The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: http://www.tandfonline.com/loi/iwbp20

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To cite this article: Heinz Grunze, Eduard Vieta, Guy M. Goodwin, Charles Bowden, Rasmus W. Licht, Jean-Michel Azorin, Lakshmi Yatham, Sergey Mosolov, Hans-Jürgen Möller, Siegfried Kasper & on behalf of the Members of the WFSBP Task Force on Bipolar Affective Disorders Working on this topic (2017): The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder, The World Journal of Biological Psychiatry

To link to this article: http://dx.doi.org/10.1080/15622975.2017.1384850

Published online: 03 Nov 2017.

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 2017
https://doi.org/10.1080/15622975.2017.1384850

WFSBP TREATMENT GUIDELINES

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder

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ABSTRACT

Objectives: Although clinically highly relevant, the recognition and treatment of bipolar mixed states has played only an underpart in recent guidelines. This WFSBP guideline has been developed to supply a systematic overview of all scientific evidence pertaining to the acute and long-term treatment of bipolar mixed states in adults.

Methods: Material used for these guidelines is based on a systematic literature search using various data bases. Their scientific rigour was categorised into six levels of evidence (A–F), and different grades of recommendation to ensure practicability were assigned. We examined data pertaining to the acute treatment of manic and depressive symptoms in bipolar mixed patients, as well as data pertaining to the prevention of mixed recurrences after an index episode of any type, or recurrence of any type after a mixed index episode.

Results: Manic symptoms in bipolar mixed states appeared responsive to treatment with several atypical antipsychotics, the best evidence resting with olanzapine. For depressive symptoms, addition of ziprasidone to treatment as usual may be beneficial; however, the evidence base is much more limited than for the treatment of manic symptoms. Besides olanzapine and quetiapine, valproate and lithium should also be considered for recurrence prevention.

Limitations: The concept of mixed states changed over time, and recently became much more comprehensive with the release of DSM-5. As a consequence, studies in bipolar mixed patients targeted slightly different bipolar subpopulations. In addition, trial designs in acute and maintenance treatment also advanced in recent years in response to regulatory demands.

Conclusions: Current treatment recommendations are still based on limited evidence, and there is a clear demand for confirmative studies adopting the DSM-5 specifier with mixed features concept.

Abbreviations: BD-I: bipolar I disorder; BD-II: bipolar II disorder; CE: category of evidence; CGI-BP: Clinical Global Impression-Bipolar; CI: confidence interval; D: depression; DBS: deep brain stimulation; DIE: depressive index episode; DM: depressive mixed; DSM: Diagnostic and Statistical Manual; DS: depressive symptoms; ER: extended release; FE: further evidence; FDA: US Food and Drug administration; HAM-D: Hamilton Rating Scale for Depression; HR: hazard ratio; ICD: International Classification of Diseases; IDS-SR: Inventory of Depressive Symptomatology (self-report); ISBD: International Society for Bipolar Disorder; ITT: intend-to-treat; LOCF: last observation carried forward; M: mania; MADRS: Montgomery–Asberg Depression Rating Scale; MDD: major

ARTICLE HISTORY
Received 12 September 2017
Accepted 15 September 2017

KEYWORDS
Mixed states; bipolar disorder; guidelines; pharmacotherapy; acute treatment; maintenance treatment; antipsychotics; antidepressants; mood stabiliser; electroconvulsive therapy

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depressive disorder; MDD-AIHM: major depressive disorder with a history of antidepressant-induced (hypo-) mania; MDE: major depressive episode; MIE: manic index episode; MMRM: Mixed Model Repeated Measurement; MM: manic mixed; MOAT: multi-state outcome analysis of treatments; MST: mood stabiliser; MS: manic symptoms; Mx: mixed episode; MxIE: mixed index episode; OFC: olanzapine-fluoxetine combination; OR: odds ratio; RCT: randomised controlled trial; RDC: research diagnostic criteria; RG: recommendation grade; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; SE: standard error; ST: safety and tolerability; STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder; TAU: treatment as usual; TEAS: treatment-emergent affective switch; YMRS: Young Mania Rating Scale

Preface

This practice guideline for the biological, mainly pharmacological treatment and prevention of mixed episodes in bipolar disorder was developed by the Bipolar Disorder Task Force of the WFSBP and is part of a series covering the acute and maintenance treatment of bipolar disorder. The preparation of these guidelines was not supported financially by any commercial organisation.

This guideline was mainly developed by psychiatrists and psychotherapists in active clinical practice. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to medicines discussed in this guideline. A number of mechanisms are in place to minimise the potential for producing biased recommendations due to conflicts of interest.

At the time of preparation of this manuscript, the US Food and Drug administration (FDA) licencing label 'Mixed Episodes' relates to the narrow Diagnostic and Statistical Manual (DSM)-IV definition of mixed states, and has been granted to some medications as an extension of a licence for the treatment of acute mania in Bipolar I disorder (BD-I). So far, no specific licencing by authorities exists for the DSM-5 specifier 'with mixed features', other mixed episodes subthreshold to DSM-IV definitions, mixed episodes in bipolar II (BD-II), cyclothymia or bipolar NOS disorder, or for the prevention of mixed episodes. Other authorities such as the EMA do not envisage a mixed episode label so far although they do now recognise the need (European Medicines Agency Scientific Commitee CfMPfHU 2016). Consequently, recommendations in this guideline targeting those subtypes and symptom clusters in bipolar disorder are often derived from data relating to mixed states in BD-I disorder, and not covered by a specific licence ('off-label use'). In addition, some drugs recommended in the present guideline may not be available in all countries, and approved doses may vary.

With the aim of having a comprehensive view of acute and maintenance treatment of mixed episodes in bipolar disorder, we reviewed published data on the efficacy of approved and non-approved pharmacological or physical therapies for mixed states, rated the evidence for their efficacy, and developed recommendations for specific symptom and treatment scenarios.

Introduction

Although already well characterised by Weygandt (1899), a medical assistant of Kraepelin, mixed states only recently experienced the attention that they deserve, given their high frequency and unfavourable prognosis (Grunze and Walden 2005). The frequent occurrence of mixed states (up to 70% of manic patients simultaneously show symptoms of depression) underlines that bipolar disorder (BD) is not a pure '*folie* à *double forme*' (dual-form insanity) as it was originally coined by the French psychiatrist Jules Baillarger, and with mania and depression being distinct opposite poles (Baillarger 1854).

Although some information on the evidence for different treatments of mixed episodes had been included in the World Federation of Societies of Biological Psychiatry (WFSBP) mania guideline (Grunze et al. 2009), it appears timely to address mixed episodes in a guideline of its own. Traditionally, the evidence for response of mixed patients to pharmacological agents was extrapolated from studies or trials that enrolled both pure and mixed manic patients, assuming a comparable antimanic response to treatment for both subgroups of patients. Few of these reports, though, have examined whether there is differential efficacy in the subset of patients with mixed manic states. Mixed depression, i.e., depression with accompanying (hypo)manic symptoms, has received even less attention than mixed mania, and therefore reliable data on its differential treatment response is even more scarce. The lack of available information results in the assumption in current

clinical guidelines that, with some exceptions, treatment of mixed presentations should be similar to that of pure manic states. However, clinical experience with the various putative antimanic agents over recent years has suggested that a drug efficacious in one subtype of mania is not necessarily the treatment of choice for the other subtypes.

For depressive mixed episodes, the evidence for optimal treatment was too sparse at the time of release of the WFSBP guideline on the treatment of bipolar depression (Grunze et al. 2010) to justify specific treatment recommendations. In the meantime, this has changed to some degree, and clinicians may welcome some guidance on the pharmacological treatment of mixed depressive episodes. Finally, some data are now available on prophylactic treatment in patients with a mixed index episode that might also be valuable to guide pharmacotherapy.

Diagnosis

Bipolar disorder can be best conceptualised as a multiplex dysregulation syndrome involving a broad spectrum of basic mental qualities besides mood. The presence of depressive symptomatology during acute mania has been recognised for centuries and has been mentioned in 19th century German textbooks as mixtures ('Mischungen' by Heinroth in 1818) or mid-forms ('Mittelformen' by Griesinger in 1845) (González-Pinto et al. 2007). In 1854, the French psychiatrist Falret described 'transitional states' that emerged during the switch from mania to depression and depression to mania (Falret 1854; Sedler 1983; Pichot 2004). He observed that during transitions from depression into mania, vestiges of depression mingled with components of mania; during transitions of mania into depression, vestiges of mania mingle with components of depression.

The first scholarly systematic descriptions of mixed states by Kraepelin and Weygandt date back to 1899 (Kraepelin 1899; Weygandt 1899); since then their operationalisation, and even their acceptance, have been a matter of controversy (Ghaemi 2008). Kraepelin described mood disorders as a continuum, with 'pure' depression and 'pure' mania being only the extremes of a spectrum that is characterised by three hallmark psychopathological items: *Denkstörung* (thought disorder), *Verstimmung* ('ill-humour', affective disturbance) and *Wille* (volition). According to Kraepelin, each of these three categories can be judged separately as increased or diminished, thus allowing multiple variations of affective states. In his model, only two variations (either all increased or all diminished) constitute the 'pure' poles, the others are mixed states, a concept described more in detail by Wilhelm Weygandt (Weygandt 1899; Salvatore et al. 2002). Kraepelin enumerated six putative subtypes of mixed states depending on the fundamental symptoms of mania or depression. The first three subtypes ('depressive–anxious mania', 'excited or agitated depression' and 'mania with thought poverty') were characterised by an admixture of the three core symptoms of mania (namely, flight of ideas, euphoria and hyperactivity) and depressive symptoms such as depressed mood, inhibition of thought and poverty of thought. The next three subtypes ('manic stupor', 'depression with flight of ideas' and 'inhibited mania') were based on the core symptomatology of depression (inhibited thought, depressed mood and avolition) accompanied by manic symptomatology such as euphoria and flight of ideas (Marneros 2001a). To illustrate further Kraepelin's holistic approach towards affective disorders, a diminished speed of thinking or negative thoughts, low mood but increased agitation would characterise what he defined as 'depressive Erregung' (depressive excitement), an affective state that today sometimes is labelled 'agitated depression', although it essentially may rather be conceptualised as a bipolar mixed state (Benazzi et al. 2004; Koukopoulos et al. 2007). Of note, the distinct subtypes of mixed states as described by Kraepelin may still hold true and have therapeutic implications, as shown by Perugi et al. (2013) in their cluster analysis of clinical subtypes of severe bipolar mixed states. Akiskal and Benazzi later aimed to verify the existence of distinct subtypes of mixed depression, an 'excited depression' subtype (defined by the core feature of psychomotor agitation, and further characterised by talkativeness, irritable mood and distractibility) and a 'depression with flight of ideas' subtype (defined by the core feature of racing/crowded thoughts, and further characterised by risky pleasurable impulses including, among others, those with intense sexual arousal) (Akiskal and Benazzi 2004; Benazzi et al. 2004).

Similarly, Carroll (1983) proposed a 'Neo-Kraepelinian' model of bipolar mixed episodes, where the three key dimensions are hedonic function, central pain regulation and psychomotor regulation. To explain mixed episodes, Akiskal also introduced the concept of temperament. He proposed a model explaining mixed episodes as states arising when an affective episode and temperament are of opposite polarities (e.g., a manic phase in a subject with a depressive temperament or a melancholic phase in a subject with a hyperthymic temperament) (Akiskal 1992). In line with Akiskal's theory, Brieger et al. (2003)

Table 1. Diagnostic criteria for a mixed episode according to DSM-IV and ICD-10, and for a mixed manic and mixed depressive features specifier according to DSM-5.

	DSM-IV (296.6x)	ICD-10 (F38 (single episode) and F31.6)	DSM-5 mixed manic features specifier	DSM-5 mixed depressive features specifier
Symptoms	The symptomatic criteria are met both for a Manic Episode and for a MDE.	The current episode is characterised by either a mixture or a rapid alternation (i.e., within a few hours) of hypomanic, manic and depressive symptoms.	Full criteria are met for a current or most-recent manic episode or hypomanic episode and at least three out of six specified core symptoms of depression are also present during the majority of days within this episode.	Full criteria are met for a MDE, and at least three out of seven specific core manic/hypomanic symptoms are present during the majority of days during the current or most-recent episode of depression.
Time criterion	Nearly every day during at least a 1-week period (time criterion for a DSM-IV manic episode).	Both manic and depressive symptoms must be prominent most of the time during a period of at least 2 weeks.	One week if the episode is manic, 4 days if the episode is hypomanic.	Two weeks (major depression time criterion).
Severity	The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features. The fifth digit codes for severity (0–4).	No specification	No specification except: for individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, due to the marked impairment and clinical severity of full mania.	No specification except: for individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.
Inclusion/Exclusion criteria	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).	The episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0. For F31.6: there has been at least one well authenticated hypomanic or manic episode (F30.-), depressive (F32.-) or mixed affective episode (F38.00) in the past.	The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication, or other treatment).	The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication, or other treatment).

examined the temperament of bipolar patients with and without a history of mixed episodes with the TEMPS-A scale and found some evidence that manic mixed episodes occur more often in patients with an inverse, depressive and anxious temperament. However, if we consider temperament as a stable and lasting personal quality, it would be difficult to explain how such a patient can still experience pure manic or depressive episodes at times.

As diverging as the models to explain mixed episodes are the categorical definitions of what constitutes a mixed episode. A major problem for including mixed states in studies is the lack of a generally accepted definition (González-Pinto et al. 2003; Cassidy et al. 2008; Vieta and Morralla 2010; Swann et al. 2013). The DSM-IV (American Psychiatric Association 1994) only recognised mania combined with depression as 'mixed states' (González-Pinto et al. 2004) but not full-blown or major depressive episodes, which may also have excitatory or hypomanic symptoms. According to the DSM-IV, mixed states imply that diagnostic criteria for a manic episode and a depressive episode (except for the duration criterion) are fulfilled concurrently, following the restrictive concept as originally proposed by Winokur et al. (1969). Clearly, these criteria are too narrow to be clinically meaningful. It has been shown in post hoc analysis of the pivotal divalproex mania study (Bowden et al. 1994) that merely a single depressive symptom predicts inferior responsiveness to lithium and better response to valproate (Swann et al. 1997); a finding that, however, may be invalid due to the cross-sectional design of the study, and the fact that it has not yet been replicated.

Indeed, DSM-IV created the most restrictive definition of a mixed episode, whereas DSM-III-R (American Psychiatric Association 1987) still allowed subthreshold manic phases to be included. Clinicians using the International Classification of Diseases (ICD)-10 (World Health Organization 1992) should be aware that the concept of mixed states in the ICD-10 is more loosely and broadly defined than in the DSM-IV since the exact number of manic or depressive symptoms is not specified (see Table 1). Among those involved in the

conception of ICD-10 there was a mutual consent that two symptoms of the opposite pole are sufficient for the diagnosis of a mixed state (A. Bertelsen, personal communication). A mixed episode can be diagnosed as a stand-alone episode (F38.00) or as part of bipolar disorder after a previous hypomanic, manic, depressed or mixed episode (F31.6). Distinct from the definitions of manic and depressed episodes, the ICD-10 does not specify the severity of mixed episodes including whether psychotic symptoms are present or not. Thus, a more detailed description of symptoms and severity of bipolar mixed states in ICD-11 is expected (Ostergaard et al. 2012).

The concept of dysphoric mania as suggested by Clothier et al. (1992) is not well-defined, but sometimes used in the context of drug trials to refer to mania with some depressed features which are either not pronounced enough or too short to fulfil the criteria for a major depressive episode. A more precise, previously used definition is found in the so-called 'Cincinnati criteria', which require at least three relevant depressive symptoms that do not overlap with DSM-III-R manic symptoms (McElroy et al. 1992) during a manic episode. This definition approximated and anticipated the DSM-5 (American Psychiatric Association 2013) concept of mania with mixed features. Future revisions of the DSM-5 might broaden the current definition of mixed features specifier (Vieta 2016), which is already far more inclusive than in the past. Hence, DSM-5 abandoned mixed states as a narrowly defined category of its own, and instead re-introduced a broadening of the concept, the mixed specifier; in other words, depression combined with some manic features ('mixed depression') or mania or hypomania combined with some depressive features ('mixed (hypo)mania'). Of note, a manic feature specifier can also be attributed to unipolar depressive disorder. The meaningfulness of this, however, remains highly controversial, since it can be implied that depressive episodes with mixed features are a part of the bipolar spectrum (Woo et al. 2015; Weibel and Bertschy 2016) as further discussed here below. It has also been noted that a mixed manic feature specifier may easily be attributed to patients with depression and comorbid borderline personality disorder, where agitated dysphoria is a common phenotype (Perugi et al. 2016; de la Rosa et al. 2017). Given the broader definition of mixed states in the DSM-5, it is not surprising that the prevalence of mixed states is higher when DSM-5 is used to diagnose patients instead of DSM-IV. For instance, a retrospective chart review of Korean patients diagnosed with BD-I, BD-II or bipolar not otherwise specified according to DSM-IVTR criteria showed that reclassification of patients according to DSM-5 criteria tripled the prevalence of bipolar with mixed features (from 6.0 to 19.6%) (Shim et al. 2015). However, sensitivity and specificity thresholds remain unclear.

The diagnosis of a mixed specifier demands the exclusion of affective symptoms due to organic conditions, substance use or medication. However, when affective symptoms outlast the acute physiological effect of substances or medication, a mixed affective specifier can be attributed, similar to DSM-5 diagnostic criteria for a manic or depressive episode. The mixed specifier carries a dimensional perspective on the concept of mixed states, making it more clinically valid, but also causes new problems: for example, anxiety, irritability, aggressiveness and agitation, the most common and pronounced symptoms of mixed states (Tohen, Calabrese, et al. 2007; Verdolini et al. 2017), are not included in the concept because of lack of specificity (Vieta and Valenti 2013; Perugi et al. 2015). This approach brings the risk of missing several true states of mixed bipolar depression, due to the rejection of overlapping symptoms in the DSM-5 'Depression with Mixed Features' criteria. This was clearly demonstrated by the late Kokoupoulos and colleague (Koukopoulos and Sani 2014) in a comprehensive review. What he called 'loss of agitation' in DSM-5 means a departure from classical definitions of Bipolar Depressive Mixed States, with no empirical supporting data for such a decision. Furthermore, due to wrong therapeutic approaches granted by this misdiagnosis, many patients might experience increased agitation and, as a consequence, a higher suicidal risk. According to Koukopoulos, agitation should be the main therapeutic target in mixed states.

Moreover, since the mixed (hypo)manic specifier can also be used in unipolar depression, the validity of a unipolar depression diagnosis or the mixed bipolar nexus in that context can be questioned. This has been well acknowledged for long time and is logically evident, that theoretically all 'unipolar' (more precisely 'nonbipolar') episodes of major depression could be part of bipolar disorder due to the well-known and not uncommon unipolar-bipolar conversion (Tondo et al. 2014; James et al. 2015). However, the opposite is not possible (e.g., conversion of bipolar disorder into unipolar depression). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study screened patients initially diagnosed with major depressive disorder for the presence of manic symptoms. Each additional manic symptom led to a 24% increased chance of a diagnosis of bipolar disorder. Thus, the results of this (Goldberg et al. 2009) and other studies (Benazzi et al. 2004; Inoue et al. 2015) demonstrated that mixed symptoms, as well as

distractibility, irritability and psychomotor agitation (which have been omitted from the DSM-5 mixed features specifier) indicate bipolarity (Malhi et al. 2016). As up to 40% of DSM-IVTR diagnosed unipolar major depressive disorder patients have clinically significant, intradepressive current or lifetime subthreshold (hypo)-manic symptoms ('unipolar depression with mixed features'), these patients could be considered and should be treated as mixed bipolar depressive patients (Rihmer et al. 2013). In line with this, unipolar depressive patients having a history of antidepressant-induced (hypo-)mania (MDD-AIHM) clearly demonstrate more similarities with bipolar patients than with unipolar patients without such history. The BRIDGE-II-MIX study showed for the MDD-AIHM group that familiality for BD, rates of atypical features and comorbid anxiety, eating and borderline personality disorders were similar to BD and significantly more frequent compared to the major depressive disorder (MDD) group without such history. In addition, MDD-AIHM patients had more than three episodes more frequently and reported higher rates of treatment resistance, mood lability and irritability following treatment with antidepressants (Barbuti et al. 2017). Treatment implications, e.g., initiation of lithium, are particularly important as, of all clinical presentations of mood disorders, mixed (agitated) major depressive episode carries the highest suicide risk regardless of the whether it develops in the context of bipolar I, bipolar II, bipolar NOS or 'unipolar' depression (Balazs et al. 2006; Isometsa 2014; Rihmer and Döme 2016).

The changing landscape moving away from categorical definitions towards a dimensional view of psychiatric illness, and especially bipolar mixed episodes, has also been recognised by regulatory agencies. In 2016, the European Medicines Agency (EMA) released a 'Concept paper on the need for revision of the note of guidance on clinical investigation on medical products for the treatment and prevention of bipolar disorder', stating that: 'Despite the fact that DSM-5 adheres to the categorical classification of psychiatric disorders, dimensional approaches are not uncommon, and often reflect current clinical practice. Bipolar disorder shares symptoms with both Schizophrenia and Major Depression. Subsequently, scientific and regulatory discussion is needed when a population with specific psychopathological characteristics is targeted (e.g., mixed features); where the data can be extrapolated and where distinct complementary data are needed for the different disorders.'

In summary, we deal with a wide range of definitions of mixed episodes that have been applied in clinical studies over the recent decades, ranging from as little as one depressive symptom during mania to the narrow DSM-IV definition. Regulatory guidance to obtain a label for mixed episodes is currently under scrutiny and may vary in different countries. As this guideline is meant for use in international clinical practice, the task force decided not to restrict evidence to the narrow DSM-IV definition currently used by the FDA for a 'mixed episode' label, but consider evidence from studies with wider definitions as equally informative.

We distinguish between the following treatment situations:

- Acute treatment of a manic episode with $\geq$3 depressive symptoms as defined by DSM-5 but also including anxiety, irritability and agitation. Agitation alone and its management is covered in a different report (Garriga et al. 2016).
- Acute treatment of a bipolar depressive episode with $\geq$3 hypomanic or manic symptoms as defined by DSM-5.
- Continuation and prophylactic treatment after a mixed index episode. This includes the prevention of relapse or recurrence not only of new mixed, but also of manic or depressive episodes. Whenever possible, we will distinguish between a mixed (hypo)manic and mixed depressive index episode.
- Prevention of mixed episodes after a manic or depressive index episode.
- Evidence derived from studies including mixed patients below the above threshold will also be detailed and valued within the category 'Further evidence' but will not be counted for the formal Category of Evidence (CE) system as established in the previous WFSBP Bipolar guidelines.

The bulk of evidence for the WFSBP bipolar task force recommendations for the best available treatment of mixed states will be still based on the DSM-IV definition, and therefore some degree of uncertainty will remain whether these recommendations can be readily extrapolated to other definitions including DSM-5.

Epidemiology and clinical relevance of mixed states

Not surprisingly, the reported incidence of mixed manic episodes in population-based studies strongly varies depending on study population and definition used, and ranges from less than 20% to almost 70%. Using DSM-III R criteria, Cassidy et al. (1998) showed that 43 out of 316 consecutively admitted manic

inpatients (14%) met the criteria for a mixed episode. On the other end of the range, Prien et al. (1988), in their NIMH collaborative study, found that 67% of admitted manic patients fulfilled mixed episode criteria as defined by the authors. The mixed episode criterion was significantly broader: a Hamilton Rating Scale for Depression (HAM-D) 17-item score of $\geq$7 while fulfilling Research Diagnostic Criteria (RDC) (Spitzer et al. 1975) for a manic episode. Notably, it is likely that the prevalence of mixed episodes increases during the course of bipolar illness, and especially so among women (Kessing 2008).

Estimates suggest that about one-third of all manic episodes meet the criteria for a DSM-5 manic episode with mixed features (Vieta et al. 2014; Young and Eberhard 2015; Reinares et al. 2015). Investigating more than 850 patients with major mood disorders, it has been found that 34% of bipolar I depressive patients, 33.8% of bipolar II depressive patients and 26% of unipolar major depressive patients met the criteria for mixed features specifier. The proportion of patients fulfilling criteria for a depressive mixed features specifier during manic or hypomanic episodes was 20.4% in bipolar I and 5.1% in bipolar II patients, respectively (McIntyre, Soczynska, et al. 2015). In first-episode bipolar disorder, more than two-thirds of episodes show a mixture of manic and depressive symptoms, which, however, may not always fulfil threshold criteria for a mixed specifier (Baldessarini et al. 2010; Vieta et al. 2014). This is in line with reports that adolescent mania is more likely than adult mania to be characterised by high rates of depressive features or to be mixed (Craney and Geller 2003; Geller et al. 2004; Birmaher et al. 2006). Summarising the different studies looking into gender preference, mixed manic episodes across definitions (mixed mania, dysphoric mania or the manic depressive dimension) are more common in manic women than in men, with the ratio being about 60:40 (González-Pinto et al. 2007). Other studies report on even higher gender ratios to the disadvantage of women (e.g., Baldessarini et al. 2014).

In their review of early studies (between 1971 and 1990) in mixed states, Cassidy et al. (1998) identified the following signs and symptoms possibly relevant to mixed manic states based on selected studies: depressed mood, anxiety, lability, paranoia, hostility and psychosis. González-Pinto et al. (2004) also found that mixed manic states had less hedonism than pure manic states. More recently, Malhi et al. and others pointed out that distractibility and psychomotor agitation might represent the very core of mixed depressive states, as they are more common in patients with mixed depression and bipolar spectrum disorder than in patients diagnosed with unipolar depression or BD-I disorder. Of note, neither distractibility nor psychomotor agitation define a major depressive episode with mixed features (Malhi et al. 2014; Perugi et al. 2015).

Several distinctive features and predictors of mixed episodes, in both narrowly defined bipolar disorder and bipolar spectrum disorder, have been described in the literature: greater female prevalence (Dell'Osso et al. 1991; Akiskal et al. 1998; Arnold et al. 2000), especially in mixed hypomanic patients (Suppes et al. 2005), younger age at onset and more recurrences during follow-up (González-Pinto et al. 2011; Mazzarini et al. 2017), more past mixed episodes (Wilhelm et al. 2007), higher probability of mixed episodes at illness onset (Perugi et al. 2001), more irritability (Swann 2000), aggressiveness (Verdolini et al. 2017), suicidality (Dilsaver et al. 1994; Strakowski et al. 1996; Balazs et al. 2006; Rihmer and Döme 2016), obesity (Petri et al. 2017) and neuropsychiatric comorbidity (Himmelhoch and Garfinkel 1986). Manic episodes with or without subsyndromal depression also differ in treatment response (Swann et al. 1997; Swann et al. 2002), severity of anxiety (Swann et al. 1986; Swann et al. 2002) and duration (Pacchiarotti et al. 2011).

The depressive burden during a manic episode obviously matters. Young and Eberhard (2015) found, in a naturalistic study, that during their current manic episode, BD-I patients 'with mixed features' according to DSM-5 had more severe symptoms of anxiety, irritability, and agitation (average composite severity score of 4.1 vs 3.4), a higher incidence of suicide attempts (38% vs 9%), and more physician dissatisfaction with treatment response (22% vs 14%), compared to patients with none up to two depressive symptoms (all $P < 0.05$). Similarly, when analysing the placebo arm of a randomised controlled trial (RCT) testing asenapine in manic and mixed patients, McIntyre et al. (2013) showed that, with increasing baseline severity of depressive features, treatment outcome became poorer. In addition, the presence of a depressive dimension and the absence of activation has been found to be linked with misdiagnosis in those BD inpatients with a first psychotic episode (Arrasate et al. 2014). In line with this, a self-reported online survey (IMPACT) in 700 bipolar patients found that patients with more than three depressive symptoms were more likely to have had a delay in diagnosis, more likely to have experienced shorter symptom-free periods, and were characterised by a marked lower prevalence of typical manic manifestations. The IMPACT survey also assessed non-mood symptoms beyond DSM-5 specifier

criteria, including anxiety, agitation and irritability. Again, anxiety associated with irritability/agitation was a key symptom among patients with DSM-5 mixed features differentiating them from pure manic patients (Vieta et al. 2014).

Most data on the course of illness relate exclusively to BD-I patients; less is known about BD-II mixed states. Tundo et al. (2015) followed 168 first-episode BD-II patients, 12 of them with broadly defined mixed state at illness onset. Mixed state in BD-II was defined according to Koukopoulos criteria of agitated depression (Koukopoulos and Koukopoulos 1999), as prior to DSM-5 BD-II mixed states were 'non-existent' in classification systems). BD-II patients were then compared to a cohort of 239 BD-I patients, with 52 of them having a mixed episode at onset. Having had a broadly defined mixed episode increased the risk of suicidal attempts and substance abuse among patients with BD-II, but not with BD-I.

It appears that mixed patients in general are more prone to substance abuse. Several reports suggested a higher rate of comorbid substance abuse in mixed patients (Tohen et al. 1998; Goldberg et al. 1999; Tundo et al. 2015; McIntyre, Soczynska, et al. 2015); however, this could not be verified in all studies (Cassidy et al. 2001b). Nevertheless, quitting cannabis improves functionality in patients with a previous mixed manic episode (Zorrilla et al. 2015).

Patients with mixed mania have higher rates of recurrence (Hantouche et al. 2006; Tundo et al. 2015), psychiatric re-admissions (Perugi et al. 2000; González-Pinto et al. 2011), more frequent prior suicide attempts (Dilsaver et al. 1994; Strakowski et al. 1996; Goldberg et al. 1998), longer and more expensive hospitalisations (González-Pinto et al. 2010), a longer duration of illness after the first hospitalisation (Cassidy and Carroll 2001), and are more difficult to treat (Kupfer et al. 2000). For planning maintenance treatment in patients with a mixed-index episode, it is also of note that they are also at a higher risk of switching, probably rapid cycling, and suicide attempts, which may then call for different therapeutic choices (Azorin et al. 2009). Mixed episodes tend to occur relatively consistently within individual patients, as demonstrated by two studies. In a study of hospitalised manic and mixed manic patients followed prospectively over three episodes, 69% of mixed manic episodes were stable from episode 1 to 2, as were 84% of manic episodes. The rate of occurrence of mixed manic episodes in the second episode among patients whose first episode had been mixed was over three times that predicted by chance, indicating much higher persistence of mixed mania across episodes than would occur randomly (Cassidy et al. 2001a). In a retrospective study of 253 bipolar patients hospitalised at least twice because of consecutive manic or mixed episodes over 20 years, depressive mood, irritability, psychomotor inhibition, psychosis and mania were highly stable over both consecutive recurrences, and over the long-term course of illness. This syndromal stability was not substantially affected by gender, age of onset or intermittent substance abuse (Sato et al. 2003). A recent meta-analysis of large naturalistic studies confirmed that mixed states beget mixed states: a mixed index episode was in almost half of the cases followed by another mixed episodes (45.9% vs 28% depressive and 26.1% manic) (Radua et al. 2017).

Little is known about quality of life (QoL) in patients with mixed states opposed to pure affective states. As the result of a small interview series, Mortensen et al. (2015) noted that participants described mixed states as worse than other bipolar disorder states but their residual symptoms as prolonged. Mixed states affected the functioning of patients in key life domains such as self-esteem, family, love and social life, physical well-being, and working capability.

In summary, bipolar mixed states are a very uncertain construct, with many conflicting definitions. The changes in categorial definitions clearly contribute to the large variability of epidemiological figures reported. In particular, there is the complexity of parsing mixed states from agitated depression and borderline personality disorder, both as a threshold disorder and a comorbidity, that presents with agitated dysphoria as a normative presentation (Coulston et al. 2012). Both agitated depression and borderline personality disorder would need a treatment approach that is very different from bipolar mixed states, so a firm diagnosis is warranted at treatment initiation.

Continuation and maintenance treatment after an acute mixed episode

Long-term treatment in bipolar patients has been traditionally divided into continuation and maintenance (or prophylactic) treatment, which are, in turn, associated with the starting points 'remission' and 'recovery', respectively. In the WFSBP guideline on long-term treatment (Grunze et al. 2013) we elaborated extensively on the definitions and timelines of continuation and prophylactic treatment, and their implications for study designs. Due to the paucity of distinct data for continuation and prophylactic treatment after an acute mixed episode, we will not elaborate on this topic in the current guideline and separate continuation from prophylactic treatment, but use a simplified approach

by combining them into one category 'Maintenance', simply implying the aim of preventing the emergence of symptoms following remission of an episode.

Prevention of mixed episodes after a manic or depressive index episode

In patients with a history of mixed episodes, prophylactic treatment after a manic or depressive episode should not only target the prevention of manic or depressive relapse, but also give special attention to mixed recurrences. This is particularly true if a prophylactic treatment might increase the risk of provoking a mixed state, e.g., long-term antidepressant continuation after a depressive index episode (El-Mallakh et al. 2008), or antipsychotic-induced dysphoria after a manic index episode (Wu and Okusaga 2015). Unfortunately, only few maintenance studies supply specific information on the prevention of mixed episodes. Especially in older studies, this information is lacking.

Scope of this review

Parts I, II and III of the WFSBP Guidelines for the Biological Treatment of Bipolar Disorders (Grunze et al. 2009; Grunze et al. 2010; Grunze et al. 2013) concerned the acute and maintenance treatment of mania and bipolar depression. At the time of compilation of the acute treatment guidelines, there were only few data available on the evidence-based treatment of mixed episodes, especially mixed depressive episodes and prophylaxis of mixed episodes. In the acute mania guideline (Grunze et al. 2009), the efficacy of medication in mixed manic episodes was also detailed and included in the recommendations if such information was available, mostly from secondary post hoc analysis of RCTs.

In keeping with the existing evidence, this guideline has its primary focus on mixed episodes in BD-I disorder. When evidence is available, we will also consider results from studies in BD-II disorder and rapid cycling patients and include them into our ranking of evidence. As the evidence has been derived largely from studies in adults aged 18–65, this guideline is primarily only applicable to this patient group. This issue is particularly relevant for this guideline because mixed states and rapid cycling may be more frequent in younger patients than adults (Grande et al. 2016). In the few cases where additional information for efficacy or safety in children or old age was retrieved, we also cited it in the body of text but did not include it for primary efficacy ratings, but as additional supportive/non-supportive evidence (category 'Further evidence (FE)').

This guideline series is dedicated to bipolar disorder as categorised in DSM-IV and DSM-5. Although it is feasible to assume that a unipolar major depressive episode (MDE) with mixed features according to DSM-5 may truly fall into the bipolar spectrum, this remains controversial and has not been consented to by all specialists. Thus, the treatment of MDD with mixed features is not part of this guideline. Instead, we would like to refer the reader to a recent expert guidance on depressive mixed states (Stahl et al. 2017). It has been hypothesised that this new diagnostic designation is a precursor of bipolar disorder and that patients meeting these criteria should be treated as such (Benazzi 2005; Benazzi 2006). At this time, controlled evidence for treatment is virtually restricted to lurasidone (Suppes, Silva, et al. 2016; Targum et al. 2016). In the absence of further evidence, this expert consensus suggests using similar principles of treatment in bipolar and unipolar depression with mixed features: avoidance of antidepressant monotherapy and preferred use of some atypical antipsychotics or mood stabilisers. Whether this approach will result in better outcomes is still up for further investigation.

As with the previous guidelines, we did not include schizoaffective disorders per se despite their wide similarities with bipolar disorder (Marneros 2001b) as it was felt that such a broad spectrum view would go beyond the scope of this paper. However, in patients with mixed episodes, psychotic symptoms are not rare (González-Pinto et al. 2011), and in clinical practice, a clear delineation of a psychotic mixed bipolar episode from a schizoaffective disorder with mixed features is often difficult and does not have therapeutic consequences (Murru et al. 2016). Cycloid psychoses, because of their polymorphous and bipolar traits, might resemble a true bipolar mixed state (Leonhard 1999). Besides calling for their recognition for clinical and research purposes, based on their heuristic value (Salvatore et al. 2008) these guidelines will not address them because of a lack of validation and specific therapeutic studies.

Besides efficacy, we will also consider safety and tolerability issues. Unfortunately, these important issues are not uniformly captured across studies, and are seldom measured as rigorously as efficacy; thus, any in-depth grading of these important aspects is difficult and subject to bias.

As with the previous guidelines of this series, we concentrate on pharmacotherapy and physical therapies. We value the contribution of psychotherapies and sociotherapies as part of a modern and individualised treatment package; however, a full evidence-

based review of these modalities is beyond the scope of the present paper.

For each medication, we will provide a grading of efficacy in monotherapy and in combination/augmentation treatment. At the end, this guideline aims to provide the reader with the following information for a specific medication (when available):

- Efficacy in the treatment of acute manic mixed episodes.
- Efficacy in the treatment of acute depressive mixed episodes.
- Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a manic, depressive or mixed episode if such detailed information is available.
- Efficacy in maintenance treatment after an acute manic or depressive episode in preventing new mixed episodes.
- Further important supportive/unsupportive evidence, e.g., from large scale naturalistic studies, post hoc analyses of very small numbers from RCTs, or in specific subgroups, e.g., children, adolescents, old age ('Further evidence (FE)').
- Brief summary of the acute and long-term safety and tolerability of the medication ('Safety and tolerability (ST)') as this has already extensively dealt with in the previous guidelines within this series (Grunze et al. 2009; Grunze et al. 2010; Grunze et al. 2013).
- Grades of recommendation for the respective treatment scenarios ('Recommendation grade (RG)').

For practicability of use and antisuicidal properties of a medication, we refer the reader to the 2013 bipolar disorder maintenance guideline.

Methods of this review

The methods of retrieving and reviewing the evidence base, and coming up with a recommendation, are in general identical to those described in the WFSBP guideline for acute mania and bipolar depression (Grunze et al. 2009; Grunze et al. 2010). For those readers who are not familiar with these guidelines, we will summarise the methods in brief.

The data used for these guidelines was extracted from a MEDLINE and EMBASE search, the Science Citation Index at Web of Science (ISI) and a check of the Cochrane library for recent meta-analyses and from recent proceedings of key conferences. The original search was conducted on 29 May 2013, and updated on 12 March 2017. Some reviews mentioned in this article were fully published after this date but were available to the authors as accepted manuscripts. Results of the initial search have also been reviewed previously (Grunze and Azorin 2014). To ensure comprehensiveness of data, we also consulted various national and international treatment guidelines, review papers, consensus statements and hand-searched several textbooks. In addition, www.clinicaltrials.gov was accessed to check for unpublished studies, and, if possible, the sponsors of those trials were approached for further information. All searches cover the time span from 1967 to March 2017. Having different sources of information appears crucial: A systematic MEDLINE search for a recent meta-analysis of the prevalence of generalised anxiety disorder in BD returned 1300 results but identified only seven out of 30 eligible articles, whereas the rest were identified by hand search in reviews, text books etc. (Preti et al. 2016).

To be eligible, studies had to enrol patients with mixed mania/mixed depression, or with both mixed and pure episodes. We retrieved evidence from long- and short-term RCTs, open-label studies, case series or reports, and retrospective and prospective studies. In the latter case, data were from stratified, post hoc, or treatment interaction analyses and reporting results on the mixed subgroup. We retrieved data on other physical therapies, such as electroconvulsive therapy (ECT) or deep brain stimulation (DBS). We excluded publications in languages other than English, French, German, Spanish or Russian, those containing duplicated data, and those in which patient data was not stratified by mixed, pure manic or pure depressive status.

Given the large heterogeneity of study designs and diverging definitions of mixed states, we did not use the results of meta-analyses as evidence of the same level as results from single RCTs fulfilling inclusion criteria. Meta-analysis cannot resolve uncertainty where the methodology of the individual RCTs is flawed (Goodwin et al. 2016). Those meta-analyses that we consulted, if the evidence remained unclear based on single studies, were selected according to the quality criteria defined by Huf et al. (2011). An exception is the category 'safety' in the case we deal with rare events that may only light up when large numbers of subjects are analysed across trials.

Network meta-analyses, as recently conducted for acute mania (Yildiz et al. 2015), bipolar depression (Taylor et al. 2014) and bipolar maintenance (Miura et al. 2014), appear methodologically sounder and may allow a more objective ranking of drugs according to their efficacy and acceptance. However, to our knowledge, no such network analysis has been

published to date covering all potential, evidence-based treatments for mixed states; only two meta-analyses have been conducted for the acute treatment with atypical antipsychotics: one for mixed mania (Muralidharan et al. 2013) and one for mixed depression (Fornaro et al. 2016).

In this review, evidence derived from combination treatments will contribute equally to the final recommendation grade as evidence derived from monotherapy with the respective drug, and we will discuss the respective combination/augmentation studies under the respective monotherapy header, considering the constant drug + placebo as the 'placebo-condition', and the constant drug + the investigational drug as the 'test-condition'. Clearly, some uncertainty of this approach remains, as we cannot exclude that the test drug is only beneficial in the specific combination, but not by itself.

To achieve a uniform and, in the opinion of this taskforce, an appropriate ranking of evidence, we adopted a similar rigorous hierarchy of evidence and level of recommendation as was used in previous WFSBP guidelines including the first published WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008) (see Table 2). In brief, a drug must have shown its efficacy in double-blind placebo-controlled studies to be recommended with substantial confidence (categories of evidence (CE) A or B, corresponding to RGs 1–3). Lower-level evidence from uncontrolled studies (CE 'C') or conflicting results (CE 'D') were accepted for a low RG 4 or 5, respectively. Substantial concerns about safety and tolerability of a drug could also result in a downgrading of the RG, especially when making a distinction between RG 1 and 2.

Depending on the number of positive trials and the absence or presence of negative evidence, different CEs for efficacy were assigned. A distinction was also made between 'lack of evidence' (i.e., studies proving efficacy or non-efficacy do not exist, CE 'F') and 'negative evidence' (i.e., the majority of controlled studies showed non-superiority to placebo or inferiority to a comparator drug (CE 'E')). When there is lack of evidence, a drug could still reasonably be tried in a patient unresponsive to standard treatment, while such an attempt should not be undertaken with a drug that showed negative evidence.

We set a minimum sample size of 25 participants for a placebo-controlled study to be considered as evidence for the categories of evidence A or B. RCTs with a smaller number of participants could still be considered for the categories 'C' or 'Further evidence (FE)' depending on their overall quality.

The role and positioning of post hoc and subgroup analyses has not been clearly defined in the first guideline of the WFSBP series using our grading system (Bandelow et al. 2008). Post hoc secondary analyses play a prominent role in studies including manic and mixed manic patients but bear the risk of inflating the chance of false-positive findings (Oxman and Guyatt 1992). Many of these analyses were done on data sets that have been not informative in their primary outcome, were not hypothesis generated, and therefore will be counted as CE 'C' (similar to uncontrolled studies). However, when a secondary analysis has been included a priori in the analysis plan and is sufficiently powered, a CE 'B' could be considered.

Another deviation from the original WFSBP guideline grading system is the role of large registry studies. Of course, they do have the risk of bias, similar to, but of a different kind, than with that encountered in single RCTs. On the other hand, they can supply valuable information about the 'real world' effectiveness and acceptance of treatment modalities, and especially in under-researched or rare indications (as mixed states are to some degree) they can help to resolve uncertainty. The task force decided to accept registry studies at least on CE 'C' level (as other retrospective studies), but only if they are of good quality and bias is minimised, e.g., each patient serving as his own control in an on-off design, they can receive the same CE 'B' as an RCT. This decision of the task force is also in line with their appreciation in other recent bipolar guidelines, such as the British Association for Psychopharmacology guideline (Goodwin et al. 2016).

FE and ST were graded with a simplified system ranging from '++' for best positive evidence to '– –' for strong negative evidence, and rated separately for acute and long-term treatment (see Table 3).

Recommendations were derived from the CE for efficacy and from additional aspects as safety and tolerability. We have not considered the direct or indirect costs of treatments as these vary substantially across different health care systems. In addition, as the approval by national regulatory authorities is dependent on a variety of factors, including the existence of a label 'mixed episodes' and the sponsor's commercial interest (or lack thereof), this guideline is exclusively based on the available evidence.

The task force is aware of several inherent limitations of these guidelines: namely publication bias (Turner et al. 2008; Flint et al. 2015), sponsor bias (Lundh et al. 2012) and, finally, the limitations of evidence itself. One of the most important clinical

Table 2. Categories of evidence (CE) and recommendation grades (RG).

Category of evidence	Description
A	Full Evidence from Controlled Studies is based on: two or more double-blind, parallel-group, randomised controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo' in a study with adequate blinding) *and* one or more positive RCTs showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B	Limited Positive Evidence from Controlled Studies is based on: one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') *or* a randomised controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial[6] *or* an a priori planned, sufficiently powered subgroup analysis as part of the investigational protocol *and* in the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least one more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomised controlled comparison showing non-inferiority to an established comparator treatment.
C	Evidence from Uncontrolled Studies or Case Reports/Expert Opinion/post hoc analyses of a RCT is based on: one or more positive naturalistic open studies (with a minimum of five evaluable patients) *or* a comparison with a reference drug with a sample size insufficient for a non-inferiority trial *and* no negative controlled studies exist *or* Case reports: one or more positive case reports *and* no negative controlled studies exist *or* post hoc analysis of a RCT (not planned a priori as part of the investigational protocol) *or* Based on the opinion of experts in the field or clinical experience.
D	Inconsistent Results Positive RCTs are outweighed by an approximately equal number of negative studies
E	Negative Evidence The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') or inferiority to comparator treatment
F	Lack of Evidence Adequate studies proving efficacy or non-efficacy are lacking
Recommendation Grades (RG)	Based on:
1	Category A evidence *and* good risk–benefit ratio
2	Category A evidence *and* moderate risk–benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

Table 3. Grading of Categories FE and ST.

	Further evidence (FE)	Safety and tolerability (ST)
++	Several supportive FE, e.g., meta-analysis or positive studies which, however, fall short of criteria to be considered as evidence for CE 'A' or 'B'	Very good
+	Some (or more) supportive FE, e.g., limited evidence from open studies	Good
0	Conflicting data or unknown	Equally advantages and disadvantages, or unknown
–	Some (or more) non-supportive FE, e.g., limited negative evidence from open studies	Some concerns
–	Several non-supportive FE, e.g., negative meta-analysis or negative studies which, however, fall short of criteria to be considered as evidence for CE 'A' or 'B'	Major concerns

questions that cannot be sufficiently answered in an evidence-based way is what to do when any first-step treatment fails, which in mixed states rather is the rule rather than the exception. Therefore, with the current level of knowledge, we can only provide suggestive guidelines and not rigorous algorithms.

Once a draft of this guideline had been prepared by the secretary and co-authors, it was sent out to the members of the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders for critical review and addition of remarks about specific treatment peculiarities in their respective countries. A second draft, revised according to the respective recommendations, was then distributed for final approval.

These guidelines were established without any financial support from pharmaceutical companies. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

Medications commonly used in mixed states and their ranking by evidence

The initial search of the literature led to the identification of 1,388 publications for further evaluation. After the exclusion of non-relevant articles for this guideline we extracted data on the efficacy outcomes of medications or physical therapies for acute or maintenance treatment of mixed episodes from 133 studies. In brief, most of the studies reported results for adult populations (89.5%), were performed in inpatients (55%), were based on short-term treatments (70%) and reported data obtained from RCTs (37.6%; followed by open-label studies [24%], case reports [17.3%], retrospective evaluations [15%], and prospective observations [6%]). The vast majority of data was therefore obtained from uncontrolled studies (62.4%), and was considered as lower-grade evidence of efficacy of the related therapy[1]. The update of the search on March 16, 2017, identified another 31 additional studies contributing to the evidence for a given treatment.

In the following sections, we will highlight pivotal studies supporting (or contradicting) efficacy of a given medication, amended by other supportive evidence if clinically relevant. We assigned ratings for efficacy as detailed in the section on 'Methods of this review', and graded the categories 'Further evidence (FE)' and 'Safety and Tolerability' in a more simplified system (ranging from ++ to – –, see Table 3). As this guideline should be useful for the practicing clinician, drugs under consideration are not exclusively those where data of randomised controlled studies are available, but those which are either used with some trust and frequency by clinicians in bipolar patients, e.g., antidepressants as a group, or in specific subgroups, e.g., clozapine in otherwise treatment refractory patients. The results are summarized in Table 4 (acute treatment) and Table 5 (maintenance treatment).

Antidepressants

Almost all guidelines recommend not initiating antidepressants when a mixed state is diagnosed, although in clinical practice they remain widely prescribed in combination with antimanic agents for the treatment of mixed states (Azorin et al. 2009). The International Society for Bipolar Disorders Task Force on antidepressants provided guidance in that regard (Pacchiarotti et al. 2013). Mixed states are best conceptualised, for both diagnostic assessment and treatment purposes, as states of substantial mood dysregulation and instability rather than just states characterised by either the simultaneous or sequential presence of various combinations of depressive and manic/hypomanic symptoms. This not only constitutes a major shift in paradigm in terms of the conceptualisation but also has significant implications for the treatment of mixed states. If mixed states were to be perceived as a combination of depressive and manic symptomatology, then the use of a combination of mood stabilisers or antipsychotics and antidepressants would appear to be an intuitive option. If the focus of treatment is on the regulation of mood and the correction of mood instability, however, then it becomes apparent that medication with potentially mood-destabilising effects, e.g., some antidepressants and typical antipsychotics, should be avoided (Wehr and Goodwin 1987; Akiskal 1994). Current evidence from prospective or retrospective studies support the notion that mixed patients are at higher risk for a maniform switch (Bottlender et al. 2004; Strejilevich et al. 2011; Valenti et al. 2011; Inoue et al. 2015; Barbuti et al. 2017). The use of antidepressants in bipolar disorder has also been associated with the de novo induction of mixed states (Dilsaver and Swann 1995; El-Mallakh et al. 2008). An antidepressant-induced 'activation syndrome' is about four times more frequent in bipolar II and bipolar NOS patients than in unipolar major depression (52% vs 14%, respectively) (Takeshima and Oka 2013). Antidepressant monotherapy might worsen the cross-sectional picture of bipolar depression and unipolar depression with bipolar features specifier by aggravating the pre-existing mixed state or by inducing de novo mixed features which, in turn, can increase the risk of suicidal behaviour (Rihmer and Döme 2016). In line with this, Musil et al. found that

Table 4. CE and RG for the acute treatment of mixed states.

Agent	CE in acute MM episodes (monotherapy)	CE in acute MM episodes (combination/ augmentation therapy)	CE in acute DM episodes (monotherapy)	CE in acute DM episodes (combination/ augmentation therapy)	FE in short-term treatment	ST in short-term treatment	RG for the acute treatment of mixed states
Antidepressants	F	F	F	F	0	–	none
Aripiprazole	B for MS B for DS	F	F	F	+	0	3 for MM (monotherapy)
Asenapine	E for MS C for DS	F	F	F	+	+	4 for MM (monotherapy, for DS only)
Carbamazepine	C for MS C for DS	F	C for DS	F	+	–	4 for MM (monotherapy) 4 for DM (monotherapy, for DS only)
Cariprazine	C for MS F for DS	F	F	F	0	+	4 for MM (monotherapy, for MS only)
Clozapine	C for MS	C for MS	F	F	+	–	4 for MM (monotherapy and combination therapy, MS only)
Gabapentin	F	C for MS C for DS	F	F	+	+	4 for MM (combination therapy)
Lamotrigine	F	F	F	F	+	+	none
Lithium	F	F	F	F	0	–	none
Lurasidone	F	F	C	F	+	+	4 for DM (monotherapy)
Olanzapine	A for MS C for DS	A for MS A for DS	C	F	++	+	2 for MM (monotherapy) 2 for MM (combination therapy with valproate) 4 for DM (monotherapy)
Oxcarbazepine	F	C for MS	F	F	0	+	4 for MM (combination therapy with lithium)
Paliperidone	B for MS E for DS	E	F	F	0	0	3 for MM (monotherapy)
Quetiapine	E	C for MS B for DS	F	F	+	0	3 for MM (combination, for DS) 4 for MM (combination, for MS)
Risperidone	C	E	F	F	+	0	4 for MM (monotherapy)
Topiramate	F	D for MS	F	F	+	0	5 for MM (combination therapy)
Typical AP	C	E	F	F	0	–	4 for MM (monotherapy)
Valproate	C for MS	F	F	F	+	+	4 for MM (monotherapy)
Ziprasidone	C for MS C for DS	F	F	B	+	+	4 for MM (monotherapy) 3 for DM (combination)
ECT	F	C	F	C	0	–	4 for MM (combination) for DM (combination)

MM: manic mixed; DM: depressive mixed; MS: manic symptoms; DS: depressive symptoms; M: mania; D: depression; Mx: mixed episode; MIE: manic index episode; DIE: depressive index episode; MxIE: mixed index episode; CE: category of evidence; FE: further evidence; ST: safety and tolerability; RG: recommendation grade.

treatment-emergent suicidality occurs in 27% of bipolar depressive and only in 7% of unipolar depressive patients. However, it should be borne in mind that the data mentioned above comes only from observational studies and case reports. Whether antidepressants can provoke mixed episodes, activation or agitation during maintenance treatment in remitted patients is unknown. These considerations imply that mixed states should be treated, if unavoidable, as a last resort, only with selected antidepressants known to be less likely to induce a treatment-emergent affective switch (TEAS), and with minimal duration and dosage.

Based on the circadian rhythm hypotheses of mixed features, where mixed features express a state of transitional unstable circadian rhythm (Lee et al. 2013), the use of antidepressants affecting circadian rhythmicity may be advantageous. However, a pivotal RCT in bipolar depression with adjunctive agomelatine failed (Yatham et al. 2016), post hoc analyses suggested contribution of a larger placebo response to the failure of the study. A small open study in 20 bipolar II patients on agomelatine monotherapy did not find any differences in efficacy between retarded and agitated (anxious) depressions as a proxy of mixed depressive states (Zimina et al. 2016).

For adjunctive treatment, post hoc data are available for fluoxetine added to olanzapine (Tohen, Vieta, et al. 2003) in depressive mixed states. That 8-week, double-blind trial of adult BD-I depression compared treatment with placebo, olanzapine or olanzapine/fluoxetine combination (OFC). Studying mixed depression was not an a priori goal of the double-blind trial, but

Table 5. CE and RG for the maintenance treatment after a mixed episode and for the prevention of mixed episodes.

Agent	CE to prevent a new episode after a mixed index episode (MxIE) (monotherapy)	CE to prevent a new episode after a mixed index episode (combination/ augmentation therapy)	CE to prevent a mixed episode after a manic (MIE) or depressed index episode (DIE) (monotherapy)	CE to prevent a mixed episode after a MIE or DIE (combination/ augmentation therapy)	FE in long-term treatment	ST in long-term treatment	RG for the maintenance treatment after a mixed episode and for the prevention of mixed episodes
Antidepressants	F	F	F	F	0	0	none
Aripiprazole	F	E for Any (+ lithium/ valproate) F for MM (+ lamotrigine) C for DM (+ lamotrigine)	E (MIE) F (DIE)	F	0	+	4 to prevent D after MxIE (combination)
Asenapine	F	F	F	F	+	+	none
Carbamazepine	F	F	E	F	+	–	none
Cariprazine	F	F	F	F	0	+	none
Clozapine	F	F	F	F	0	–	none
Gabapentin	F	F	F	F	+	+	none
Lamotrigine	F	F	E	F	0	++	none
Lithium	B (any type) B (manic)	F	D	F	+	–	3 to prevent a new manic and any type episode after MxIE (monotherapy) 5 to prevent a mixed episode after an unspecified index episode
Lurasidone	F	F	F	F	0	+	none
Olanzapine	B	F	D	F	+	–	3 to prevent a new episode after MxIE (monotherapy)
Oxcarbazepine	F	F	F	F	0	0	none
Paliperidone	F	F	F	F	0	0	none
Quetiapine	B (for manic, depressed, any type)	A (for manic, depressed, any type)	E	F	0	–	2 to prevent a new episode after MxIE (combination) 3 to prevent a new episode after MxIE (monotherapy)
Risperidone	F	C	F	F	0	–	4 to prevent a new episode after MxIE (combination therapy)
Topiramate	F	F	F	F	0	0	none
Typical AP	F	F	F	F	0	–	none
Valproate	E	F	B	F	+	–	3 to prevent a mixed episode after an unspecified IE (monotherapy) or manic or mixed index episode
Ziprasidone	C	F	F	F	0	+	4 to prevent mania after MxIE (monotherapy)
ECT	F	C	F	F	0	–	4 to prevent a new episode after MxIE (combination therapy)

MM: manic mixed; DM: depressive mixed; M: mania; D: depression; Mx: mixed episode; MIE: manic index episode; DIE: depressive index episode; MxIE: mixed index episode; CE: category of evidence; FE: further evidence; ST: safety and tolerability; RG: recommendation grade.

among the study participants (diagnosed with BD-I disorder, current episode MDE according to DSM-IV) a fair number of patients having $\geq$2 manic/hypomanic symptoms (i.e., $\geq$2 Young Mania Rating Scale (YMRS) items scoring $\geq$2) were identified. Response was defined as a $\geq$50% reduction in Montgomery–Asberg Depression Rating Scale (MADRS) score and $<$2 concurrent manic/hypomanic symptoms. Of the patients with mixed depression (which represented almost 50% in all arms), patients treated with OFC showed a significantly higher response rate versus patients treated with placebo (odds ratio (OR) = 3.91; 95% confidence interval (CI), 1.80–8.49; $P = 0.0006$), but no statistically significant difference was observed between OFC and olanzapine in the rate of responders (OR= 2.00; 95% CI, 0.96–4.19; $P = 0.065$). Thus, in summary, addition of fluoxetine to olanzapine did not lead to a statistically significant increase of responders compared to

olanzapine monotherapy in mixed depression, but the study was not powered to show such difference. No worsening of mania was seen among the fluoxetine-treated patients (Benazzi et al. 2009). Categorisation of the evidence from this study in our grading system is difficult; as it was not an a priori planned secondary analysis, it would count as 'C' evidence if positive. Assigning a category 'E', however, for negative evidence may be not justified given that it is a single and underpowered exploratory analysis, whereas the definition of category 'E' asks for a 'majority of studies' that are negative. Thus, category 'F' (lack of evidence) may be most appropriate.

CE in acute manic mixed episodes (monotherapy) is 'F'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.
CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'
CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.
Rating of FE: 0 for short-term treatment, 0 for long-term treatment
Rating of ST: – for short-term treatment, 0 for long-term treatment

Recommendation grade (RG)

None

Based on the evidence, the use of antidepressants for the acute and continuation treatment of mixed episodes or for the prevention of mixed episodes cannot be recommended and may be potentially hazardous.

Aripiprazole

Efficacy in acute manic mixed episodes

The first pivotal RCT of aripiprazole in acute manic or mixed patients included 86 subjects (33%) with DSM-IV mixed states (Keck, Marcus, et al. 2003). Unfortunately, separate results for pure manic and mixed patients were not reported in the paper. Aripiprazole was then studied in a second 3-week RCT that again included both DSM-IV manic and mixed patients with the subgroup of mixed patients now consisting of 113 subjects. As confirmed by the principal investigator (P. Keck, personal communication), the subgroup analysis in mixed patients was part of the protocol and planned a priori and not post hoc. In DSM-IV mixed episode patients, aripiprazole produced significantly greater improvements from baseline compared with placebo in YMRS total score ($P = 0.01$), and significantly greater improvements from baseline in MADRS total score compared with placebo at endpoint ($P = 0.04$) (Sachs et al. 2006). The effect of aripiprazole on depressive symptoms in mixed patients appears genuine given the mean baseline severities and improvements of MADRS total scores (mean baseline: aripiprazole 18.39, placebo 20.06, both corresponding to mild to moderate depression when measured in pure depression; mean change: aripiprazole −7.93; placebo −4.29, $P = 0.041$) However, in mixed patients depression scores may be inflated by non-specific symptoms also present in mania, e.g., sleep (MADRS item 4) and concentration (MADRS item 6) problems. A single-item analysis of the MADRS scores in this study was not available to the authors, and we cannot rule out that improvement of depression was largely due to improving symptoms overlapping between mania and depression rating scales.

The mean dosage of aripiprazole was 27.2 mg/day, which is in line with recommended dosages for acute mania, but considerably higher than those used as augmentation treatment for unipolar depression. When these patients were pooled with the subgroup of mixed patients of the first similarly designed RCT (Keck, Marcus, et al. 2003), aripiprazole was found to be superior to placebo in improving manic symptoms in both manic and mixed subgroups and regardless of the severity of depressive symptoms. Moreover, aripiprazole was associated with higher percentages of responders and remitters than placebo regardless of patients presenting with a manic or mixed episode ($P = 0.0006$ for responder rates, and $P = 0.01$ for remission rates in mixed patients) (Suppes et al. 2008).

No separate outcome analyses have been published for further RCTs including manic and DSM-IV mixed patients, namely the positive studies by Young et al. (2009), Keck, Orsulak, et al. (2009) and Zimbroff et al. (2007), and the negative acute study by El-Mallakh et al. (2010) despite including reasonable numbers of mixed patients. Another acute RCT, the AMAZE study, conducted in an Asian population,

included only 28 DSM-IV mixed patients, a sample too small to allow for a separate meaningful analysis (Kanba et al. 2014). A randomised, double-blind comparison of aripiprazole against haloperidol was also underpowered for a separate analysis of mixed patients (Vieta et al. 2005).

We identified one RCT testing aripiprazole in combination/augmentation therapy in acute manic and DSM-IV mixed episodes (Vieta, T'joen, et al. 2008). Again, no separate analysis for mixed patients has been reported in the paper.

CE in acute manic mixed episodes (monotherapy) is 'B' both for manic and depressive symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

No data is available for the acute treatment of DSM-5 bipolar depression with mixed features or otherwise classified depressive mixed states.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

For the 48 patients with mixed index episodes participating in the aripiprazole oral continuation studies (Keck et al. 2006; Keck et al. 2007), no separate outcome data have been reported. A recently finished study (ClinicalTrials.gov Identifier: NCT01567527) testing aripiprazole long-term injectable included only manic patients at baseline.

Yatham et al. (2013) conducted a post hoc analysis of a 52-week maintenance combination study (aripiprazole + lithium or valproate versus placebo + lithium or valproate), in 107 patients with DSM-IV mixed mania at entry but stabilised at baseline (ClinicalTrials.gov Identifier: NCT00261443, original publication (Marcus et al. 2011)). They found no significant advantage of aripiprazole for the group of mixed patients for time to any relapse. Another smaller maintenance study comparing aripiprazole + valproate versus placebo + valproate after a manic or mixed index episode included only a very small number of mixed patients, and separate outcomes have not been reported (Woo et al. 2011).

Post hoc interaction analysis of a 52-week study testing aripiprazole + lamotrigine versus placebo + lamotrigine (Carlson et al. 2012) demonstrated that there were differential treatment effects according to a patient's index episode, manic or mixed presentation, for time to depressive episode ($P = 0.044$). The results from subgroup analyses showed that time to relapse to a depressive episode was significantly longer with the aripiprazole combination compared with the placebo combination in the subgroup of the 173 patients presenting with a mixed episode at baseline ($P = 0.041$), but not in the subgroup of patients with a manic episode at baseline ($P = 0.468$). For any relapse, manic or mixed relapses, no separate data were reported in the original paper. As a separate analysis of pure manic and mixed patients is not listed as primary or secondary outcome on clinicaltrials.gov (ClinicalTrials.gov Identifier NCT00277212), we have to assume that this analysis was not part of the original investigational plan. Thus, according to our criteria, this will not be eligible for a CE 'B' rating, but only CE 'C'.

CE to prevent a new episode after a mixed index episode (monotherapy): is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy): 'E' for 'any' (in combination with lithium or valproate), 'F' for 'manic' and 'mixed', 'C' for depressive (in combination with lamotrigine).

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

For the 48 patients with manic index episodes participating in the aripiprazole oral continuation studies (Keck et al. 2006; Keck et al. 2007), no separate outcome data for mixed recurrences have been reported. The same is true for the combination studies (Marcus et al. 2011; Carlson et al. 2012).

Some recent data are available for aripiprazole long-term injectable. A randomised, double-blind, placebo-controlled trial assessed the time to recurrence of any mood episode in BD-I disorder after maintaining stability on aripiprazole long-term injectable for at least 8 weeks. Study entry criterion was a manic index episode with an YMRS total score $\geq$20. The absolute number of mixed recurrence was small (11 out of 103 recurrences in total). At study end (week 52) the investigators found a reduction in mixed recurrences according to DSM-IV-TR criteria with aripiprazole long-

term injectable compared to placebo that just missed significance ($P = 0.06$) (Calabrese, Sanchez, et al. 2017).

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'E' for a manic index episode and 'F' for a depressive index episode.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'

Further evidence (FE)

In a 24-week, observational, prospective study in Taiwanese adolescents with a manic, depressive or mixed episode, aripiprazole was effective in reducing the CGI severity and BPRS total scores from baseline to endpoint. However, aripiprazole performed significantly better in manic than in depressive or mixed patients, and improvement of BPRS ratings in mixed patients was only marginal (Tang et al. 2010).

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

In the combined analysis of the two 3-week acute studies, the most common TEAS that occurred in more patients receiving aripiprazole were somnolence, dyspepsia, akathisia, and accidental injury (Suppes et al. 2008).

In a 52-week study comparing aripiprazole and lithium and including a significant number of DSM-IV mixed index episode patients (27 out of 63), modest increases in body weight were observed in both groups: + 0.97 kg (2.1 lb) for aripiprazole ($n = 127$) and +0.74 (1.6 lb) for lithium ($n = 136$), $P = 0.60$. A significant difference in body weight increase was observed only among patients with a BMI <25: + 2.66 kg (5.9 lb) for aripiprazole ($n = 35$) and +0.40 kg (0.9 lb) for lithium ($n = 37$), $P = 0.02$. Mean changes from baseline to week 52 in fasting levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, plasma glucose, triglycerides, or insulin (last observation carried forward) were small in both aripiprazole and lithium treatment groups; no significant differences were observed. Mean laboratory values were within the normal or borderline range for both treatment groups across all BMI categories (McIntyre et al. 2011).

Aripiprazole is in the FDA 'C' pregnancy category, meaning that risk cannot be ruled out as human studies are lacking, and animal studies are either positive for foetal risk or lacking as well (Nguyen et al. 2009).

Rating of ST: 0 for short-term treatment, + for long-term treatment

Recommendation grade (RG)

The RG is '3' for the acute treatment of manic mixed episodes for manic and depressive symptoms

The RG is '4' for prevention of depression after a mixed manic index episode (in combination with lamotrigine).

Asenapine

When asenapine entered the market, there was already a large portfolio of antimanic treatments available and thus an obvious need to demonstrate additional benefits. There are many post hoc analyses based on only two acute monotherapy studies (McIntyre et al. 2009; McIntyre et al. 2010a). Probably as a result of those post hoc analyses, clinicians tend to use adjunctive asenapine in patients with less severe manic symptoms but more complex clinical profile, including more mixed episodes in the past as shown by a recent survey (Grande et al. 2015). Thus, it is of interest to see whether this clinical usage is fully reflected by the evidence.

Efficacy in acute manic mixed episodes

The efficacy of asenapine in mixed states was first studied as monotherapy versus placebo and versus olanzapine as an active comparator in a short-term 3-week trial in 488 patients with DSM-IV diagnosis of manic/mixed episodes (McIntyre et al. 2009). A post hoc ANCOVA with last observation carried forward (LOCF) on a modified intend-to-treat (ITT) population found that the subgroup of patients with a mixed episode at baseline ($n = 150$) showed only a trend towards significant mean changes in manic symptoms with asenapine versus placebo ($P = 0.05$), whereas olanzapine was superior to placebo ($P < 0.006$). Using mixed model repeated measurement (MMRM) analysis, both asenapine and olanzapine missed significance in the mixed patient subgroup. A second, identically designed acute study included 158 patients with DSM-IV mixed episodes; however, separate analyses for manic and mixed patients have not been reported for this study. Both acute studies (McIntyre et al. 2009; McIntyre et al. 2010a) also captured changes of depressive symptomatology finding significant superiority versus placebo for olanzapine, but not for

asenapine. However, they did not supply separate post hoc data for reduction of depressive symptoms in mixed patients.

A combined post hoc analysis of the two acute studies reporting on the whole mixed population of 302 patients analysed DSM-IV mixed patients as a separate group, and in addition subgroups of patients with significant depressive symptoms as defined by the authors (MADRS total score $\geq$20 or Clinical Global Impression for Bipolar Disorder-Depression severity scale (CGI-BP-D) severity score $\geq$4), which are likely to correspond to patients with more extended definitions of mixed episodes (Szegedi et al. 2011). In all three groups, asenapine (but not olanzapine) was significantly superior to placebo in reducing least squares (LS) mean changes in baseline MADRS total score, with higher effect sizes in patients with significant depressive symptoms.

Finally, a further post hoc analysis of the two pivotal acute studies (McIntyre et al. 2009; McIntyre et al. 2010a) combined two criteria of the analysis of Szegedi et al. (2013) and examined a subgroup of patients ($n = 98$) meeting criteria both for DSM-IV-TR criteria for mixed episodes and a baseline MADRS total score $\geq$20 (Berk et al. 2015). Decreases in MADRS scores (LS mean ± standard error (SE)) were significantly greater in the asenapine group than in the placebo group from baseline to day 21 (−14.03 ± 2.01 vs −7.43 ± 2.09; $P = 0.0264$), and endpoint (LOCF analysis, −10.71 ± 1.76 vs −5.19 ± 1.98; $P = 0.039$). Decreases in YMRS mean total score were greater also with asenapine than with placebo (−16.58 vs −10.27; $P = 0.0229$).

We identified one study in acute manic ($n = 198$) and mixed states ($n = 126$) investigating asenapine in combination with lithium or valproate (Szegedi et al. 2012). Asenapine was effective in the overall study population in reducing YMRS score from baseline to endpoint (day 21), but not different from placebo in reducing depressive symptoms. No separate analysis for mixed patients was supplied.

In conclusion, the evidence from post hoc analysis is negative for asenapine monotherapy to be effective against acute manic symptoms (McIntyre et al. 2009), whereas there is evidence from combined post hoc analysis for efficacy against depressive symptoms (Szegedi et al. 2011). For combination treatment, no separate data for mixed patents was published.

CE in acute manic mixed episodes (monotherapy) is 'E' for manic symptoms, and 'C' for depressive symptoms[2].
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

We could not identify any studies testing asenapine in depressive mixed episodes or a bipolar MDE with a manic feature specifier[3]. Although tempting, extrapolation from post hoc analyses of mixed mania studies with prominent depressive symptoms (Szegedi et al. 2011; Berk et al. 2015) should not be made as their key diagnostic feature is still full criteria of a manic episode.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

Two 40-week extension studies of acute trials comparing asenapine with olanzapine have been conducted; one in monotherapy including patients who had finished the two acute trials (McIntyre et al. 2010b), and one in combination treatment including those patients recruiting from patients who finished the combination acute study (Szegedi et al. 2012). None of them supplied separate information on outcomes for patients with a mixed index episode. Both studies had their primary focus on safety, not efficacy, and numbers of mixed patients entering and finishing the extension studies are very small. However, safety profiles can likely be expected to follow that of other published trials, especially regarding differential risks of metabolic syndrome.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

Again, both extension studies (McIntyre et al. 2010b; Szegedi et al. 2012) did not supply separate data for mixed relapses after a manic index episode. A further double-blind, placebo-controlled maintenance study (NCT01396291) has been presented at the 28th Annual United States Psychiatric and Mental Health Congress, 10–13 September 2015, San Diego, CA, USA, and the manuscript is now in press (Szegedi et al. 2017). Patients were recruited while acutely manic or mixed

according to DSM-IVTR criteria. After a 12–16-week open-label run-in phase with asenapine, stable responders were randomised to the double-blind discontinuation phase over 26 weeks. Time to recurrence of any mood event during the double-blind period was significantly longer for asenapine than placebo. Post hoc analyses were performed for time to first recurrence of manic, mixed, or depressive episodes using the Kaplan–Meier method and Cox proportional hazard models. Time to recurrence for a mixed episode was numerically, but not significantly longer for asenapine (HR (95% CI) = 0.10 (0.01–1.06), $P = 0.0739$), whereas it was statistically significantly longer for manic or depressive recurrences. The number of patients with a mixed index episode entering the double-blind phase of the study was small ($n = 55$) and no subanalysis for these mixed patients at entry has been reported.

Given the fact that the study was likely underpowered for a post hoc analysis in mixed patients the task force decided not to assign a CE 'E' but 'F' for asenapine monotherapy maintenance.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

Combining both acute studies (McIntyre et al. 2009; McIntyre et al. 2010a) in a post hoc analysis, Azorin et al. (2013) reported that the change in YMRS total score from baseline to week 3 was significantly greater ($P = 0.015$) with asenapine (-15.0 ± 0.9) compared to placebo (-11.5 ± 1.2). The difference between olanzapine and placebo, however, was not statistically different ($P = 0.169$) on the mean YMRS total score change from baseline to week 3 (-13.3 ± 0.9). The authors also reported significant MADRS improvement with asenapine but not with olanzapine. However, the combined analysis was conducted using observed cases, not with the ITT population. For this reason, and due to some inconsistencies and gaps in reporting, the task force decided to dismiss the combined analysis as a primary evidence[4]. A synopsis of clinical cases is in line with a good efficacy and safety profile of asenapine (Young et al. 2013). With the emergence of DSM-5, McIntyre et al. (2013) tested post hoc whether the positive findings for asenapine with respect to depressive symptoms in mixed mania still hold true when applying a proxy of the depressive mixed feature specifier by using MADRS or PANSS items. Of the 960 patients analysed from the two acute studies (McIntyre et al. 2008; McIntyre et al. 2010a), 34%, 18% and 4.3% of patients, respectively, had ≥ 3 depressive features with mild (score ≥ 1 for MADRS items and ≥ 2 for PANSS item), moderate (score ≥ 2 MADRS, ≥ 3 PANSS) and severe (score ≥ 3 MADRS, ≥ 4 PANSS) symptoms. In patients with ≥ 3 depressive features and independent of treatment, MADRS remission (score ≤ 12) rate decreased with increasing severity (61–43%) and YMRS remission (score ≤ 12) was similar for mild and moderate patients (36–37%), but higher for severe (54%). In asenapine-treated patients, the MADRS remission rate was stable regardless of baseline depressive symptom severity (range 64–67%), whereas remission decreased with increasing severity with olanzapine (63–38%) and placebo (49–25%). Reduction in YMRS was significantly greater for asenapine compared with placebo at day 2 ($P \leq 0.01$) across the three severity cut-offs and continued to decrease throughout the treatment period. These analyses confirm that depressive features are frequent in bipolar patients with manic episodes and have an impact on manic symptom remission rates. With increasing baseline severity of depressive features, treatment outcome was poorer with olanzapine and placebo, but remained stable with asenapine (McIntyre et al. 2013).

Considering long-term treatment, a pharmacoeconomic model was developed to simulate the management of Italian BD-I patients with mixed episodes over a 5-year time horizon by combining clinical parameters with resource utilisation (Caresano et al. 2014). An expert panel of Italian psychiatrists and health economists, supported by an unrestricted grant from the manufacturer of asenapine, adapted a UK model to the Italian context. The primary outcome measure of the economic evaluation was the incremental cost-effectiveness ratio, where effectiveness is measured in terms of quality-adjusted life-years gained. Scenario analyses, sensitivity analyses, and a probabilistic sensitivity analysis were performed to test the robustness of the model. This pharmacoeconomic model showed that asenapine was superior to olanzapine, being associated with lower direct costs (derived largely by the savings from hospitalisations avoided) and a better QoL. These findings were also confirmed by another health-economic study using a Markov-model and looking also at mixed patients (Sawyer et al. 2014).

Rating of FE: + for short-term treatment, + for long-term treatment

Safety and tolerability (ST)

The safety and tolerability profile of asenapine in short- and long-term treatment is generally considered as reasonably good, and especially better than, e.g., olanzapine with respect to metabolic issues (Vita et al. 2013). Asenapine' s effects on weight and metabolic variables appear modest, as are its effects on the QTc interval and on prolactin (Citrome 2014). Asenapine has no appreciable affinity for muscarinic receptors and induces few anticholinergic side effects. In acute and continuation monotherapy, side effects occurring twice as frequently with asenapine as placebo (and in >10% of subjects) included depression, dizziness, nausea, parkinsonism, tremor and constipation (McIntyre et al. 2010b). Adverse effects reported in combination with lithium or valproate by 5% or more of patients and at twice the rate of placebo were sedation, somnolence, depression, constipation, oral hypoesthesia, irritability and dyskinesia (Szegedi et al. 2012).

A brief comment needs to be made on the issue of practicability: asenapine is only available as a sublingual formulation. Intake and transient oral hypoesthesia as a possible side effect may constitute a problem for some patients.

Rating of ST: + for short-term treatment, + for long-term treatment

Recommendation grade (RG)

The RG is '4' for the acute treatment of manic mixed episodes (for depressive symptoms only).

Carbamazepine

Efficacy in acute manic mixed episodes

Two identically designed RCTs compared the acute efficacy of extended-release carbamazepine versus placebo in DSM-IV acutely manic and mixed patients. The first study (Weisler et al. 2004) demonstrated significantly greater improvement of depressive symptoms in the subgroup of mixed patients for carbamazepine than placebo ($P = 0.0003$), while no difference was observed for manic symptoms. The second study (Weisler et al. 2005) saw improvement for manic symptoms only ($P < 0.0001$) but not for depressive symptoms ($P = 0.07$). A combined analysis pooling the data from both trials was conducted and included 280 manic and 147 mixed patients. Unfortunately, the paper does not detail whether this was an a priori planned analysis as part of the study protocol or post hoc. We have assumed the latter. The improvement in manic and depressive symptoms was significant in the mixed subgroup of patients ($P < 0.01$ and $P < 0.05$, respectively), while in the case of pure manic patients this was only the case for manic but not depressive symptoms (Weisler et al. 2006).

In summary, the two studies yielded conflicting results with one supporting antimanic efficacy and the other supporting antidepressant efficacy in subgroup analyses of mixed patients. However, the pooled analysis supports efficacy both against manic and depressive symptoms, so a CE 'C' can be justified.

We could not identify any acute combination treatment studies with carbamazepine in mixed patients fulfilling quality criteria.

CE in acute manic mixed episodes (monotherapy) is 'C' both for manic and depressive symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

Although recommended as a third-line monotherapy or together with lithium in a recent expert guideline on the management of mixed depression, we could not identify any published controlled study dedicated to carbamazepine in acute depressive mixed episodes. Dilsaver et al. (1996) published a case series of carbamazepine monotherapy in bipolar depression, including nine patients with depressive mania (defined as meeting full criteria of mania and depression simultaneously). Improvement of depressive symptoms as measured with the HAM-D was the primary outcome; because of the chosen outcome measure and the context of the overall study (bipolar depression) we decided to count the study towards evidence for the treatment of acute depressive mixed episodes (and not mixed mania). The authors reported significant improvement of depression with a mean reduction in HAM-D score in the course of treatment of 17.7 ± 10.3 ($df = 8$, $t = 5.12$, $P = 0.0009$), and two of nine patients entering remission after 2 weeks of treatment.

CE in acute depressive mixed episodes (monotherapy) is 'C' for depressive symptoms.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

A 6-month, open-label study enrolled 92 patients with DSM-IV bipolar disorder (most-recent episode: 67%

(*N* = 62) mixed, 33% (*N* = 30) manic) who had participated previously in the two 3-week, double-blind, placebo-controlled studies (Weisler et al. 2004; Weisler et al. 2005). Extended-release carbamazepine (200–1600 mg/day) was titrated at investigators' discretion to a final mean dose of 938 mg/day. The primary efficacy measure was time to relapse, and secondary efficacy measures included the YMRS, Clinical Global Impressions scale (CGI) and HAM-D scores. The authors reported long-term maintenance of the effect on depressive symptoms in the subgroup of mixed patients ($P = 0.0003$) when comparing baseline HAM-D scores of the double-blind studies with endpoint scores of the present open-label study (Ketter et al. 2004). Unfortunately, no separate results for mixed patients were supplied for the other outcomes.

This finding is difficult to rate in our grading system. Maintaining low HAM-D scores is suggestive of prophylactic efficacy against new depressive or mixed depressive episodes, but not confirmative in the absence of reported numbers for relapses. Thus, the

CE to prevent a new episode after a mixed index episode (monotherapy and combination therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

A recent Swedish national registers study identified 35,182 individuals diagnosed with bipolar disorder. The registers provided information on lithium, valproate, carbamazepine, lamotrigine, quetiapine and olanzapine treatment, as well as hospitalisations in psychiatric in-patient facilities between 2006 and 2009. A total of 72.4% were prescribed these drugs during the study period and 26.6% were hospitalised in in-patient psychiatric care. With each patient serving as his own control, there was no advantage of taking carbamazepine to prevent hospitalisation for a mixed episode (hazard ratio (HR) 1.65 (0.59–4.62)).

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'E'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

A retrospective chart analyses in 22 RDC/DSM-III manic patients by Post et al. (1989) supplied the first evidence that carbamazepine might be a preferred treatment in mixed patients. Patients who responded better to carbamazepine ($n = 12$; improvement >2 points) were more severely manic at baseline, and tended to be more dysphoric (higher baseline ratings of depression) compared with seven non-responders. The degree of improvement in the dysphoric components of mania was highly correlated with the initial baseline severity of manic dysphoria, e.g., the highest depression ratings during mania, the greater improvement in depression ($P < 0.001$).

In line with this, a randomised three-arm study from Iran reported significant efficacy of carbamazepine in reducing both manic and depressive symptoms in DSM-IV dysphoric mania (mania with two to four symptoms of MDD). Unfortunately, the paper was contradictory as far as the design of the study is concerned, at one occasion stating that it is single-blind, at another double-blind. In addition, it used comparators with unproven efficacy in mixed states: Gabapentin and lamotrigine, and numbers were small in each arm (Mokhber et al. 2008).

Mosolov (1991) conducted a comparative maintenance trial comparing for at least 1 year monotherapy with lithium, carbamazepine and valproate (30 patients each arm) in bipolar I disorder. All three medications seemed to be effective in reducing overall affective symptomatology and frequency of episodes. Mixed episodes were not analysed separately, but carbamazepine had more pronounced preventive efficacy than lithium or valproate for depressive episodes and manic episodes with any depressive symptoms, particularly in those with anxiety and somatic symptoms.

Findling and Ginsberg (2014) conducted a 26-week open study of extended-release carbamazepine in 157 children and adolescents suffering from a DSM-IV manic or mixed episode. Unfortunately, no separate outcomes were supplied for manic and mixed patients, but more than half of the participants were classified as mixed. At endpoint and compared to baseline, carbamazepine treatment resulted in a significant improvement in YMRS, Children's Depression Rating Scale, Revised (CDRS-R), the CGI-S and the CGI – Improvement (CGI-I).

Post hoc analysis of the MAP study comparing lithium and carbamazepine prophylaxis over 2.5 years was also supportive for a better outcomes with carbamazepine than lithium in mixed patients. Thirty-six patients (32%) were classified as mixed states. Whereas in 'classical' BD-I patients lithium was significantly better than carbamazepine in preventing hospitalisation ($P = 0.031$); see Figure 1) there was the tendency in favour of carbamazepine in the mixed group (Greil et al. 1998).

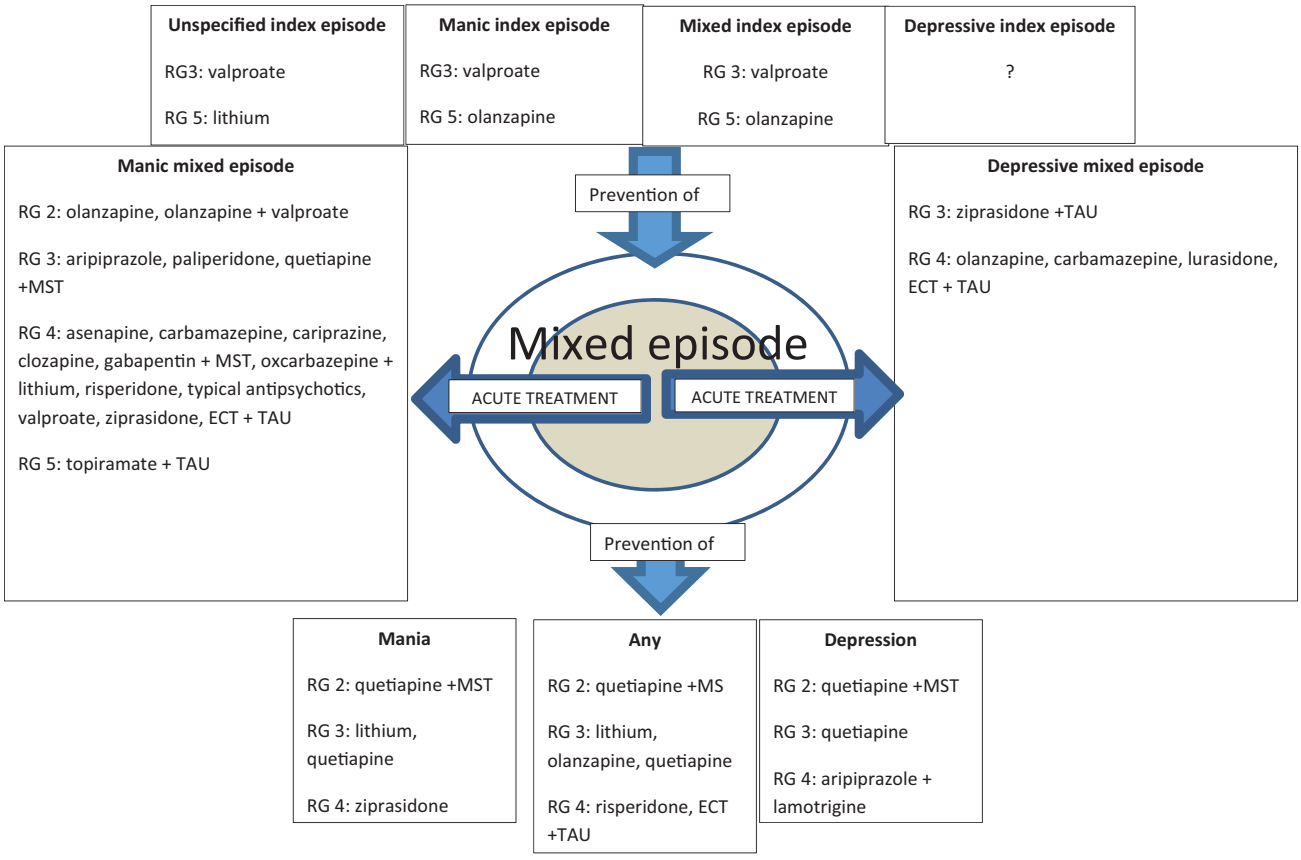

Figure 1. Evidence-based treatments for mixed episodes, in mono- or combination treatment. For details (e.g., monotherapy or combination, and which combination partner) we refer to the respective chapters. MST, mood stabiliser (lithium or valproate); TAU, treatment as usual. Please see Table 2 with regard to how the recommendation grades (RG) relate to the categories of evidence (CE).

Rating of FE: + for short-term treatment, + for long-term treatment

Safety and tolerability (ST)

Common side effects of carbamazepine include oversedation and blurred vision, especially with high dosages and rapid titration. Rare, but potentially severe side effects include allergic reactions, lupus erythematosus, agranulocytosis and hyponatremia. Tolerability issues may be less problematic with extended-release formulations as used in the more recent studies. Carbamazepine is teratogenic with an estimated risk of neural tube defects of 0.5–1%, and should be avoided during pregnancy (FDA pregnancy category 'D') (Ernst and Goldberg 2002). The use of carbamazepine can be complicated due to interaction with other psychotropic medication, including several antipsychotics, antidepressants and anticonvulsants (Spina et al. 1996), and auto-induction of its own metabolism may result in a need for constant adaption of dosage.

Rating of ST: – for short-term treatment, – for long-term treatment

Recommendation grade (RG)

The RG is '4' for the acute treatment of manic mixed episodes for manic and depressive symptoms.

The RG is '4' for the acute treatment of depressive mixed episodes for depressive symptoms.

Cariprazine

Efficacy in acute manic mixed episodes

Carprazine is a newly developed dopamine D3-preferring D2/D3 receptor partial agonist and currently licenced for the treatment of patients with schizophrenia. Three double-blind, placebo-controlled studies investigated the efficacy of cariprazine monotherapy in DSM-IV manic and mixed BD-I patients (Calabrese et al. 2015; Sachs et al. 2015; Durgam et al. 2015) that were also subject to a pooled analysis (Vieta et al.

2015). The phase II study (Durgam et al. 2015) did not supply a separated subgroup analysis for mixed patients, probably because the numbers were too low (45 out of 236 patients), and only patients with mild depressive symptoms were allowed into the study. Of the phase III studies, none does supply any information (size, outcomes) about the mixed subgroup (Calabrese et al. 2015; Sachs et al. 2015), nor does the first pooled analysis of all studies. However, a more recent pooled analysis of the three studies examined outcome by index episode. Of the 1037 patients in the ITT population, 14% met criteria for mixed episodes (placebo, 62; cariprazine, 83). The least squares mean difference for cariprazine versus placebo in YMRS total score change from baseline to week 3 was –4.0 ($P = 0.0254$) in the mixed subgroup (Vieta et al. 2017).

CE in acute manic mixed episodes (monotherapy) is 'C' for manic and 'F' for depressive symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

In an 8 week, placebo-controlled, multinational phase II monotherapy study, cariprazine 1.5 mg/day demonstrated antidepressant efficacy compared to placebo. The YMRS was administered at baseline and throughout the study, but no information is supplied about baseline scores or whether there was a substantial subgroup with depressive mixed states included into the study.

A second phase II monotherapy study (NCT00852202), conducted in the US, has been finished but, so far, results have not been fully published. However, a poster presented by Yatham and colleagues at the 29th Annual US Psychiatric & Mental Health Congress, held 21–24 October 2016, in San Antonio, Texas, reports that the outcome was negative, most likely due to a high placebo response rate. No information on depressive mixed patients is supplied.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

No maintenance data following a mixed index episode has been published so far.

CE to prevent a new episode after a mixed index episode (monotherapy): is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy): 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

No maintenance data for cariprazine in bipolar disorder has been published so far.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

Rating of FE: 0 for short-term treatment, 0 for long-term treatment.

Safety and tolerability (ST)

The most commonly reported adverse events in the acute trials (incidence >5% and twice placebo) were extrapyramidal disorder, akathisia, vomiting, restlessness, somnolence, diarrhoea, blurred vision and pyrexia. With the exception of akathisia and extrapyramidal disorder, the differences in incidence versus placebo for these events were generally small. The reported figures for akathisia range from 4.8% (for 1.5 mg in bipolar depression) to approximately 25% with dosages up to 12 mg in the acute mania studies (Citrome 2013; Durgam et al. 2016; Earley et al. 2017).

In long-term treatment, cariprazine shows some advantages compared to other atypical antipsychotics, especially the low propensity of weight gain, QTc Prolongation, prolactin elevation and metabolic abnormalities (Citrome 2013).

Rating of ST: + for short-term treatment, + for long-term treatment

Recommendation grade (RG)

The RG is '4' for the acute treatment of manic mixed episodes for manic symptoms.

Clozapine

See 'Other atypical antipsychotics used in bipolar disorder'

Gabapentin

See 'Other anticonvulsants used in bipolar disorder'.

Lamotrigine

Efficacy in acute manic mixed episodes

No randomised controlled studies in manic mixed patients nor subgroup analyses of studies in acute mania with lamotrigine have been reported.

CE in acute manic mixed episodes (monotherapy) is 'F'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

No randomised controlled studies in depressive mixed patients or subgroup analyses of studies in acute bipolar depression with lamotrigine have been reported. A multivariate analytical study was performed on two large depressed samples (one bipolar and the other MDD) that had been recruited for separate, contemporaneous, double-blind placebo-controlled trials of lamotrigine. The results suggest that the clinical benefits of lamotrigine in acute bipolar depression are primarily upon depressive cognitions and psychomotor slowing, symptoms clearly not associated with mania.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

Two randomised, placebo and comparator (lithium)-controlled studies over 18 months demonstrated the prophylactic efficacy of lamotrigine in BD-I patients, recently (hypo)manic or depressed (Calabrese et al. 2003; Bowden et al. 2003). The articles do not report on the inclusion of any mixed patients.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

In the study by Bowden et al., numerically more interventions for mixed episodes were needed in the placebo group ($n = 6$) than in the lamotrigine ($n = 4$) or lithium ($n = 2$) group. Unfortunately, neither the second study (Calabrese et al. 2003) nor a pooled analysis (Goodwin et al. 2004) supply additional separate data by medication for mixed recurrences. The Swedish registry study by Joas et al. (2017) could not establish a prophylactic effect of lamotrigine in preventing hospitalisation due to a mixed episode.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'E'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

The already mentioned randomised three-arm study from Iran (Mokhber et al. 2008) reported significant efficacy of lamotrigine in reducing both manic and depressive symptoms in DSM-IV dysphoric mania comparable to what was seen with carbamazepine. However, as discussed, the limitations of this study appear too substantial to regard its findings as reliable evidence for lamotrigine in mixed mania.

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

In summary, the tolerability and long-term impact on weight and metabolic parameters of lamotrigine is good, but there are concerns with birth defects and allergic reactions. The incidence of a serious rash, however, appears low with the recommended slow titration scheme. Major congenital defects have been described with lamotrigine in 1.0–5.6% of pregnancies. Despite an FDA pregnancy category 'C' rating, a teratogenic risk with lamotrigine treatment is suggested at doses exceeding 200 mg/day (Morrow et al. 2006).

Rating of ST: + for short-term treatment, ++ for long-term treatment

Recommendation grade (RG)

None

Lithium

Efficacy in acute manic mixed episodes

Theoretically, lithium appears to be an effective acute treatment in mixed states, as it may alleviate both

manic and depressive symptoms. However, the presence of a mixed state may be a predictor of poor response to lithium (Secunda et al. 1987; Swann et al. 1997). In a post hoc analysis of the acute mania study by Bowden et al. (1994), there was no difference in treatment efficacy between lithium and placebo in the subgroup of patients with mixed mania in this randomised, double-blind study (Swann et al. 1997). The authors concluded that the presence of pre-treatment depressive symptoms is a predictor of non-response to lithium. However, as this was a post hoc analysis in a small number of patients, we would rather consider the evidence insufficient than negative. Unfortunately, the article did not supply any information on the effect on depressive symptoms.

Lithium or valproate have also been used as a basic treatment in add-on studies of different atypical antipsychotics versus placebo, in both acute and maintenance treatment. The contribution of lithium to any improvement is impossible to grade, as there is no placebo comparison for the lithium treatment.

CE in acute manic mixed episodes (monotherapy) is 'F'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

We could not identify any study of reasonable quality testing lithium in depressive mixed states

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

A retrospective study found that the presence of three symptoms of the opposite polarity was a predictor of poor long-term outcome in lithium-treated mixed patients (Backlund et al. 2009). Observational maintenance studies with lithium also indicate that patients with an index episode of mixed mania were less likely to recover with long-term lithium treatment than were patients with an index episode of elated mania or bipolar depression (Keller et al. 1993). Subanalysis of a randomised maintenance study comparing lithium, imipramine and the combination of the two revealed a higher rate of recurrences in mixed than pure manic patients (82% versus 6%) (Prien et al. 1988). However, as we have no comparison against placebo or an established effective prophylactic treatment for mixed states (which imipramine is not), the efficacy of lithium for mixed states remains speculative based on these studies.

On the other hand, the risk of re-hospitalisation in patients with a mixed index episode was lower with lithium than with valproate as shown by a large Danish nationwide cohort study (Kessing, Hellmund, Geddes, et al. 2011). Based on a post hoc analysis of the maintenance study by Bowden et al. (2000) valproate was considered more effective than lithium as a prophylactic agent after a mixed index episode (Bowden et al. 2005), although neither medication separated from placebo. If we attribute a large register study a similar strength of evidence as we do for a post hoc analysis of an RCT, we are left with conflicting evidence for the propensity of lithium to prevent a new episode after an index mixed episode. However, there is a planned secondary analysis of a large RCT over 104 weeks comparing the prophylactic efficacy of quetiapine and lithium versus placebo supplies controlled evidence for lithium. Patients with a mixed index episode had a significantly lower risk of a relapse into a new manic episode (HR (95% CI) 0.34 (0.12–0.95)) and episode of any type compared to placebo (HR (95% CI) 0.48 (0.27–0.86))(Weisler et al. 2011; Nolen and Weisler 2013).

CE to prevent a new episode after a mixed index episode (monotherapy): is 'B' for a manic episode and 'B' for any type.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy): 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We identified one controlled study reporting the prophylactic efficacy of lithium specifically against new mixed episodes. In a head-to-head comparison, olanzapine ($n = 217$) was compared to lithium ($n = 214$, target blood level: 0.6–1.2 mmol/l) in a double-blind, 1-year study in patients previously stabilised for 6–12 weeks on the combination of both agents while manic, and then randomised to continuation on either substance (Tohen et al. 2005). The primary outcome was testing non-inferiority of olanzapine against lithium for time to relapse/recurrence in the total population. Secondary results showed that compared with lithium, olanzapine had a significantly lower risk of symptomatic mixed episode relapse/recurrence (Tohen et al. 2016).

However, this result is at odds with a large analysis of the prophylactic efficacy of standard mood stabilisers using Swedish registry data (Joas et al. 2017). Whereas several drugs were efficacious in preventing manic or depressive recurrences, lithium and valproate were the only drugs significantly associated with a reduced rate of admissions due to a mixed episode (Joas et al. 2017). Compared to other cohort studies, selection bias will be lower as each patient served as his own control comparing time periods on and off a specific medication; however, the order in which patients tried the respective medication could be a confounding factor. In a sensitivity analysis where the authors only included patients who had lithium prior to the other medications, the effect of lithium was attenuated whereas the effect of other medications was slightly enhanced. This suggests that patients who switched from lithium to a second drug were more likely to be non-responders to lithium.

CE to prevent a mixed episode after an unspecified index episode (monotherapy) is 'D'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

Kessing, Hellmund, and Andersen (2011) compared rates of switch to, or addition of, another psychotropic, and rates of psychiatric hospitalisation for patients treated with lamotrigine or lithium in clinical practice. From the Danish registry they identified 730 patients who received lamotrigine and 3,518 patients receiving lithium between 1995 and 2006. The overall rate of switch to or addition of another psychotropic was higher for lamotrigine compared with lithium (HR = 2.60, 95% CI: 2.23–3.04), regardless of whether the index episode was depressive, manic, mixed or remission. In addition, the overall rate of psychiatric hospitalisation was increased for lamotrigine compared with lithium (HR = 1.45, 95% CI: 1.28–1.65), as were the rates for patients with a depressive (HR = 1.31, 95% CI: 1.01–1.70) and patients with a manic (HR = 1.65, 95% CI: 1.31–2.09) index episode. Rates did not differ significantly between the drugs for patients with a mixed index episode and for patients in remission.

Another point which should be considered in clinical decision making is the high rate of suicidality and suicide attempts in mixed patients (Strakowski et al. 1996; Balazs et al. 2006). Lithium may exert a protective effect across the diagnostic spectrum in BD (Schaffer et al. 2015; Popovic et al. 2015).

Rating for FE: 0 for short-term treatment, + for long-term treatment

Safety and tolerability (ST)

Side effects of lithium are well known and in their majority dependent on plasma level. Up to 75% of patients on lithium experience some side effects, but most are minor (transient metallic taste in mouth, polyuria, polydipsia, weight gain, mild oedema, concentration difficulties, sedation) and can be reduced or eliminated by dose adjustment or dosage schedule. Mild neurological symptoms with higher plasma levels of lithium are frequent.

From the patient perspective, in addition to the above-mentioned adverse effects, the risk of weight gain and the risk of mental side effects (cognitive impairment and/or reduced intensity of perceptions and emotions) may be most crucial (Licht 2011).

Long-term lithium treatment affects kidney function (Tredget et al. 2010; Kessing et al. 2015), and close monitoring of the eGRF is essential part of lithium safety measures (Jefferson 2010). Hypothyroidism is frequent with lithium treatment, and substitution treatment is often indicated. Women seem to be at increased risk (women 14% vs men 4.5%) (Johnston and Eagles 1999). First laboratory signs of deterioration of thyroid or kidney function due to lithium might be observable in some instances within the first 3 months of treatment (Bowden, Mosolov, et al. 2010).

Lithium's teratogenic effect hardly ever is a reason not to initiate lithium treatment, possibly because the risk is well characterised and relatively low in absolute terms, although the agent needs specific management in pregnancy.

Rating for ST: – for short-term treatment, – for long-term treatment

Recommendation grade (RG)

Based on the evidence, *lithium monotherapy can be recommended to prevent a new manic or mood episode of any type after a mixed index episode (RG '3'). For the prevention of a mixed state after an unspecified index episode, the RG is' 5'.*

Lurasidone

Efficacy in acute manic mixed episodes

No randomised controlled studies testing the efficacy of lurasidone in manic and mixed bipolar patients have been published.

CE in acute manic mixed episodes (monotherapy and combination therapy) is 'F'.

Efficacy in acute depressive mixed episodes

One placebo-controlled monotherapy (Loebel, Cucchiaro, Silva, Kroger, Hsu, et al. 2014) and one placebo-controlled combination treatment study (Loebel, Cucchiaro, Silva, Kroger, Sarma, et al. 2014) support the efficacy of lurasidone in acute bipolar depression. In a second controlled combination treatment trial lurasidone failed to separate from placebo-condition (Suppes, Kroger, et al. 2016).

Whereas the two combination treatment studies do not report on depressive mixed patients as a separate subgroup, the monotherapy study was subject to a post hoc analysis looking at patients with mixed manic features at study entry (McIntyre, Cucchiaro, et al. 2015). At baseline, mixed features were present in 56% of patients (lurasidone, $n = 182/323$; placebo, $n = 90/162$). Treatment with lurasidone (versus placebo) was associated with significantly greater reductions in MADRS scores in the mixed features group (–15.7 vs –10.9; $P = 0.001$; week 6; MMRM analysis). Of note, rates of protocol-defined treatment-emergent hypomania or mania were similar for patients with mixed features (lurasidone, 2.2%; placebo, 3.2%) and without mixed features (lurasidone, 3.4%; placebo, 0.0%) suggestive of TEAS preventive capabilities of lurasidone.

CE in acute depressive mixed episodes (monotherapy) for depressive symptoms is 'C'.

CE in acute depressive mixed episodes (combination therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

One study (Calabrese, Pikalov, et al. 2017) investigated the efficacy of lurasidone versus placebo, in both combination with valproate or lithium, for preventing relapses over 28 weeks. The protocol followed an enriched design with patients being openly stabilised on lurasidone + lithium or valproate. The authors report on 29% less relapses in the lurasidone + lithium or valproate group compared to the placebo + lithium or valproate group, (not significant). Eighty-four of 496 randomised patients were classified as having a DSM-IV mixed state index episode; however, no separate outcome has been reported for this group.

Patients who completed the controlled acute treatment trials were also eligible for a 6-month open-label extension study (Ketter et al. 2016), which was then prolonged for an additional 18 months of continuation treatment with flexible, once-daily doses of lurasidone in the range of 20–80 mg (Pikalov et al. 2017). Improvement in depressive symptoms was maintained in most patients treated with lurasidone, with relatively low rates of relapse, and with minimal effects on weight and metabolic parameters. Unfortunately, again no separate analysis for patients with a depressive mixed index episode is supplied.

CE to prevent any episode after a mixed index episode (monotherapy and combination therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

In addition, the study of Calabrese, Pikalov, et al. (2017) does also not differentiate between manic and mixed relapses in the total population.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy and combination therapy) is 'F'.

Further evidence (FE)

A small open, naturalistic, retrospective trial in BD-I and -II patients was also supportive of antidepressant and long-term mood stabilising properties of lurasidone add-on to treatment as usual (TAU) (Schaffer et al. 2016). As previously mentioned, unipolar depression with mixed manic features is not within the scope of this guideline. Nevertheless, the positive result of a study with lurasidone in this patient group should be counted as supporting evidence. In a study involving patients with MDD associated with subthreshold hypomanic symptoms (mixed features), lurasidone significantly improved depressive symptoms and overall illness severity, assessed by LS mean change at week 6 in the MADRS and CGI-S scores: –20.5 compared with –13.0 (effect size, 0.80) and –1.8 compared with –1.2 (effect size, 0.60), respectively. Significant improvement in manic symptoms, assessed by the YMRS, was also observed, in addition to other secondary efficacy endpoints (Suppes, Silva, et al. 2016).

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

TEAS reported in the lurasidone monotherapy study occurring with >5% and more frequent than placebo were nausea, akathisia and sedation. Akathisia was

also more than twice as frequent in mixed versus non-mixed bipolar depression (12.4% vs 5.5%) suggestive that true akathisia might have been be mingled with manic agitation. In the long-term study, there were no clinically meaningful, treatment-emergent differences between lurasidone and placebo in metabolic parameters as total cholesterol, HDL, LDL, triglycerides, glucose or HbA1c. During the randomised study phase, there was also no difference in weight gain between study arms.

Rating of ST: + for short-term treatment, + for long-term treatment

Recommendation grade (RG)

In acute depressive mixed episodes, for depressive symptoms the RG is '4'.

Olanzapine

Efficacy in acute manic mixed episodes

The efficacy of olanzapine as monotherapy was demonstrated in two consecutive short-term RCTs, which compared olanzapine efficacy versus placebo in patients with DSM-IV criteria for manic and mixed episodes. In the first 3-week study (Tohen et al. 1999) conducted in 139 patients (17.3% mixed), the olanzapine group showed significantly greater mean improvement in manic symptoms (YMRS score) in both pure and mixed manic patients, but there were no treatment advantages regarding improvement of depressive symptoms (HAM-D score) in both subgroups. The second study (Tohen et al. 2000), a 4-week RCT that recruited 115 patients (42.6% mixed) confirmed the advantage of olanzapine versus placebo on manic symptoms and response rate in both manic and mixed patients. In addition, and distinct from the first study, among those patients with moderate-to-severe depressive symptoms (HAM-D $\geq$20 at baseline), there was a greater improvement in the olanzapine group in the reduction of ratings in depressive symptoms.

Two post hoc analyses looked into the pooled data of the above two RCTs: one confirmed that olanzapine was superior to placebo in improving both manic and depressive symptoms in both mixed ($n = 73$) and non-mixed patients ($n = 181$) (Baldessarini et al. 2003). The other study (Baker et al. 2003) focussed on those patients with moderate-to-severe depressive symptoms (or dysphoric, defined by a HAM-D score $\geq$20 at baseline; $n = 68$), and compared them against the non-dysphoric patients ($n = 178$). The study found that, while manic symptoms improved in both groups, depressive symptoms improved only in the dysphoric group ($P = 0.04$), suggesting that olanzapine is effective for treating co-existing manic and depressive symptoms, especially when depressive symptoms are moderate to severe. A third post hoc analysis also including a Japanese study (Katagiri et al. 2012), looking at a total of 125 patients with mania with DSM-5 mixed depressive features specifier. Olanzapine was significantly more efficacious in patients both with and without DSM-5 mixed features compared to placebo, in both reducing YRMS and HAM-D scores; however, an even greater efficacy was observed in patients with DSM-5 mixed features (Tohen, McIntyre, et al. 2014). Finally, a post hoc analysis of the first acute RCT with asenapine (McIntyre et al. 2009) found that the subgroup of patients with a mixed episode at baseline ($n = 150$) had only a trend towards significant mean changes in manic symptoms with asenapine versus placebo ($P = 0.05$), whereas olanzapine was superior to placebo ($P < 0.006$).

There is also reasonable evidence for olanzapine as an add-on treatment in mixed states. Some studies have analysed the subgroup of mixed patients post hoc, or specifically recruited mixed patients. There is also evidence from two RCTs and one post hoc analysis. The first study, a 6-week RCT (Tohen et al. 2002), enrolled both DSM-IV manic and mixed patients (179 and 165, respectively), and compared the efficacy of olanzapine plus lithium/valproate versus placebo plus lithium/valproate. Among patients with a current mixed episode, olanzapine co-therapy was superior to monotherapy in reducing the YMRS score from baseline (co-therapy: -12.92 (± 8.37), $n = 121$; monotherapy: -7.46 (± 10.15), $n = 54$; $P < 0.001$). The results showed that, among mixed patients, olanzapine was superior when adjunctive to valproate ($P < 0.0001$), but not to lithium in regarding manic symptoms, while there was no difference between lithium and valproate in pure manic patients. A subsample of patients with moderate-to-severe depressive symptoms was defined by having a current mixed episode and a HAM-D score $\geq$20 at baseline. These patients exhibited better response and improvement in depressive symptoms in the olanzapine + lithium or valproate group. A secondary post hoc analysis (Baker et al. 2004) of this original study selected 85 patients with mania or a mixed episode who had substantial comorbid depression at baseline, also defined as a HAM-D score $\geq$20 (dysphoric mania), and compared the efficacy of adjunctive olanzapine versus non-dysphoric manic patients. Dysphoric patients showed greater improvement of depressive symptoms than non-dysphoric patients

($P < 0.001$), while improvement in manic symptoms was independent of dysphoric/non-dysphoric categorisation. Although the findings on improvement of manic symptoms appear valid, the reported greater improvement of depressive symptoms in dysphoric patients should be viewed with caution, as baseline values were not comparable. Finally, a 6-week RCT specifically enrolled DSM-IV-TR mixed patients partially non-responsive to ≥14 days of valproate monotherapy (Houston et al. 2009). Adjunctive olanzapine resulted in greater improvements in manic symptoms, depressive symptoms, or mania severity versus valproate only ($P < 0.001$, $P = 0.022$ and $P = 0.05$, respectively), and a shorter time to partial response and response with adjunctive olanzapine. This study is, so far, the only large placebo-controlled RCT especially designed and conducted for testing a medication in mixed states.

CE in acute manic mixed episodes (monotherapy) is 'A' for manic and 'C' for depressive symptoms.

CE in acute manic mixed episodes (combination/augmentation therapy) is 'A' for manic and depressive symptoms.

Efficacy in acute depressive mixed episodes

A post hoc analysis (Benazzi et al. 2009) of an 8-week, double-blind trial of adult BD-I depression treated with placebo, olanzapine or OFC (Tohen, Vieta, et al. 2003) found that patients treated with olanzapine showed a significantly higher response rate versus patients treated with placebo (OR = 1.95; 95% CI, 1.14–3.34; $P = 0.014$). This study, together with a second study in Japanese patients with bipolar depression (Tohen et al. 2012) was also subject to a pooled analysis (Tohen, Kanba, et al. 2014). Patients with bipolar depression ($n = 1214$) were categorised according to the number of concurrent manic symptoms (0, 1, 2 or ≥3, the latter being a proxy for DSM-5 mixed manic features specifier). Olanzapine was significantly better than placebo in reducing depressive symptoms, and no significant difference in MADRS response was observed between the four groups. The author concluded that olanzapine monotherapy was effective in the treatment of bipolar depression irrespective of the presence of concurrent manic symptoms.

In summary, we have two post hoc analyses showing efficacy for olanzapine in depressive mixed states. However, the patient sample overlapped between these two analyses, and it is not clear whether these analyses were planned a priori as part of the protocol.

CE in acute depressive mixed episodes (monotherapy) for depressive symptoms is 'C'.

CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

An RCT studied the efficacy of olanzapine versus placebo as monotherapy for maintenance treatment in 361 patients with a DSM-IV diagnosis of manic or mixed episodes ($n = 121$ mixed) (Tohen et al. 2006). In both patients with a manic or mixed index episode, the time to symptomatic relapse into any mood episode was significantly longer for patients who received olanzapine than for patients who received placebo ($P < 0.001$). Furthermore, a post hoc analysis of this maintenance trial that focussed on the subgroup of mixed patients (DSM-IV definition) found that olanzapine-treated patients had significantly lower rates of symptomatic relapse of any kind. The median times to relapse of any kind was three times longer in the olanzapine group versus the placebo group ($P < 0.001$). Olanzapine-treated patients also experienced longer time to depressive symptomatic relapse (85 versus 22 days, $P = 0.001$) and manic symptomatic relapse (too few relapses to calculate versus 42 days, $P < 0.001$) than did placebo-treated patients (Tohen et al. 2009).

No firm data are available for maintenance treatment with olanzapine in combination with lithium or valproate. A randomised, placebo-controlled study over 18 months included patients with a manic or mixed index episode (Tohen et al. 2004). No separate results for mixed patients or for relapses into mixed episodes are reported as the total number of patients entering the randomised maintenance phase was small ($n = 99$).

CE to prevent a new episode after a mixed index episode (monotherapy) is 'B'.

CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not identify a placebo-controlled maintenance study analysing specifically prevention of mixed episodes. However, we found information potentially supportive for the use of olanzapine versus lithium. A re-analysis of the 1-year maintenance study of olanzapine versus lithium in recently manic or mixed

patients (Tohen et al. 2005) utilising Multi-state Outcome Analysis of Treatments (MOAT) revealed that patients taking lithium spent significantly more time in mixed states than did patients taking olanzapine (Tohen et al. 2016). In contrast to this result, the Swedish registry study by Joas et al. (2017) established a prophylactic effect of lithium, but not olanzapine, in preventing hospitalisation due to a mixed episode (HR for olanzapine: 0.78 (0.52–1.17)).

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'D'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

There are several more studies on the use of olanzapine as monotherapy, some performed in mixed/manic patients, and some having analysed the subgroup of mixed patients post hoc. In 1999, a first case report reported the short-term improvement in both manic and depressive symptoms of a patient with mixed BD treated with olanzapine monotherapy that was unresponsive to mood stabilisers and neuroleptics (Zullino and Baumann 1999). Olanzapine monotherapy versus placebo has also been studied in the acute treatment of manic/mixed episodes in a population of adolescents. There were no significant differences for improvement of manic symptoms versus placebo in either manic or mixed subgroups (Tohen, Kryzhanovskaya, et al. 2007). Finally, four RCTs have studied the efficacy of monotherapy olanzapine versus an active comparator. The first one included manic and mixed patients and compared olanzapine versus haloperidol; both therapies were equally effective in reducing manic and depressive symptoms (Tohen, Goldberg, et al. 2003). Another RCT compared the efficacy of olanzapine versus risperidone in manic/mixed patients, and reported no significant differences in manic and depressive improvement, or rates of response or remission between treatments in either manic or mixed patients (Perlis et al. 2006). Finally, another RCT compared the efficacy of olanzapine versus valproate or placebo in manic/mixed patients (Tohen et al. 2008). Both manic and mixed subgroups showed greater improvement in manic symptoms if treated with olanzapine ($P = 0.004$). The first evidence for adjunctive olanzapine treatment came from a case report of two mixed bipolar patients who achieved complete remission of symptoms after the addition of olanzapine to mood stabilisers (Ketter et al. 1998). In keeping with this, a small open-label study in nine patients with a mixed episode reported improvement in manic and depressive symptoms after the addition of olanzapine to mood stabilisers or neuroleptics (Sharma and Pistor 1999). An open-label study in rapid cycling mixed patients reported that the addition of olanzapine to mood stabilisers resulted in a reduction of both manic and depressive symptoms in ten out of the 13 enrolled subjects (76.9%) (González-Pinto et al. 2002). Moreover, a prospective open-label study over 12 months in manic/mixed patients compared subjects who received adjunctive or monotherapy olanzapine versus those who did not have olanzapine. The likelihood of achieving remission for patients in the olanzapine group was significantly higher compared with patients in the non-olanzapine group for both patients with manic and mixed symptoms ($P = 0.003$ and $P = 0.2$, respectively) (Garcia-Bonetto et al. 2009).

Rating of FE: ++ for short-term treatment, + for long-term treatment

Safety and tolerability (ST)

The short- and long-term tolerability and safety profile has been described in great detail in previous publications (Grunze et al. 2009; Grunze et al. 2010; Grunze et al. 2013). Whereas short-term tolerability is reasonable, there are profound concerns about weight gain and long-term metabolic effects of olanzapine. For detailed information we refer the reader to the respective publications (Nasrallah and Newcomer 2004).

Rating for ST: + for short-term treatment, - for long-term treatment

Recommendation grade (RG)

The RG is '2' (monotherapy) for acute treatment in manic mixed states for manic symptoms and '4' for depressive symptoms, and '2' (combination treatment) for acute treatment in manic mixed states for manic and depressive symptoms. The RG is '4' (monotherapy) in depressive mixed states for depressive symptoms, RG '3' (monotherapy) for maintenance after a mixed index episode and RG '5' (monotherapy) to prevent a mixed state after an episode of mania or mixed mania.

Oxcarbazepine

See 'Other anticonvulsants used in bipolar disorder'.

Paliperidone

Efficacy in acute manic mixed episodes

Positive evidence for the use of paliperidone monotherapy comes from two different 3-week RCTs. The first one compared the efficacy of extended-release (ER) paliperidone with quetiapine and placebo in 439 adult DSM-IV BD-I patients ($n = 268$ manic and $n = 171$ mixed). Three weeks of ER-paliperidone was superior to placebo in manic symptom reductions, and was non-inferior to quetiapine at 9-weeks follow-up, an effect not due to the baseline diagnosis of mixed or manic episode ($P = 0.3$) (Vieta et al. 2010). However, the article does not supply information of whether quetiapine was superior to placebo in the mixed subgroup on its own. The other trial compared three different dosages of ER-paliperidone (3, 6 and 12 mg) versus placebo in 469 patients with DSM-IV criteria for a manic or mixed episode ($n = 163$ mixed). The highest dose was found to be superior in reducing manic symptoms to placebo in both the manic and mixed subgroup of patients ($P = 0.025$), but not different from placebo in reducing depressive symptoms (Berwaerts, Xu, et al. 2012). However, in a further RCT patients with a mixed index episode had no benefit from paliperidone treatment in combination with lithium or valproate (Berwaerts et al. 2011). A post hoc subgroup analysis by baseline diagnosis suggested that paliperidone + lithium or valproate treatment was superior to lithium or valproate monotherapy only for patients with a diagnosis of 'acute manic episode' for reducing manic (YMRS) scores ($P = 0.02$), but not in mixed patients.

CE in acute manic mixed episodes (monotherapy) is 'B' for manic and 'E' for depressive symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'E'.

Efficacy in acute depressive mixed episodes

We could not identify any studies examining paliperidone in bipolar depressive mixed states.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

We could not identify any studies examining paliperidone in maintenance treatment in patients with a mixed index episode and separate reporting of outcomes for mixed patients. The maintenance study by Berwaerts, Melkote, et al. (2012) only reports combined outcomes for manic and mixed patients.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not identify any studies examining paliperidone in maintenance treatment reporting a separate outcome for newly emerging mixed episodes. In the study by Berwaerts, Melkote, et al. (2012) manic and mixed relapses are lumped together.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

We could not identify any other relevant evidence for the use of paliperidone in BD-I patients with a mixed episode.

Rating of FE: 0 for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

A meta-analysis including 15 studies with paliperidone, mostly in schizophrenia, found as adverse events with the greatest incidence extrapyramidal symptoms (23%), headache (14%), insomnia (11%), somnolence (9%), tachycardia (9%) and weight gain (8%) (Harrington and English 2010). Short- and long-term safety and tolerability of paliperidone have also been described in a previous articles (Grunze et al. 2013). So far, there is little known about the risks of paliperidone in pregnancy. It can be assumed that they may be similar to the parent substance, risperidone.

Rating of ST: 0 for short-term treatment, 0 for long-term treatment

Recommendation grade (RG)

Paliperidone is graded RG '3' (monotherapy) for the acute treatment of manic mixed episode based on its efficacy against manic symptoms.

Quetiapine

Efficacy in acute manic mixed episodes

A 3-week randomised, placebo-controlled trial investigated extended-release quetiapine in manic or mixed episodes. For mixed patients (134 out of 316) as a subgroup, quetiapine was not better than placebo for improving of manic or depressive symptoms (Cutler et al. 2011). The study by Vieta et al. (2010), in which quetiapine served as an internal comparator for assay sensitivity unfortunately reported a separate subgroup analysis only for the paliperidone, but not the quetiapine patients.

As for its use as add-on therapy, there is a case report of a patient with mixed bipolar disorder with psychotic features not responding to the combination of valproate, olanzapine and fluoxetine, who after the replacement of olanzapine by quetiapine improved in terms of manic and psychotic symptoms (Catapano-Friedman 2001). A retrospective study of patients with bipolar disorder and other bipolar spectrum disorders, reported that the proportion of mixed patients responding to quetiapine was 77% (Zarate et al. 2000). Finally, there is an RCT in hypomanic patients with mixed features (BD-II (DSM-IV-TR) with YMRS scores $\geq$12 and MADRS scores $\geq$15), which found that adjunctive quetiapine was superior to adjunctive placebo in improving overall severity as measured with the CGI-BP and depressive symptoms, but not (hypo)-manic symptoms (Suppes et al. 2013).

CE in acute manic mixed episodes (monotherapy) is 'E' both for manic and depressive symptoms.

CE in acute manic mixed episodes (combination/augmentation therapy) is 'C' for manic symptoms and 'B' for depressive symptoms.

Efficacy in acute depressive mixed episodes

We could not find any study investigating quetiapine monotherapy or adjunctive treatment in bipolar patients with a depressive mixed episode, only an add-on study in unipolar agitated depression (see 'Further evidence').

CE in acute depressive mixed episodes (monotherapy) is 'F'.

CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

A large, placebo and lithium-controlled relapse and recurrence prevention study with quetiapine included a subgroup of 223 randomised mixed patients who responded to quetiapine acutely during the open-label run-in phase (Weisler et al. 2011). Quetiapine was significantly better than placebo in delaying time to recurrence for any mood episode (HR 0.26, 95% CI 0.14–0.48), a new manic (HR 0.18, 95% CI 0.06–0.53) and a new depressive episode (HR 0.32, 95% CI 0.14–0.70). Unfortunately, new mixed episodes were not recorded as a category on its own, but were summarised under new manic episodes.

We found two identically designed RCTs that studied maintenance treatment in mixed, manic, or depressive bipolar patients, and compared the efficacy of quetiapine + lithium or valproate versus placebo + lithium or valproate (Vieta, Suppes, et al. 2008; Suppes et al. 2009). Both studies found that, for the subgroup of mixed patients, the quetiapine combination increased the time to recurrence to a mood event (any, manic or depressed). Furthermore, a post hoc analysis of the mixed patients included in these two previous RCTs confirmed these results, and further described that both manic and depressive symptoms improved with quetiapine combination ($P = 0.004$ and $P = 0.011$, respectively) (Vieta et al. 2012).

CE to prevent a new episode after a mixed index episode (monotherapy) is 'B' for 'any', 'B' for 'manic' and 'B' for 'depressive'.

CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'A' for 'any', 'A' for 'manic' and 'A' for 'depressive' (all in combination with lithium or valproate).

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

Unfortunately, the cited monotherapy and combination maintenance studies did not examine mixed recurrences as an outcome on its own. The Swedish registry study by Joas et al. (2017) established a prophylactic effect of lithium and valproate, but not quetiapine, in preventing hospitalisation due to a mixed episode (HR for quetiapine: 0.92 (0.62–1.39)).

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'E'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

An RCT examined quetiapine add-on in 90 outpatients with BD-I or II, ten of whom had a mixed mood state

and current alcohol dependence. All primary outcomes were alcohol related. In the secondary outcomes, a non-significant greater reduction in the self-rated Inventory of Depressive Symptoms (IDS-SR) was observed with quetiapine; however, a separate analysis for mixed patients is not reported (Brown et al. 2014). Otherwise, we did not find any evidence for quetiapine in bipolar mixed episodes; however, some evidence was shown in unipolar depression. A 6-week open-label study compared adjunctive quetiapine to venlafaxine in 21 patients experiencing acute agitated major depression to patients only taking venlafaxine as an antidepressant (Dannlowski et al. 2008). The decrease in depressive symptoms was markedly significant in the quetiapine group versus venlafaxine monotherapy, being significant at week 1, and increased until week 6 ($P = 0.005$); the remission rate was slso higher in the quetiapine group. However, whether results generated in unipolar mixed depression can be generalised to bipolar mixed states remains highly questionable.

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

The short-term side effects of quetiapine include sedation, orthostatic hypotension and nausea, the long-term side effects include weight gain and metabolic issues, although to a lesser degree as with, e.g., olanzapine. For more detailed information we refer the reader to the previous papers of this series (Grunze et al. 2009; Grunze et al. 2010; Grunze et al. 2013). Data on safety in pregnancy with quetiapine are sparse. Animal studies suggested that quetiapine may delay skeletal ossification as well as reduce birth weight (Nguyen et al. 2009), and as a consequence it is listed by the FDA as a category 'C' medication for safety in pregnancy.

Rating of ST: 0 for short-term treatment, – for long-term treatment

Recommendation grade (RG)

The RG is '3' (combination treatment) for the acute treatment of manic mixed episodes for depressive symptoms and' 4' for manic symptoms.

The RG is '2' for prevention of any mood episode, mania and depression after a mixed manic index episode in combination with lithium or valproate, and '3' for prevention of any episode, mania and depression, after a mixed manic episode, monotherapy.

Risperidone

Efficacy in acute manic mixed episodes

The only risperidone monotherapy trial including mixed patients did not show improvement of manic symptoms versus placebo (Khanna et al. 2005). Changes at endpoint in YMRS scores were significantly higher for risperidone only in the manic patients ($P > 0.001$), but not significant for the mixed patients. However, only nine patients with mixed episodes were included in the study, so the result cannot be interpreted.

The best quality evidence for risperidone monotherapy stems from a 3-week, randomised and double-blind head-to-head comparison of risperidone versus olanzapine, which can be considered as an efficacious and valid comparator or mixed episodes (Perlis et al. 2006). Of the 329 patients included, approximately two-thirds were diagnosed with a DSM-IV mixed episode. No significant differences in manic and depressive improvement, or rates of response or remission between treatments in either manic or mixed patients were found. The study was not powered to prove non-inferiority of risperidone compared to olanzapine.

A controlled combination treatment study compared risperidone + lithium or valproate, haloperidol + lithium or valproate and placebo + lithium or valproate, including 97 mixed patients (Sachs et al. 2002). Patients with a mixed episode showed similar YMRS improvements with risperidone + lithium or valproate, haloperidol + lithium or valproate, and not different from improvement observed with placebo + lithium or valproate

CE in acute manic mixed episodes (monotherapy) is 'C'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'E'.

Efficacy in acute depressive mixed episodes

We could not identify any study with risperidone in patients with a bipolar depressive mixed episode.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

An open-label 6-month study in 26 adult BD-I patients with a mixed index episode and additional treatment

with lithium or valproate supplied some evidence for acute efficacy maintained for 6 months. Statistically significant reductions in YMRS score were seen at week 1 ($P < 0.005$) and 6-month endpoint ($P < 0.0001$). Highly significant improvements in CGI and PANSS score were seen from week 4 and onward ($P < 0.0001$). At week 4, 74% of patients were considered responders (50% YMRS reduction and decrease of 2 points in CGI). Improvements in HAM-D were significant from week 1 onward ($P = 0.0001$) and remained significant until 6-months endpoint ($P < 0.0001$) (Benabarre et al. 2001).

A prospective open-label study from South Korea, examining adjunctive risperidone (plus mood stabiliser) in manic and mixed patients ($n = 44$) reported significant improvement of both manic and depressive symptoms in both subgroups over 24 weeks (Woo et al. 2010)

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) 'C'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not identify any study with risperidone examining mixed relapses or recurrences

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

An early case report was suggestive of efficacy of risperidone in treatment refractory dysphoric mania (Vieta et al. 1995).

Different from the outcome in the controlled study (Sachs et al. 2002), a 12-week, open-label study including 102 patients, but only 17 with mixed episodes, suggests efficacy for risperidone combined with lithium or valproate. Subjects with mixed episodes showed a significant reduction in mean YMRS score from baseline to week 1 ($P = 0.0002$), to week 3 ($P = 0.0001$) and to week 12 ($P < 0.0001$). The mean reductions in depressive symptoms scores were significantly reduced at week 3 ($P < 0.03$) but not at week 12 in mixed patients (Yatham et al. 2003).

A retrospective chart review looking at 28 children and adolescents with DSM-IV bipolar disorder (25 mixed and three hypomanic) supports efficacy of risperidone in reducing manic and psychotic symptoms (Frazier et al. 1999).

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

The safety and tolerability profile of risperidone has been described in great detail in previous articles of this series (Grunze et al. 2009; Grunze et al. 2013) and in key review papers (Seemüller et al. 2005). In brief, extrapyramidal symptoms (especially with higher dosages), akathisia and insomnia in short-term and weight gain and prolactin elevation in long-term treatment may constitute problems.

The FDA safety-in-pregnancy category rating for risperidone is 'C'.
Rating of ST: 0 for short-term treatment, – for long-term treatment

Recommendation grade (RG)

The RG is '4' for the acute treatment of manic mixed episodes (monotherapy)

The RG is '4' to prevent a new episode after a mixed index episode (combination/augmentation therapy)

Typical antipsychotics (first-generation antipsychotics)

Efficacy in acute manic mixed episodes

A controlled 12-week head-to head comparison of olanzapine and haloperidol (Tohen, Goldberg, et al. 2003) included a small subgroup of 24 mixed patients. Rates of symptomatic remission (YMRS scores) were not different between olanzapine and haloperidol groups, and there was no significant interaction for the treatment by manic or mixed subtypes. Secondary analysis revealed that, for patients who entered the study with a mixed state, both therapies were effective in reducing depressive symptoms.

A controlled combination treatment study compared risperidone + lithium or valproate, haloperidol + lithium or valproate and placebo + lithium or valproate, including 97 mixed patients (Sachs et al. 2002). Patients with a mixed episode showed similar YMRS improvements with risperidone + lithium or valproate, haloperidol + lithium or valproate not different from improvement observed with placebo + lithium or valproate.

CE in acute manic mixed episodes (monotherapy) is 'C'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'E'.

Efficacy in acute depressive mixed episodes

We could not identify any study with a typical antipsychotic in patients with a bipolar depressive mixed episode.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

We could not identify any maintenance study with a typical antipsychotic in patients with a bipolar mixed index episode.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not identify any study with typical antipsychotics examining mixed relapses or recurrences.

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

No further studies of typical antipsychotics in mixed states were identified

Rating of FE: 0 for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

As was also the case for antidepressants, this is not a homogenous group of medications. The safety and tolerability profile varies. The use of most typical antipsychotics is associated with extrapyramidal motor symptoms in both the short and long term, with tardive dyskinesias and probably CNS neurotoxic effects in the long run, as well as with differing degrees of prolactin elevation and weight gain. As far as weight gain is concerned, some typical AP are by and large weight neutral, such as molindone, fluphenazine, perphenazine, pimozide or haloperidol, others may cause significant weight gain, e.g., chlorpromazine. Finally, typical antipsychotics put patients on greater risk of a malignant neuroleptic syndrome than atypical antipsychotics (Tural and Onder 2010).

A special concern in mixed patients is the propensity of typical AP, especially with haloperidol, that they might provoke depressive symptoms (Tohen, Goldberg, et al. 2003).

The risk of major congenital malformations in pregnancy might differ between agents. Haloperidol is generally considered as a relatively safe option (Diav-Citrin et al. 2005).

Rating of ST: – for short-term treatment, – for long-term treatment

Recommendation grade (RG)

The RG is '4' for the acute treatment of manic mixed episodes (monotherapy with haloperidol).

Valproate (including divalproate, divalproex, valpromide)

Efficacy in acute manic mixed episodes

In contrast to several evidence-based recommendations we could not identify a placebo-controlled randomised study that proves efficacy of valproate in mixed patients. Subgroup analyses in mixed patients have either not been conducted/reported (Freeman et al. 2002; Bowden et al. 2006) or did not differentiate from placebo (Swann et al. 1997). Swann et al. reported on a post hoc analysis of a 3-week RCT (Bowden et al. 1994) that enrolled 179 adult patients with RDC criteria for acute mania. One hundred and three patients also met mixed mania criteria (or, as the authors named it, 'depressive mania') defined as the presence of least two items of the Schedule for Affective Disorder and Schizophrenia Change [SADS-C] depression subscale. The study found that patients with depressive mood improved more in their manic symptoms when treated with valproate than with lithium ($P < 0.005$). The study also demonstrated that the presence of even a modest level of pre-treatment depressive symptomatology was indicative of a superior response to valproate over lithium. However, this finding needs to be viewed with caution as the

numbers of patients with mixed mania were small, valproate did not differentiate from placebo on a significant level in the subgroup with mixed mania (only from lithium), the analysis was post hoc. Further, and from today's point of view, lithium would not be considered as a gold standard for acute mixed states against which new medications should be evaluated for comparative efficacy.

A small case series tested valproate as an intravenous infusion in seven severely manic, mixed or bipolar depressed patients (two manic, two mixed, one mixed with RC, two depressed). Four of seven patients were classified as responders as far as a reduction of manic symptoms and overall improvement are concerned, only the rapid cycling patient and the two depressed patients did not improve (Grunze et al. 1999).

CE in acute manic mixed episodes (monotherapy) is 'C' for manic symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

We could not identify any study with valproate in patients with a bipolar depressive mixed episode.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

A post hoc analysis of the 12-month maintenance study comparing valproate, lithium and placebo (Bowden et al. 2000) was published in 2005 (Bowden et al. 2005). Of 372 patients, 123 were classified as having dysphoric mania (mania $+ \geq 2$ depressive symptoms). Compared to placebo, there were no significant treatment-related differences in the dysphoric patients on time to a depressive or manic episode. Among both euphoric and dysphoric patients, maintenance treatment with valproate was superior to lithium (but not placebo) in delaying time to any mood episode or premature discontinuation. Dysphoric mania appeared to predispose patients to more side effects when treated with either valproate or lithium compared to placebo treatment.

Kessing, Hellmund, Geddes, et al. (2011) conducted an observational cohort study with linkage of nationwide registers of all people with a diagnosis of bipolar disorder in psychiatric hospital settings who were prescribed valproate or lithium in Denmark between 1995 and 2006. They included a total of 4,268 participants, among whom 719 received valproate and 3,549 received lithium subsequent to the diagnosis of bipolar disorder. The overall rate of hospital admissions was significantly increased for valproate compared with lithium in patients with a mixed index episode (HR = 1.59, 95% CI 1.16–2.18), which is in contrast to previous reports suggestive of better outcomes with valproate than lithium maintenance.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'E'.
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

The (already cited) Swedish registry study by Joas et al. (2017) showed that valproate was the only drug apart from lithium that significantly reduced mixed relapses. As detailed previously, we consider this registry study due to its size and quasi-experimental design minimising selection bias as providing sufficient evidence to qualify for a CE 'B'.

In a 20-month maintenance RCT comparing valproate and lithium in recently manic rapid cycling patients who were initially stabilised on combined treatment with lithium and valproate (Calabrese et al. 2005), no statistical difference emerged between valproate and lithium in preventing a mixed episode. However, the number of mixed recurrences was low: none on valproate and one on lithium in a total of 60 patients (Cipriani et al. 2013). In addition, the study is difficult to interpret as it had no placebo arm, analysis was post hoc for the purpose of a meta-analysis, and lithium may be not the ideal standard comparator.

CE to prevent a mixed episode after an unspecified, a manic or depressed index episode (monotherapy) is 'B'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

The study by Freeman et al. (1992) was the first controlled study that indicated that valproate was effective in the treatment of depressive symptoms that occurred concomitantly in patients with mania. Another open, randomised monotherapy study

comparing lithium and valproate in acute and continuation treatment of manic symptoms suggests that valproate acts more rapidly on co-existing depressive symptoms than lithium, although the overall efficacy was not different at study end after 12 weeks (Mosolov, Kostiukova, Kapiletti, et al. 2009).

A single case report also suggests the efficacy of valproate in an adolescent patient with dysphoric mania and learning disability (Whittier et al. 1995).

Mixed features appear frequent in geriatric patients with bipolar disorder (Sajatovic et al. 2011). A open study by Niedermier and Nasrallah (1998) is suggestive of efficacy of valproate in this patient group.

A 3-week RCT study, recruiting DSM-IV-TR mixed or manic patients ($n = 166$ mixed, 45% of total study population) showed that extended-release valproate was superior to placebo in improving manic scores ($P = 0.13$) and response ($P = 0.012$). The article states that the treatment difference was independent of presenting a manic or a mixed episode; however, a separate subanalysis for mixed patients is not supplied. (Bowden et al. 2006).

There is also some indirect evidence that valproate may be more effective for prevention of newly emerging depressive symptoms in continuation treatment after an acute manic episode. In a randomised, open 12-week comparative trial of valproate versus lithium in 270 patients with mania or mixed mania, the MADRS score after 3 months increased in comparison to the 3-week score in the lithium group, but this was not the case in the valproate group. Moreover, 5% of patients in the lithium group required antidepressants during the course of the study, compared to 2.5% in the valproate group (Bowden, Mosolov, et al. 2010).

Rating of FE: + for short-term treatment, + for long-term treatment

Safety and tolerability (ST)

Usually valproate is well tolerated but may give rise to potentially life-threatening problems. More frequent dose-dependent acute side effects include neurological symptoms such as tremor and mild sedation, thrombopenia or leukopoenia and asymptomatic increase of liver transaminases. These side effects are usually benign and fully reversible after discontinuation of valproate. Hair loss or change of hair texture may occur. Of the severe and potentially life-threatening adverse events, idiosyncratic hepatic failure occurs in approximately 1 in 50,000 patients with valproate and is not dose dependent. Acute haemorrhagic pancreatitis with valproate has been observed in a few cases and occurs most likely in the first 3 months of treatment. Valproate-induced encephalopathies are described in epilepsy treatment.

Weight gain is probably the most prominent side effect in long-term treatment and may affect medication adherence. Polycystic ovary syndrome (PCOS) in valproate-treated female patients is also an important issue, and together with valproate's teratogenicity (FDA pregnancy category 'D') makes it unsuitable in young women of child-bearing age. Valproate is associated with the highest rate of major congenital malformations (6.2–16%) (Nguyen et al. 2009). In addition, lasting developmental delays in children of mothers who had taken valproate during pregnancy has been described (Meador et al. 2009).

Rating of ST: + for short-term treatment, – for long-term treatment

Recommendation grade (RG)

The RG is '4' (monotherapy) for the acute treatment of manic mixed episodes

The RG is '3' for preventing a mixed episode after a manic, mixed or unspecified index episode.

Ziprasidone

Efficacy in acute manic mixed episodes

Two RCTs showing the efficacy of ziprasidone in acute treatment of mixed states used monotherapy. The first study is a 3-week RCT including both DSM-IV manic and mixed patients with BD-I disorder (BPI) ($n = 127$ manic and $n = 70$ mixed) (Keck, Versiani, et al. 2003). The results of this trial showed that ziprasidone was superior to placebo in improving manic symptoms (decrease in Mania Rating Scale (MRS) scores) and mania severity (Clinical Global Impression-Severity scale (CGI-S)), being associated with a higher rate of responders that was comparable in both manic and mixed subsets of patients. However, the paper unfortunately does not supply information on the significance of these findings in the respective subgroups. The replication trial by Potkin et al. (2005) included 83 mixed patients, but did not report a separate subgroup analysis. So the controlled evidence rests with a post hoc pooled analysis of these short-term studies that re-examined the subgroup of 179 patients with subsyndromal depressive symptomatology (Cincinnati Criteria, or experiencing ≥ 2 prominent depressive symptoms) (Stahl et al. 2010). The analysis showed that improvement in manic symptomatology was greater in the ziprasidone group ($P < 0.001$), and depressive symptoms were significantly lower at all

visits ($P < 0.05$), with higher response and remission rates than placebo.

CE in acute manic mixed episodes (monotherapy) is 'C' both for manic and depressive symptoms.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'F'.

Efficacy in acute depressive mixed episodes

A 6-week, randomised, placebo-controlled trial enrolled 73 patients with BD-II ($n = 43$) or MDD who met DSM-IV criteria for an MDE together with two or three DSM-IV mania criteria (Patkar et al. 2012). Patients were maintained on their ongoing TAU while ziprasidone was added. The study reported that both mixed BD-II and MDD patients on ziprasidone had higher response and remission rates ($P = 0.04$ and $P = 0.0045$, respectively); manic symptoms (MRS scores) did not change over time, but there was a reduction in depressive symptoms (MADRS scores; $P = 0.001$) versus placebo. The effect of ziprasidone on MADRS scores was significantly different in the two diagnosis subtypes ($P = 0.036$), with more benefit in BD-II than in MDD.

The same study was also subject to an earlier report (Pae et al. 2012) that did not find any significant effects. In this earlier report, statistical significance was conservatively set at a P value ≤ 0.003 to detect at least a medium-to-large effect size. The power analysis in the second report (Patkar et al. 2012) set a less ambitious $\beta = 0.20$ and two-tailed $\alpha = 0.05$ based on pilot studies previously conducted for the mania registration trials. In this case of double reporting the task force decided to go along with the report by Patkar et al. (2012) using standard significance levels.

CE in acute depressive mixed episodes (monotherapy) is 'F'.
CE in acute depressive mixed episodes (combination/augmentation therapy to TAU) is 'B' for depressive symptoms.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

Sixty-two patients, 19 with a DSM-IV mixed index episode, participated in a 1-year extension after participating in the previously described acute study by Keck, Versiani, et al. (2003), having received ziprasidone in this study. The mean reduction in the MRS, as well as CGI-S ratings, compared to baseline of the acute study, was sustained in the mixed subgroup. The overall MRS response rate was 86% (88% in the manic, 79% in the mixed subgroup) (Keck, Versiani, et al. 2009). Unfortunately, measurements of depressive symptoms are not reported. Only 17 patients finished the study after 1 year, which makes the results less reliable and warrants further investigations.

Another study investigated the prophylactic efficacy of ziprasidone plus lithium or valproate in a randomised, placebo-controlled design in 240 patients who had recovered from a manic (56%) or mixed (44%) index episode. The overall result was that add-on ziprasidone resulted in a significantly longer time to intervention than placebo; unfortunately, no detailed outcome for those with mixed episodes at entry nor the numbers for mixed recurrences are supplied (Bowden, Vieta, et al. 2010).

CE to prevent a new episode after a mixed index episode (monotherapy) is 'C' (for manic relapse).
CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'F'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not identify any study with ziprasidone examining mixed relapses or recurrences

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.
CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

A case report by Mech (2008) reports good efficacy in three out of four treatment-refractory mixed patients, both for manic and depressive symptoms.

Rating of FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

The safety and tolerability profile of ziprasidone appears favourable (Citrome 2011). Of note is the negligible impact on metabolic parameters, prolactin and the fact that ziprasidone is relatively weight neutral (Kemp et al. 2012). Some sedation, although less than with several other APs, and EPS, especially tremor and akathisia, are more frequent side effects (Seemüller et al. 2005). Although ziprasidone can prolong the QTc interval, this has not resulted in increases in sudden

death or cardiac sudden death (Camm et al. 2012). Ziprasidone is in the FDA 'C' pregnancy category meaning that risk cannot be ruled out as there are no controlled data in human pregnancy, but animal studies have revealed evidence of developmental toxicity including possible teratogenic effects, an increase in the number of offspring born dead and a decrease in postnatal survival. However, a developmental delay after in utero exposure has been observed for ziprasidone in a preliminary report, so for now, ziprasidone should be used even more cautiously in pregnancy than other antipsychotics (Nguyen et al. 2009).

Rating of ST: + for short-term treatment, + for long-term treatment

Recommendation grade (RG)

The RG is '3' (monotherapy) for the acute treatment of manic mixed episodes for manic and depressive symptoms.

The RG is '3' (combination treatment) for the acute treatment of depressive mixed episodes for depressive symptoms.

The RG is '4' (monotherapy) for prevention of mania after a mixed manic index episode.

Other atypical antipsychotics used in bipolar disorder

We identified two small studies on the use of clozapine in mixed state. A retrospective chart review examined clozapine in dysphoric manic patients (according to Cincinnati Criteria (McElroy et al. 1992)) as monotherapy or combined with lithium, valproate or an antidepressant. All seven patients improved significantly in both their psychotic and affective symptoms (Suppes et al. 1992). Further evidence comes from another study that was open-label, and enrolled 10 adolescents with treatment-resistant manic/mixed episodes. With clozapine alone or in combination with mood stabilisers, all patients (five pure manic, five mixed) were considered responders, and with significant improvements in manic and depressive outcomes (all P values <0.001) (Masi et al. 2002). Issues exist with safety (especially agranulocytosis) and the metabolic syndrome making frequent blood checks mandatory (ST '–').

In summary, we would consider for clozapine a *CE 'C' evidence for acute manic mixed episodes (mono- and combination/augmentation therapy).*

We could not identify any published studies for other atypical antipsychotics used occasionally in mania, namely amisulpride, sulpiride or zotepine supporting their use in bipolar mixed states.

Other anticonvulsants used in bipolar disorder

Oxcarbazepine is infrequently used in bipolar patients as an alternative to carbamazepine in patients not tolerating carbamazepine well, or in need of co-medication that strongly interferes with carbamazepine. However, oxcarbazepine also has an interaction potential with other medication, and the risk of hyponatremia might be higher than with carbamazepine (Van Amelsvoort et al. 1994). There is some evidence from an open 8-week add-on study by Benedetti et al. (2004) that oxcarbazepine has some efficacy in DSM-IV mixed manic states. Eighteen adult patients with BD-I ($n = 16$) and BD-II ($n = 2$) with a DSM-IV diagnosis of bipolar manic ($n = 4$), depressive ($n = 8$) or mixed episode ($n = 6$), and unsatisfactory clinical response to current treatment with lithium salts administered for at least 1 month received add-on oxcarbazepine. Five out of six mixed patients were classified as responders (CGI-I score of 2 or 1 at week 8). Thus, we would consider it as a *CE 'C' evidence for acute manic mixed episodes (combination/augmentation therapy).* A randomised open comparison of oxcarbazepine versus carbamazepine maintenance showed a similar extent of reduction in time spent with manic or depressive symptoms; however, a separate analysis of patients with mixed index episodes was not conducted (Mosolov, Kostiukova, Ladyzhenskii 2009).

The 8-week controlled monotherapy study in dysphoric mania[5] by Mokhber et al. (2008), which was described in detail above, found that gabapentin is superior to carbamazepine in mania ratings, and better than lamotrigine and carbamazepine in depression ratings. However, the previously discussed shortcoming in design and reporting makes it difficult to consider this study. As an adjunct to mood-stabiliser therapy, gabapentin has been studied in five small open-label studies. In one of them, eight of nine Bipolar I or II patients with mixed symptoms inadequately responsive to mood stabilisers, improved in their manic symptoms in the short term (1–3 months), and maintained response (1–7 months) (McElroy et al. 1997). In another one, which recruited 21 patients with BD-I mixed episode, found that 50% of them were responders (CGI 1 or 2 points), and that while there was no significant reduction of manic symptoms, depressive symptoms were greatly reduced ($P = 0.0001$), a reduction positively correlated with mixed residual symptomatology ($P = 0.003$) (Perugi et al. 1999). In another study on BD-I or BD-II patients, inadequately

responding to standard therapy, five out of the nine mixed patients included had a positive response although lower and with a time to response longer than for manic or hypomanic patients (Altshuler et al. 1999). Another study enrolled 10 mixed bipolar patients who improved quickly in both manic ($P < 0.01$) and depressive ($P < 0.05$) symptoms when GBP was added (Sokolski et al. 1999). Finally, another open-label study which enrolled BD-I or -II patients with subsyndromal features (YMRS > 6 or HAM-D > 12, and CGI-B > 3) found again that, while mania scores did not substantially improve, depression was significantly improved ($P < 0.002$) (Vieta et al. 2000). Thus, we would consider it as a *CE 'C' evidence for acute manic mixed episodes, both for manic and depressive symptoms (combination/augmentation therapy)*.

Topiramate has been tested in five RCT's of acute mania, but failed to separate from placebo and was inferior to lithium (Grunze et al. 2009; Pigott et al. 2016). None of these studies supplied a subgroup analysis for patients with mixed states, so evidence for topiramate derives only from one retrospective chart review and two open studies that used it as adjunctive therapy in patients refractory to other treatments. In the retrospective chart review, which included 58 patients with bipolar or schizoaffective disorder refractory to mood stabiliser treatment, three out of the seven patients with a mixed affective disorder (DSM-IV criteria) showed marked improvement (42%), while the remaining patients showed mild or no improvement (29%), or deteriorated (28%) (Marcotte 1998). The open-label study by Chengappa et al. (1999) also included patients resistant to mood stabiliser or antipsychotic treatment; out of the five mixed patients included, three (60%) responded with regard to a reduction in manic and depressive symptoms. The other open-label study, which recruited bipolar spectrum patients, found that, out of the three mixed subjects, one was responding (50% decrease in both manic and depressive symptoms), while two had a depressive episode relapse and one a mixed relapse (Vieta et al. 2002). A retrospective study in adolescents evaluated adjunctive topiramate, and found that 59% of patients with mixed mania (10 out of 17) responded to treatment (CGI-I ≤ 2) (Barzman et al. 2005).

The safety/tolerability profile of topiramate appears reasonable in low doses commonly used in bipolar disorder (rating '+'). However, neurological side effects are not entirely dose dependent, including cognitive impairment and rare cases of transient hemiparesis (Jones 1998).

In summary, the magnitude of change, and thus the efficacy of topiramate in mixed states, appears unconvincing and may just represent spontaneous improvement and placebo effects. We consider the CE for topiramate added to ongoing treatment in acute mixed states conflicting (CE 'D'), the corresponding RG '5'.

We could not identify any published studies for other anticonvulsants sometimes used in bipolar disorder, namely clonazepam, phenytoin, pregabalin, zonisamide, eslicarbazepine, levetiracetam, barbiturates and bromides supporting their use in bipolar mixed states. However, our search may have missed evidence, especially for the first-generation antiepileptics, as it may have been published prior to the inclusion period of our literature search.

Other medication tested in bipolar mixed states

Burt et al. (1999) conducted an open-label trial with the cholinesterase inhibitor donepezil add-on in 11 adult patients with a diagnosis of BD-I disorder partially or non-responsive to lithium. Of the five mixed patients, two showed a marked and one a slight response. Available evidence for the calcium channel blocker verapamil comes from two open-label studies. In the first one, verapamil (with adjunctive chlorpromazine if necessary) was tested in mania with mood-congruent or mood-incongruent psychotic features, or mixed episodes. The two mixed patients in the study achieved a partial, but not a full resolution of symptoms (Lenzi et al. 1995). The other open-label study tested verapamil add-on to TAU in women (some pregnant) with BD-I or BD-II. Seventy-seven percent of the woman (seven out of nine) with mixed states fulfilled response criteria on the mania scale, and two responded on the depression scales as well (Wisner et al. 2002). In addition, it needs to be noted that verapamil was equally efficacious as lithium in one double-blind study in acute mania (Pal Singh 2008), but inferior to lithium in another single-blind, head-to-head study (Walton et al. 1996).

The task force feels that data are still too sparse to make any recommendation either for donepezil or for verapamil.

Electroconvulsive therapy (ECT)

Efficacy in acute manic mixed episodes

In 1938, Cerletti and Bini switched from animal studies to the first ever human trial of ECT in a patient allegedly suffering from a mixed episode with psychotic symptoms (Shorter and Healy 2007). Unfortunately, after this successful start, the role of

ECT in the treatment of mixed states diminished over time due to the continued stigma attached to, and lack of access to, this treatment. But evidence from several case series suggest that ECT is effective in the treatment of acute mixed episodes (Valenti et al. 2008). Unfortunately, the original articles did not detail whether patients had ECT as sole therapy or were continued on their medication. As it is the usual clinical practice, we assume that all evidence falls into the categories 'combination/augmentation therapy'.

In a retrospective study in Aarhus Psychiatric Hospital (Strömgren 1988), a high response to ECT in a sample of 20 patients with ICD-9 manic depressive mixed states was observed. Thirteen treatment series were classified as satisfactory response, five as moderate response, one as slightly effective, and one as ineffective. Gruber et al. (2000) reported a significant reduction in depressive and manic symptoms in a small case series of seven mixed state patients treated with ECT. Other studies (Devanand et al. 2000) that compared the response to ECT in mixed state, bipolar depression, and mania, showed robust response rates in all groups: 80% in the mixed group, 100% in the manic group, and 76% in the depressed group. Nevertheless, the mixed group required longer hospitalisations and more ECT trials compared to the other two groups. Ciapparelli et al. (2001) did not find any difference between treatment-resistant bipolar patients with depression ($n = 23$) and mixed manic episodes ($n = 41$) in terms of number of ECT sessions needed, but reported a higher response rate of 56% for mixed mania compared to 26% for bipolar depression. Overall, he response rates for the bipolar depressed group were slightly lower than those of most other studies. It is possible that the efficacy of ECT was compromised in this study by the concurrent administration of anticonvulsant medications in all patients. Medda et al. (2010) evaluated the ECT response in a sample of BD-I patients, in which 46 patients exhibited depression and 50 patients demonstrated a mixed state. The response rate was similar in bipolar depression and mixed state (67.4% and 76.0%, respectively), and no difference was found in the remission rate between depression (41.3%) and mixed state (34.8%), However, at the end of the ECT course, mixed state may present more residual agitation and psychotic features compared with depressive patients.

The largest case series with mixed patients comes from Medda et al. (2015), who performed an analysis using data obtained from 197 of 203 consecutive patients with a bipolar mixed state, according to DSM-IV-TR diagnostic criteria, who were treated with ECT between January 2006 and May 2011. At the end of the ECT course, conducted bilaterally with a brief pulse stimulator twice weekly, 55 patients (27.9%) were considered non-responders, 82 patients (41.6%) were responders, and 60 patients (30.5%) were remitters. Of note, both depressive and manic symptoms were highly responsive to ECT as the significant reductions of respective rating scale scores (YMRS, HAM-D, BPRS and CGI) suggest. Regarding ECT tolerability, in six patients the ECT course was terminated prematurely (one severe confusion, one severe headache, two cardiac arrhythmias, one respiratory complications and one consent withdrawal). In summary, there are no RCTs evaluating the efficacy of ECT relative to other treatments in mixed affective states. However, the above reports provide reasonable evidence for the safe and effective use of ECT, including in patients refractory to pharmacotherapy. In addition, response to ECT usually occurred within 3–4 weeks in patients who had previously failed many weeks of pharmacotherapy.

CE in acute manic mixed episodes (monotherapy) is 'F'.
CE in acute manic mixed episodes (combination/augmentation therapy) is 'C' both for manic and depressive symptoms.

Efficacy in acute depressive mixed episodes

We could not locate a trial conducted exclusively in bipolar depressive mixed states, but subanalyses of two studies supply some evidence that ECT is effective in what we would term a depressive mixed state. The Pisa group analysed in detail which subgroup of mixed patients from the trial by Medda et al. (2015) had the most benefit from ECT (Perugi et al. 2013). Cluster analysis identified four groups, including 63 (31.2%) subjects with Agitated-Irritable Mixed-Depression, 59 (29.2%) with Psychotic Mixed-Mania, 17 (8.5%) with Anxious-Irritable-Psychotic Mixed-Mania, and 63 (31.2%) with Retarded-Psychotic Mixed-Depression. The Agitated-Irritable Mixed-Depression group had the most benefit from ECT in terms of remission rates defined as a CGI severity score ≤ 1, which were significantly higher than for the other subgroups.

Retrospectively applying mixed states criteria according to the Cincinnati criteria (McElroy et al. 1992) and Akiskal's criteria (MDE plus two to three manic/hypomanic symptoms), which may be considered as a DSM-5 mixed specifier proxy, Palma et al. (2016) analysed ECT data from a total of 50 ECT course treatments that were performed in 41 bipolar patients in the Department of Psychiatry at Amadora, Portugal, over 5 years. The mixed state group represented

36.6% ($n = 15$), the depressed group 53.7% ($n = 22$), and the manic group 9.8% ($n = 4$) of the total population of patients. All affective episodes, except one mixed state, showed a positive clinical response as documented by retrospective rating of a CGI ≤ 3. No differences were found in terms of number of ECT sessions performed, length of hospital admission, referral to continuation ECT treatment, number of re-admissions, and time until next readmission.

CE in acute depressive mixed episodes (monotherapy) is 'F'.

CE in acute depressive mixed episodes (combination/augmentation therapy) is 'C'.

Efficacy in maintenance treatment after an acute mixed episode in preventing episodes of any polarity or a new manic, depressive or mixed episode

Little is known about the impact of acute ECT on the long-term outcome of bipolar patients. A first case series reported that maintenance ECT was useful in patients with bipolar disorder initially treated with a course of ECT for an index episode of mania, depression or mixed state, including rapid cyclers ($N = 4$) (Vanelle et al. 1994). Medda et al. (2013) published a prospective naturalistic study that followed 36 bipolar patients with a medication-resistant severe depression or mixed state index episode that responded to acute ECT (mean duration $= 55.3 \pm$ SD, 30.4 weeks). Of these, 13 had a depressive relapse, 5 months on average after the end of acute treatment; one patient had a mixed state relapse. In the more recent study by Palma et al. (2016), eight out of ten (80.0%) of the depressive episodes that started cECT were kept on maintenance regime, while the proportion in mixed state group was of seven out of 11 (63.6%). The mean duration of follow-up was 136.4 ± 80.1 weeks (range: 10.1–249.9 weeks), and no significant differences were observed between depressed and mixed state groups (depressed group $= 149.0 \pm 86.0$ (SD) weeks versus mixed group $= 125.7 \pm 76.4$ weeks, $P = 0.344$). The mixed state group presented a higher percentage of episodes followed by readmission due to affective relapse in comparison to the depressive group. The absolute number of re-admissions that followed the index admission, however, did not differ between both groups (average number of re-admissions: depressed group $= 0.6 \pm$ SD 1.3 versus mixed group $= 0.9 \pm 1.3$; $P = 0.353$), neither did the average time to readmission (mixed readmitted patients $= 48.3 \pm 62.0$ weeks versus depressed readmitted patients $= 47.3 \pm 48.3$ weeks; $P = 0.424$).

There may be a special benefit of ECT in rapid cycling patients so far unresponsive to prophylactic mood stabiliser treatment (Mosolov and Moshchevitin 1990). Twenty bipolar ($n = 16$) and schizoaffective ($n = 4$) patients with a rapid cycling course presented with different mixed states, retrospectively assessed with DSM-5 specifier criteria as five mixed manias, nine mixed depressions and six cases with mood fluctuations too rapid to diagnose a predominant syndrome. ECT was very effective in eight patients (40%) with maintaining remission continuing on previously ineffective mood stabiliser (seven of them were on lithium, four had mixed depression, two mixed mania and two frequent daily mood fluctuations), six patients showed partial response and six patients had no improvement at all (three of them were on carbamazepine, two had mixed mania, one mixed depression and three frequent daily mood fluctuations). There were some signs of switching to mixed mania or hypomania during ECT treatment in four patients with mixed depression, but in all cases the duration of manic symptoms was very short.

CE to prevent a new episode after a mixed index episode (monotherapy) is 'F'.

CE to prevent a new episode after a mixed index episode (combination/augmentation therapy) is 'C'.

Efficacy in maintenance treatment after an acute manic or depressed episode in preventing new mixed episodes

We could not locate a study that specifically looked into mixed relapses after a manic or depressive index episode

CE to prevent a mixed episode after a manic or depressed index episode (monotherapy) is 'F'.

CE to prevent a mixed episode after a manic or depressed index episode (combination/augmentation therapy) is 'F'.

Further evidence (FE)

Based on the previously cited case reports and series, we rate the FE: + for short-term treatment, 0 for long-term treatment

Safety and tolerability (ST)

Progressive cognitive symptoms, especially of memory, is a main worry associated with repetitive ECT sessions. In addition, every session has the inherited risks

associated with short-term anaesthesia. Thus, clinicians should take these concerns seriously.

Rating of ST: – for short-term treatment, – for long-term treatment

Recommendation grade (RG)

Given the overall evidence, we would assign an *RG '4' both for acute and continuation/maintenance ECT in mixed states*. Due to the methodological limitations of ECT research (lack of randomisation and placebo control) the evidence is restricted. Nevertheless, ECT may be a useful option in otherwise treatment refractory or frequently relapsing mixed patients.

Other physical treatments

Some exploratory work has been carried out in the acute treatment of bipolar mixed patients with repetitive transcranial magnetic stimulation (rTMS), Uncontrolled evidence for the use of rTMS in mixed patients derives from three case reports, of which at least two report on the same patient. The first one reported the case of a treatment-resistant mixed BD-I patient, who showed immediate improvement of depressive, but not manic symptoms after treatment with rTMS (Zeeuws et al. 2010a). The same outcome, improvement in depressive but not manic symptoms, was reported in an additional cases of one mixed episode in a patient not responding to ECT (Zeeuws et al. 2010b; Zeeuws et al. 2011).

The use of vagus nerve stimulation and DBS to treat bipolar patients has evolved quite recently, but we could not locate any evidence specifically for mixed patients.

In conclusion, the evidence for physical treatments other than ECT is still too weak to give a recommendation for bipolar mixed patients.

The role of psychotherapy and psychoeducation

As we clarified at the beginning, this guideline does not focus on the evidence of psychotherapies and psychoeducation in the treatment of bipolar disorder. The role of psychological factors, personality and social factors in driving depression (and agitation) is well understood, and it is known that psychological approaches are needed. The important role of these techniques for improving compliance and resilience against mood instability are also well documented. They are an integrative and established component of treatment, accompanying medication. However, the evidence so far is restricted to acute bipolar depression and maintenance treatment, and to our knowledge, no results on psychotherapy in acute mixed patients have been published so far. With regards to prevention of mixed episodes, Colom et al. (2003) showed in a RCT that adjunctive psychoeducation was effective in delaying the time to a new mixed episode as defined in DSM-IV.

Conclusions

Using the established approach of the WFSBP guideline series, and making minor modifications to suit the topic of bipolar mixed states, we identified a few medications that appear efficacious in mixed patients. However, none of these medications can fully cover all phases of treatment or all subgroups of mixed patient groups equally well; in summary, the paucity of evidence leaves us with more questions than answers.

Olanzapine, paliperidone and aripiprazole have the best evidence for the treatment of acute mixed manic states. Evidence on a comparative level (RG 1–3) in bipolar depressive mixed states only exists for ziprasidone in combination treatment, and on a RG 4 level for carbamazepine, lurasidone, olanzapine and ECT. Thus, especially in bipolar depressive mixed states, the evidence is rather weak, also keeping in mind that the ziprasidone study was very small and conducted in BD-II patients. It remains uncertain whether results in BD-II can be extrapolated to BD-I (and vice versa). For the prevention of a new episode after a mixed index episode, quetiapine, lithium and olanzapine appear to be best choice treatments, either in mono- or combination treatment. Less is known about how to prevent best a mixed episode after a manic, mixed or depressive index episode, but valproate, olanzapine and lithium have demonstrated at least some effectiveness. In summary, evidence suggests that olanzapine (in mono- or combination treatment) appears as the medication that covers most treatment scenarios and subgroups in mixed patients, albeit at a major long-term tolerability and safety cost. Overall, it may be speculated that, similarly to rapid cycling, combination therapy could be more efficacious than monotherapy for the treatment of mixed states, and may be preferable at least in severe cases (Takeshima 2017).

Historically, valproate has been considered an effective treatment in mixed states while lithium was thought to be less effective. In the absence of reliable data for lithium, this may be true for acute treatment, although on low level evidence (RG 4 for valproate). Finally, and similar to mania and depression, clozapine and especially ECT are options to consider when other treatments have failed.

All these results and recommendations have to be viewed with caution. Many treatments have not been assessed systematically, the majority of evidence was derived from naturalistic data and from post hoc analyses. These studies were often underpowered to detect a signal in the mixed patient subgroup, and failure to beat placebo does not necessarily mean lack of efficacy if the medication were more carefully tested. Thus, recommendations are based on limited data and have a fair degree of uncertainity. This clearly underscores the future need of more and conclusive studies in bipolar mixed states.

Notes

1. The appropriate grading of open, but randomized large studies, and of large, prospectively collected data sets with quasi-experimental designs, with patient-relevant outcomes in comparison to small RCTs triggered a vivid discussion among the task force members. Following the logic of the recent BAP Guideline (Goodwin et al. 2016), the recent commitment of the NIH to prioritize effectiveness studies (Lauer and Collins 2010), and based on the quantity and quality of the data, and reliability of the source, it was finally decided to attribute the study of Joas et al. (2017) the same weight as an RCT.
2. Although the combined post hoc analysis by Szegedi et al. (2013) and Berk et al. (2015), are conducted in reasonably large samples, it is not apparent whether they have been planned a priori as part of the investigational plan and study protocols. Therefore, the grading is 'C', not 'B'.
3. The title of the analysis of Berk et al. (2015) 'Effects of asenapine in BD-I patients meeting proxy criteria for moderate-to-severe mixed major depressive episodes: a *post hoc* analysis' is misleading; patients are still defined by having a DSM-IV mixed episode, which implies the preponderance of mania. This is also reflected by the YMRS baseline severity of >27 in all study arms. For this reason, the task force also feels that the inclusion of this post hoc analysis in the meta-analysis by Fornaro et al. (2016) entitled 'Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials' is not justified.
4. The Azorin et al. (2013) paper states that 'These post hoc efficacy and safety analyses were based on the ITT dataset, which comprised all randomised patients who took at least one dose of study medication and had at least one valid post-baseline YMRS assessment', the ANCOVA of the YMRS and MADRS scores, however, were conducted on OC. Additionally, the paper does not supply the numbers of OC subject to analysis. Furthermore, the combined analysis reports on 295 ITT mixed patients, whereas adding the numbers of the individual studies leaves us with 302 ITT mixed patients, and the discrepancy between these numbers remains unclear. Due to these inconsistencies, the task force decided to dismiss the combined analysis as evidence in favour or against asenapine and olanzapine. In the opinion of the task force, this also makes the result for asenapine in the meta-analysis of Muralidharan et al. (2013) questionable, as the evidence for asenapine is only based on the publication by Azorin et al. (2013), and, in addition, questions the validity of the whole meta-analysis which obviously mixes OC and LOCF data.
5. Applying DSM-IV definition of dysphoric mania as a period that includes two to four symptoms of depression while someone is in a manic state.
6. As a result of a consensus process within the task force, we decided to grant a CE 'B' also to large size registry studies with real world endpoints and minimized risk of a selection bias, e.g., with each patient serving as his own control. This is the case for one study selected for this review (Joas et al. 2017).

Acknowledgements

We would like to especially thank Mrs Monica Gratacos for her great support in the initial literature search, and Helen Sigurdardottir, WJBP editorial office, for editorial assistance.

Financial disclosures of principal authors

Heinz Grunze received grants/research support, consulting fees and honoraria within the last three years from Gedeon Richter, Genericon, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Servier.

Eduard Vieta received grants/research support, consulting fees and honoraria within the last three years from Ab-Biotics, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Johnson & Johnson, Lundbeck, Otsuka, Pfizer Inc, Sanofi-Aventis, Servier, Sunovion, Takeda, and Tecnifarma.

Siegfried Kasper received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe and Servier.

Guy Goodwin is a NIHR Senior Investigator, holds a grant from Wellcome Trust, holds shares in P1vital and has served as consultant, advisor or CME speaker for Angelini, Compass pathways, MSD, Lundbeck (/Otsuka or/Takeda), Medscape, P1Vital, Pfizer, Servier and Shire. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Charles Bowden has no conflicts of interest to report.

Rasmus W. Licht received research grants, consulting fees and honoraria within the last three years from Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, Servier and Sunovion.

Jean-Michel Azorin received grants/research support, consulting fees and honoraria within the last three years from

Allergan, AstraZeneca, Janssen-Cilag, Lundbeck, Otsuka, Servier, Takeda and Teva.

Laksmi Yatham has been on speaker/advisory boards for, or has received research grants from Allergan, AstraZeneca, Bristol-Myers Squibb, CANMAT, CIHR, DSP, Eli Lilly, Forrest, GlaxoSmithKline, Janssen, the Michael Smith Foundation for Health Research, Pfizer, Servier, Sunovion, and the Stanley Foundation.

Sergey Mosolov has been a speaker or consultant for Gedeon Richter, Janssen-Cilag, Pfizer, Sanofi-Aventis, Servier and Minerva.

Hans-Jürgen Möller received grant/research support, consulting fees and honoraria within the last years from Eli Lilly, Lundbeck, Servier and Schwabe.

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