden CL, Mosolov S, Young AH, Barbuti M, Guiso G, Popovic D, Vieta E, Pacchiarotti I; BRIDGE-II-Mix Study Group.
Acta Psychiatr Scand. 2017 Oct;136(4):362-372. doi: 10.1111/acps.12777. Epub 2017 Jul 25. PMID:28741646
research article, first author, IF: 4.984, Q2, citations 3

- The aggressor at the mirror: Psychiatric correlates of deliberate self-harm in male prison inmates.
Verdolini N, Murru A, Attademo L, Garinella R, Pacchiarotti I, Bonnin CDM, Samalin L, Pauselli L, Piselli M, Tamantini A, Quartesan R, Carvalho AF, Vieta E, Tortorella A.
Eur Psychiatry. 2017 Jul;44:153-160. doi: 10.1016/j.eurpsy.2017.04.002. Epub 2017 Apr 14. PMID:28641217
research article, first author, IF: 4.129, Q1, citations 2

- Thyroid autoimmunity in bipolar disorder: A systematic review.
Barbuti M, Carvalho AF, Köhler CA, Murru A, **Verdolini N**, Guiso G, Samalin L, Maes M, Stubbs B, Perugi G, Vieta E, Pacchiarotti I.
J Affect Disord. 2017 Oct 15;221:97-106. doi: 10.1016/j.jad.2017.06.019. Epub 2017 Jun 13. Review. PMID:28641149
review, IF: 3.786, Q2, citations 3

- Modifiable and non-modifiable factors associated with functional impairment during the inter-episodic periods of bipolar disorder.
Murru A, Pacchiarotti I, **Verdolini N**, Reinares M, Torrent C, Geoffroy PA, Bellivier F, Llorca PM, Vieta E, Samalin L.
Eur Arch Psychiatry Clin Neurosci. 2017 May 22. doi: 10.1007/s00406-017-0811-0. [Epub ahead of print] PMID:28534186
research article, IF: 3.617, Q2, citations 0

- Residual depressive symptoms, sleep disturbance and perceived cognitive impairment as determinants of functioning in patients with bipolar disorder.
Samalin L, Boyer L, Murru A, Pacchiarotti I, Reinares M, Bonnin CM, Torrent C, **Verdolini N**, Pancheri C, de Chazeron I, Boucekine M, Geoffroy PA, Bellivier F, Llorca PM, Vieta E.
J Affect Disord. 2017 Mar 1;210:280-286. doi: 10.1016/j.jad.2016.12.054. Epub 2017 Jan 3. PMID:28068616

research article, IF: 3.786, Q2, citations 6

- Predictors of Length of Stay in an Inpatient Psychiatric Unit of a General Hospital in Perugia, Italy.
Pauselli L, **Verdolini N**, Bernardini F, Compton MT, Quartesan R.
Psychiatr Q. 2017 Mar;88(1):129-140. doi: 10.1007/s11126-016-9440-4. PMID:27167133

research article, IF: 1.327, Q3, citations 4

2016

- Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder.
Pacchiarotti I, León-Caballero J, Murru A, **Verdolini N**, Furio MA, Pancheri C, Valentí M, Samalin L, Roigé ES, González-Pinto A, Montes JM, Benabarre A, Crespo JM, de Dios Perrino C, Goikolea JM, Gutiérrez-Rojas L, Carvalho AF, Vieta E.
Eur Neuropsychopharmacol. 2016 Oct;26(10):1562-78. doi: 10.1016/j.euroneuro.2016.08.008. Epub 2016 Aug 24. Review. PMID:27568278

review, IF: 4.239, Q1, citations 8

2015

- The psychosomatic spectrum: a clinical-analytic survey of the relationship between eating disorders and migraine.

Verdolini N, De Giorgio G, Moretti P, Piselli M, Quartesan R.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S332-5. PMID:26417790

research article, corresponding author, IF: 1.879, Q3, citations 0

- Comparison of assessment and management of suicidal risk for acute psychiatric assessment between two state sponsored hospitals in England and Italy.
Singh R, **Verdolini N**, Agius M, Moretti P, Quartesan R.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S292-5. PMID:26417782

research article, IF: 1.879, Q3, citations 0

- Personality and psychotic symptoms as predictors of self-harm and attempted suicide.
Del Bello V, **Verdolini N**, Pauselli L, Attademo L, Bernardini F, Quartesan R, Moretti P.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S285-91. PMID:26417781

research article, IF: 1.879, Q3, citations 0

- The developmental stages of Bipolar Disorder: a case report.

Chaudhry FI, **Verdolini N**, Agius M.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S198-200. PMID:26417761

case report, corresponding author, IF: 1.879, Q3, citations 0

- The comorbidity between bipolar disorder and ADHD in a young adult: a focus on impulsivity.
Ashcroft S, **Verdolini N**, Zaman R, Agius M.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S195-7. PMID:26417760

case report, corresponding author, IF: 1.879, Q3, citations 0

- The Cambridge-Perugia Inventory for assessment of Bipolar Disorder.
Agius M, **Verdolini N**.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S185-7. PMID:26417758

review, IF: 1.879, Q3, citations 0

- Bipolar and Borderline Personality Disorders: a descriptive comparison of psychopathological aspects in patients discharged from an Italian Inpatient Unit using PANSS and BPRS.
Pauselli L, **Verdolini N**, Santucci A, Moretti P, Quartesan R.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S170-6. PMID:26417755

research article, IF: 1.879, Q3, citations 0

- Traumatic events in childhood and their association with psychiatric illness in the adult.
Verdolini N, Attademo L, Agius M, Ferranti L, Moretti P, Quartesan R.
Psychiatr Danub. 2015 Sep;27 Suppl 1:S60-70. Review. PMID:26417738

review, first author, corresponding author, IF: 1.879, Q3, citations 0

- The State of the Art of the DSM-5 "with Mixed Features" Specifier.
Verdolini N, Agius M, Ferranti L, Moretti P, Piselli M, Quartesan R.
ScientificWorldJournal. 2015;2015:757258. doi: 10.1155/2015/757258. Epub 2015 Aug 25. Review. PMID:26380368

review, first author, corresponding author, no IF

2014

- Co-Morbidity Part 2 - Neurobiology and Suicide Risk; Modelling the consequences of Bipolar and Anxiety Co-Morbidity.
Agius M, **Verdolini N**, Aquilina FF, Butler S.
Psychiatr Danub. 2014 Nov;26 Suppl 1:336-9. PMID:25413561

review, IF: 1.301, Q3, citations 0

- Can metabolic side effects of antipsychotics be reversed by lifestyle changes?
Bolger A, **Verdolini N**, Agius M.
Psychiatr Danub. 2014 Nov;26 Suppl 1:330-5. PMID:25413560

review, IF: 1.301, Q3, citations 0

- Bipolar disorder: The importance of clinical assessment in identifying prognostic factors - An Audit. Part 3: A comparison between Italian and English mental health services and a survey of bipolar disorder.
Verdolini N, Dean J, Massucci G, Elisei S, Quartesan R, Zaman R, Agius M.
Psychiatr Danub. 2014 Nov;26 Suppl 1:309-14. PMID:25413557

research article, corresponding author, IF: 1.301, Q3, citations 0

- Bipolar disorder: The importance of clinical assessment in identifying prognostic factors - An Audit. Part 2: Mixed state features and rapid cycling.
Verdolini N, Dean J, Elisei S, Quartesan R, Zaman R, Agius M.
Psychiatr Danub. 2014 Nov;26 Suppl 1:301-8. PMID:25413556

research article, corresponding author, IF: 1.301, Q3, citations 0

- Bipolar disorder: The importance of clinical assessment in identifying prognostic factors - An Audit. Part 1: An analysis of potential prognostic factors.
Verdolini N, Dean J, Elisei S, Quartesan R, Zaman R, Agius M.
Psychiatr Danub. 2014 Nov;26 Suppl 1:289-300. PMID:25413555

research article, corresponding author, IF: 1.301, Q3, citations 0

- Mixed States: a "new" nosographic entity.
Verdolini N, Agius M, Quartesan R, Elisei S.
Psychiatr Danub. 2014 Nov;26 Suppl 1:103-11. PMID:25413522

review, corresponding author, IF: 1.301, Q3, citations 0

- Bipolar disorder comorbid with borderline personality disorder and treatment with mood stabilisers.
Agius M, **Verdolini N**.
BMJ. 2014 Nov 13;349:g6798. doi: 10.1136/bmj.g6798. No abstract available. PMID:25395471

case report, IF: 17.445, Q3, citations 1

- Assessing and staging bipolar disorder.
Agius M, Rogers J, Bongards E, O'Connor S, **Verdolini N**, Elisei S.
Br J Psychiatry. 2014 Jun;204(6):493-4. doi: 10.1192/bjp.204.6.493a. No abstract available. PMID:25029698

case report, IF: 7.991, Q3, citations 1

2013

- Comparing a Community Mental Health team in Bedford (UK) with Community Mental Health Services in Perugia (Italy): description of teams and caseloads.
Elisei S, Agius M, Bongards EN, Salierno G, Massucci G, Anastasi S, **Verdolini N**, Quartesan R.
Psychiatr Danub. 2013 Sep;25 Suppl 2:S315-23. PMID:23995200

research article, IF: 0.653, Q4, citations 0

- Resilience and depressive disorders.
Elisei S, Sciarma T, **Verdolini N**, Anastasi S.
Psychiatr Danub. 2013 Sep;25 Suppl 2:S263-7. Review. PMID:23995190
review, IF: 0.653, Q4, citations 8

2012

- The continuum between Bipolar Disorder and Borderline Personality Disorder.
Elisei S, Anastasi S, **Verdolini N**.
Psychiatr Danub. 2012 Sep;24 Suppl 1:S143-6.
PMID:22945209
review, IF: 0.633, Q4, citations 4

- Suicidal attempts among Emergency Department patients: one-year of clinical experience.
Elisei S, **Verdolini N**, Anastasi S.
Psychiatr Danub. 2012 Sep;24 Suppl 1:S140-2.
PMID:22945208
research article, IF: 0.633, Q4, citations 9

CONFERENCE PRESENTATIONS

Oral presentations

- at "The Cambridge Luton International Conference on Mental Health, Clare College, 2013" with the lecture "Comparing a Community Mental Health Team in Bedford (UK) with Community Mental Health Services in Perugia (Italy): description of teams and caseloads"
- at "The 2014 WPA Regional Congress, Ljubljana, Slovenia" with the lecture "Comparing Mental Health Services in Italy and UK".
- at "The International Twined Congress: The Psychiatry beyond the DSM-5" at Iseo – Italy (2014) with the lecture "Bipolar Disorder: the importance of clinical assessment in identifying prognostic factors".
- at "The 4th International Congress on Neurobiology, Psychopharmacology and Treatment Guidance" at Agios Nikolaos, Creete – Greece (2015) with the lecture "The mixed states: A "new" nosological entity".
- co-author of the Conference lecture "Resilience and Depressive Disorders" at the "WFSBP 2015, 12th World Congress of Biological Psychiatry" in Athens, Greece.
- co-author of the conference lecture "Mixed states: beyond the diagnoses, towards a differentiation of the clinical subtypes" presented at the "5th International Congress on Neurobiology, Psychopharmacology, and Treatment Guidance-Chalkidiki, 2017".
- at the " XXI Congresso Nazionale SOPSI" (SOPSI 2017) in Rome with the lecture "L'aggressore allo specchio: uno studio osservazionale sull'autolesionismo in carcere (The aggressor at the mirror: a observational study on deliberate self-harm in prison)".
- at the "XX Congreso Nacional de Psiquiatria 2017" in Barcelona with the lecture "Hipomania/mania inducida por antidepresivos en pacientes con deprésion mayor: evidencias del estudio BRIDGE-II-MIX" ("Antidepressant-induced hypomania/mania in

patients with major depression: evidence from the BRIDGE-II-MIX study").

Posters
- at "The Cambridge Luton International Conference on Mental Health, Clare College, 2013"
- at "The Cambridge Luton International Conference on Mental Health, Clare College, 2012"
- at "SOPSI 2011" Conference in Rome
- at "SOPSI 2014" Conference in Turin
- at "The World Congress of Psychiatry 2014" in Madrid
- at "The 23rd European Congress of Psychiatry" (EPA 2015) in Vienna.
- at "American Psychiatric Association - IPS: The Mental Health Conference 2015" in New York.
- at "The 24rd European Congress of Psychiatry" (EPA 2016) in Madrid.
- at "The 25th European Congress of Psychiatry" (EPA 2017) in Florence.
- at "The 29th ECNP Congress" (ECNP 2017) in Paris.

RESEARCH PROJECTS

Non-funded research projects

2018	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia, ACADIA Pharmaceuticals Inc.
2017	Janssen Esketamine 54135419TRD3008, Janssen
2017	Janssen 54135419SUI3001/54135419SUI3002, Janssen
2017	Determinación retrospectiva de actividad del protocolo Código Riesgo Suicidio en las Urgencias de Hospital Clínic de Barcelona. Eduard Vieta Pascual; Norma Verdolini; Eva Solé Roiger, Hospital Clinico y Provincial de Barcelona
2012	Angelini 039(C)SC11063-Trazodone Once a Day in Major Depression Disorder, Aziende Chimiche Riunite Angelini Francesco S.p.A
2012	Observational cohort study to evaluate the safety of agomelatine in standard medical practice in depressed patients-CLE-20098-068, Laboratorios Servier

Funded research projects

2017	Oral vs. long-acting antipsychotics: hospitalization rate of psychotic patients discharged from an Italian Psychiatric Unit, Universidad de

	Perugia. Alfonso Tortorella; Norma Verdolini; Valentina del Bello; Patrizia Moretti
2016	PSICHIATRIA E DETENUTI (Psiquiatria y presos), Universidad de Perugia, Alfonso Tortorella; Norma Verdolini
2014	DCA-emicrania (Trastornos alimentarios y migraña), Universidad de Perugia, Roberto Quartesan; Patrizia Moretti; Norma Verdolini
2014	Gli stati misti: diagnosi e clinica (Los estados mixtos: diagnosis y clinica), Universidad de Perugia, Norma Verdolini; Alfonso Tortorella; Roberto Quartesan; Patrizia Moretti
2013	Competence-TSO (capacidad de dar consentir al tratamiento en pacientes con ingreso involuntario), Universidad de Perugia Roberto Quartesan; Stefano Ferracuti

AD-HOC PEER REVIEW

Participation as a reviewer for the following journal(s):

- the "Journal of Affective Disorders"
- the "BMC Psychiatry"
- the "Psychiatria Danubina"
- the "Journal of Forensic and Legal Medicine"
- the "International Journal of Women's Health"
- the "International Neuropsychiatric Disease Journal"
- "CNS Spectrums"
- "the Journal of Childhood and Developmental Disorders"
- "Journal of Psychiatry and Mental Health"
- "Frontiers in Psychiatry"

SCIENTIFIC COURSES (selection)

2017-2018	"*Técnicas de neuroimagen avanzada*", FIDMAG Research Foundation, Sant Boi de Llobregat, Spain.
2015-2016	"*SPSS*". Hospital Clínic de Barcelona, Barcelona, Spain.

LANGUAGES

Italian	*Mother tongue.*

English	▪ *Cambridge First Certificate in English (2003).*
French	▪ *DELF certificate (2003)*
Spanish	Fluent

COMPUTER SKILLS
Operating systems: *Windows 7, Mac OS X.*

Applications: *Microsoft Office, Statistical Package for the Social Science (SPSS), Mendeley reference manager, SAP and Itk-SNAP*.

Barcelona, September 2018