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Canadian Network for Mood and Anxiety Treatments (CANMAT)/ International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder

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Abstract

The Canadian Network for Mood and Anxiety Treatments (CANMAT) has previously published treatment guidelines for bipolar disorder in 2005, along with international commentaries and subsequent updates in 2007, 2009, and 2013. The last two updates were published in collaboration with the International Society for Bipolar Disorders (ISBD).

These 2018 CANMAT/ISBD Bipolar Treatment Guidelines represent the significant advances to the field since the last full edition was published in 2005; including updates to diagnosis and management, as well as new research into pharmacological and psychological treatments. These advances have been translated into clear and easy to use recommendations for first, second, and third line treatments; with consideration given to levels of evidence for efficacy, clinical support based on experience, as well as consensus ratings of safety, tolerability, and treatment emergent switch risk. New to these guidelines, a hierarchical order was created for first and second line treatments recommended for acute mania, acute depression and maintenance treatment in bipolar I disorder. Created by considering impact of each treatment across all phases of illness, this hierarchy will further assist clinicians in making evidence based treatment decisions.

Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine alone or in combination are recommended as first line treatments for acute mania. First line options for bipolar I depression include monotherapy or combination treatment with quetiapine, lamotrigine, lithium, or lurasidone. While medications which have been shown effective for the acute phase should generally be continued for the maintenance phase in bipolar I disorder, there are some exceptions (such as with antidepressants); and available data suggest

that lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination treatments should be considered first line for those initiating or switching treatment during the maintenance phase.

In addition to addressing issues in bipolar I disorder, these guidelines also provide an overview and recommendations surrounding clinical management of bipolar II disorder; as well as advice on specific populations such as women at various stages of the reproductive cycle, children and adolescents, as well as older adults. There is also discussions on the impact specific psychiatric and medical comorbidities such as substance use, anxiety, and metabolic disorders. Finally, an overview of issues related to safety and monitoring is provided. The CANMAT/ISBD group hopes that these guidelines become a valuable tool for practitioners across the globe.

Table of Contents

Section 1: Introduction

In the 20 years since the Canadian Network for Mood and Anxiety Treatments (CANMAT) first published guidelines on the management of bipolar disorder (1), there has been an explosion of research on treatment of this illness. During this time period, CANMAT has strived to translate advances in research to international consensus on evidence based clinical management; first by publishing 2005 guidelines accompanied by expert commentaries, then by providing updates in 2007 (2), 2009 (3) and 2013 (4) in collaboration with the International Society for Bipolar Disorders (ISBD). The main objective of these publications was to synthesize the wealth of evidence on the efficacy, safety, and tolerability of the range of interventions available for this complex and varied illness; with the goal of providing clear, easy to use recommendations for clinicians to improve outcomes in their patients.

Given that 13 years have elapsed since the publication of the last full edition in 2005, the objective of these 2018 CANMAT/ISBD Bipolar Disorder Management Guidelines is to provide a comprehensive, up to date review of research evidence on the treatment of various phases of bipolar disorder; translated into clinical recommendations for evidence based management. Updated principles related to diagnosis and management are also included, in response to significant changes made with 5th edition of American Psychiatric Association Diagnostic and Statistical Manual for Mental Disorders (DSM-5)(5). With increased research into various treatments for bipolar disorder, the evidence ratings have also been modified to increase rigor- for instance, minimum sample sizes are now specified for randomized controlled trials (RCTs) at each level of evidence (Table 1.1).

Figure 1.1: What are Hierarchical Ratings?

Hierarchical Orders of Treatment are new to the 2018 Guidelines. They were created for first and second line treatment recommendations for acute mania, depression, and maintenance treatment of bipolar I disorder; and will further assist clinicians in making evidence based treatment decisions.

These orders were created by considering the efficacy of each treatment across all phases, as well as acute and maintenance safety and tolerability and the risk for treatment emergent switch. Thus, for example if two treatments were shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, or had better safety or tolerability, that treatment would be placed higher in the hierarchical recommendation.

When making treatment decisions, we recommend that agents listed higher in the hierarchy be tried first, unless there are patient-specific reasons for choosing an agent lower in the order (such as patient preference, prior treatment non/response, or clinical features which favor treatments lower in the ranking).

As with previous editions of CANMAT guidelines, clinical support for efficacy was an important consideration in arriving at the final treatment recommendations (Table 1.2). Major conflicting data are addressed in text boxes (figures) to clarify the rationale for arriving at a specific level of evidence for efficacy.

In the current edition, an additional distinction is made between safety and tolerability, and a consensus rating is assigned to each medication on these two measures for its use in acute or maintenance phase. Further, a rating is also assigned to each medication for its propensity to switch patients into mania or depression. More information on these ratings can be found in the respective treatment sections, as well as in Section 8.

The final grading of recommendations into first, second, or third line considers levels of evidence for efficacy, clinical support based on experience, as well as consensus ratings of safety, tolerability, and risk of treatment emergent switch. In addition, a hierarchical order of treatments was created and listed in the tables for first and second line recommendations for acute mania, depression and maintenance treatment in bipolar I disorder. This hierarchy was

created by considering impact of each treatment across all phases of illness (Figure 1.1). The rationale for the hierarchical approach is that bipolar disorder is a chronic lifetime condition with recurrent syndromal mood episodes and subsyndromal mood symptoms, and hence most if not all patients will require maintenance treatment. Since treatments that are prescribed for an acute mood episode are usually continued into maintenance treatment, maintenance efficacy should be considered when choosing acute-phase treatments. Treatments that have demonstrated efficacy across the spectrum of the illness should thus be tried first before treatments that have demonstrated efficacy for only selective phases of the disorder. Thus, for example if two treatments were shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, the treatment with evidence for maintenance is placed higher in the hierarchical recommendation.

Of note, when a treatment is listed as a monotherapy, that also implies that it can be used on its own or in combination with other ongoing treatments- even if there are no specific studies demonstrating the efficacy of that combination. In this situation, the assumption is that the previous ongoing treatment was partially effective, and the addition of the new agent will provide benefits in either an additive or synergistic manner. In contrast, agents specifically listed as adjunctive therapy may have no evidence for efficacy as monotherapy, and are only recommended for use in combination with other evidence based agents.

As with previous editions, these guidelines also have a “not recommended” category which includes treatments that have clearly been shown to be ineffective in double blind RCTs. Further, we have added a new category called “no specific recommendation/ agents which require further study” to include treatments with insufficient evidence or clinical experience to make a

recommendation, or where there is a reason to believe that negative trials failed because of methodological problems- especially when the results are inconsistent with what is expected based on the pharmacological properties of treatment and clinical experience. Inclusion in this category means the efficacy of these agents is unknown at this time.

As in previous editions, these guidelines are organized into eight sections (Table 1.3), including the introduction. Foundations of Management (Section 2) discusses the epidemiology of bipolar disorder, screening and diagnostic considerations, importance of monitoring risk for suicide, the chronic disease management model and patient centred care (including shared decision making), as well the importance of incorporating psychoeducation and other psychosocial treatment strategies into treatment. Additional information on presentation and hierarchical treatment algorithms for acute mania (Section 3) and depression (Section 4) are reviewed, and include descriptions of clinical features that may help direct treatment choices. The importance of long-term maintenance treatment and promotion of treatment adherence for mood stability, as well as hierarchical listings of treatment options are discussed in Section 5. An expert review of the available evidence for treatments of bipolar II disorder and recommendations based on those findings are presented in Section 7. The management issues related to specific populations, including women at various stages of the reproductive cycle, children and adolescents, older adults, and those with psychiatric or medical comorbidity are each discussed in Section 7. Finally, the principles of medical monitoring and an overview of safety and tolerability concerns for recommended treatments are provided in Section 8.

For convenience and to avoid confusion, these guidelines also include a table of common terms used (with explanation of intended meaning) that may have overlapping definitions or criteria in the literature (Table 1.4).

These guidelines are intended for use by psychiatrists and primary care providers who care for patients with bipolar disorder throughout the lifespan; supporting them to provide evidence-based assessment, treatment of acute symptoms, prevention of episode recurrence, and management of comorbidities. These guidelines are not meant to replace clinical judgement or define standards of care. While designed with Canadian physicians in mind, input from experts from the ISBD makes these guidelines applicable for practitioners from across the globe. As with previous publications, CANMAT will strive to publish regular updates to these guidelines, incorporating new knowledge useful for practicing clinicians.

As not all medications included in these guidelines will be available in all countries, including Canada, clinicians are advised to follow the recommendations of local regulatory bodies.

Section 2: Foundations of Management

Epidemiology

Prevalence

Bipolar disorder is a common and disabling mental illness with significant morbidity and mortality. The estimates of prevalence of bipolar disorder vary. The World Mental Health Survey Initiative reported total lifetime (and 12 month) prevalence estimates of 2.4% (1.5%) across bipolar I (BDI), bipolar II (BDII) and sub-threshold bipolar disorder subtypes. While the

prevalence rates for each subtype varied across the nine countries studied, sub-threshold bipolar disorder was the most common at 1.4% (0.8%), followed by BDI 0.6%(0.4%) and BDII 0.4%(0.3%) (6). While Canada was not included in this study, similar results were seen from the Canadian Community Health Survey- Mental Health which found the lifetime prevalence of BDI was 0.87% and BDII 0.67% (7).

Age of Onset

Bipolar Disorder frequently manifests in late adolescence and young adulthood, with an overall average age of onset of 25 years. Statistical models suggest the presence of three age of onset subgroups within bipolar I disorder and these can be categorized into a largest early (17.24 ± 3.20 years), and smaller middle (23.93 ± 5.12 years), and late onset (32.20 ± 11.96 years) groups, with the proportion of individuals falling into each category being 41.7%, 24.7% and 33.6% of the total sample, respectively (8). However, the ages of onset tend to differ somewhat depending upon the origins of samples analysed. For instance, a recent study showed that the mean age of onset for the USA sample was 20 years with ages of onset of 14.5 ± 4.9 years (63%), 26.5 ± 7.6 years (28.5%), and 39.5 ± 12.5 years (8.5%) for early, middle and late onset groups respectively while the European sample showed a relatively later mean age of onset of 29 years and a later onset in each of the three categories with 19 ± 2.7 years (24.8%), 27.2 ± 6.3 years (50.7%), and 41.8 ± 10.7 years (24.5%) as the ages of onset for early, middle and late onset groups (9). Those with an earlier age of onset tend to have a longer delay to treatment, greater depressive symptom severity, and higher levels of comorbid anxiety and substance use (10). While manic episodes can occur for the first time after the age of 50 as a part of bipolar I disorder, the possibility of organic mania should be considered and investigated in these cases (11).

Burden of Illness

People living with bipolar disorder suffer substantial impairment, being symptomatic with syndromal or subsyndromal symptoms for approximately half of their lives (12, 13). Patients with BDI experience syndromal and subsyndromal depressive symptoms for up to 30% of the time while those with BDII are burdened with depressive symptoms nearly 50% of the time. Patients are unable to maintain proper work role function approximately 30% or more of the time (14). Quality of life is reduced in both symptomatic and non-symptomatic patients when compared to healthy controls (15-17), and several domains of functioning have been identified by patients as being of particular importance, including physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, and education (18). For both psychosocial functioning and quality of life, impairments are more pronounced in patients with depressive symptoms (19-21), in those with more previous episodes/ longer duration of illness (20, 22), and in those with lower cognition (23).

Consistent with these observations, the Global Burden of Disease Study attributed 9.9 million years lost to disability (YLD) to bipolar disorder- making it the 16th leading cause of YLDs worldwide (24). The impact that bipolar disorder has on young people is even greater, it being the sixth leading cause of disability adjusted life years among people aged 10-24 worldwide (25). The burden of this disease was further emphasized in a systematic review addressing cost of illness studies, with findings demonstrating that the worldwide annual costs per person with bipolar disorder range from $1,904 to $33, 090 USD; higher per person costs were associated with BDI, delayed or misdiagnosis, frequent psychiatric interventions, use of atypical antipsychotics, treatment non-adherence, poor prognosis, relapse, and comorbidity (26).

Diagnostic Assessment

DSM-5 Diagnostic Criteria

Bipolar Disorder encompasses a spectrum of diagnostic subgroups primarily divided according to the severity of mood elevation experienced during acute episodes (5) (Table 2.1). On this spectrum, BDI is placed at one pole due to the presence of threshold manic episodes in which features include inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risky behavior that leads to significant functional impairment, may include psychotic features, and/or necessitate hospitalization. At the other end of the spectrum, cyclothymia is characterized by subthreshold presentation of hypomanic and depressive symptoms that while chronic, do not meet diagnostic criteria for a major depressive episode or manic/hypomanic episode. Bipolar II Disorder (BDII) sits between the two conditions with hypomanic episodes, qualitatively like manic periods but which, although distinct and observable are not of a sufficient duration or severity to cause significant functional impairment, hospitalization, or psychosis as well as threshold depressive episodes.

DSM-5 has replaced the bipolar disorder not otherwise specified (NOS) category in DSM-IV with two new categories; other specified bipolar and related disorder and unspecified bipolar and related disorder. As well, DSM-5 includes substance/medication induced bipolar and related disorder and bipolar and related disorder due to another medical condition (Table 2.1 for details). For more detailed discussion of diagnostic categories, the reader is advised to consult DSM.5 and recent Royal Australian and New Zealand College of Psychiatrists guidelines for treatment of mood disorders (27).

DSM-5 Specifiers for Bipolar and Related Disorders

The DSM-5 also includes a range of specifiers that clinicians may use to further clarify the specific course, severity, and features of bipolar disorder. While a more detailed description can be found in the DSM-5 manual, the available specifiers and their use across the spectrum are listed in Table 2.2. Many of these specifiers may also be used to guide treatment decisions for acute mania (Section 3) and depression (Section 4). Amongst these, the mixed features specifier, which has replaced mixed episodes, warrants consideration because of the multiple and complex presentations of mixed states it can give rise to. Furthermore, the nascency of this terminology has meant that treatment data is as yet sparse. The DSM-5 has added mixed features as a specifier for MDD as well, which will likely pose some pragmatic diagnostic challenges and management dilemmas for clinicians.

Staging Bipolar Disorder

The course of bipolar disorder is heterogeneous but on average, the risk of recurrence increases with the number of previous episodes (28). In addition, data examining the effect of episodes on the course of illness showed that the number of previous episodes is associated with increased duration and symptomatic severity of subsequent episodes. Moreover, the number of episodes is associated with a decreased threshold for developing further episodes and with an increased risk of dementia in the long term (28). The progressive course of illness in patients with multiple episodes is called clinical progression and the biological basis of clinical progression is defined as neuroprogression (28, 29).

The concepts of clinical progression and neuroprogression have provided the basis for the development of staging systems in bipolar disorder(30). Overall, the staging models describe three broad clinical stages: I. Individuals at increased risk for developing bipolar disorder due to family history as well as certain subsyndromal symptoms predictive of conversion into full-blown bipolar disorder, II. Patients with fewer episodes and optimal functioning in the interepisodic periods and III. Patients with recurrent episodes as well as decline in functioning and cognition (31). So far, the heterogeneity intrinsic to bipolar disorder has prevented the clinical use of staging systems (32). In addition, the field of staging is in its infancy and the ability of staging systems to guide prognosis and treatment is still to be determined. Overall, the model of staging has helped clinicians to appreciate the importance of early identification and treatment as well as illness trajectories in bipolar disorder (33).

Screening and Diagnosis of Bipolar Disorder

Due to frequent depressive onset, variable help seeking for hypomanic or manic periods, temporal instability of symptoms, and high rates of comorbidity; an accurate, timely identification of bipolar disorder can be difficult to achieve in many cases. Indeed, many individuals are not accurately diagnosed until up to 10 years after onset of symptoms with on to four alternate diagnoses typically being given prior to correct recognition and treatment (34) (35). This delay has important consequences, including inadequate initial treatment and worse prognosis in terms of episode recurrence and functional outcome (36, 37).

The most frequent misdiagnosis is that of major depressive disorder, as patients are more likely to present for the treatment of depressive symptoms and may not recall periods of hypomania or

mania, or may not interpret them as being pathological. Recall and insight are particularly impaired during periods of acute depression with pronounced memory or concentration difficulties. There are several features of depression that may increase suspicion of bipolarity, and prompt more careful investigation including earlier age of illness onset, highly recurrent depressive episodes, a family history of bipolar disorder, depression with psychotic features, psychomotor agitation, atypical depressive symptoms such as hypersomnia, hyperphagia, and leaden paralysis, postpartum depression and psychosis, past suicide attempts, and antidepressant-induced manic symptoms or rapid-cycling (Table 2.3) Given the recent change in DSM-5 to allow the possibility of depression symptoms with subthreshold simultaneous hypomanic symptoms (mixed specifier) it is also important to explore if an individual is experiencing mixed symptoms. (38, 39). Schizophrenia and other psychotic disorders are the second most common misdiagnosis, occurring as the initial diagnosis in as many 30% of patients (40).

In addition to this under-diagnosis, there are also concerns that bipolar disorder may be over-diagnosed in some circumstances (41). For instance, the symptoms of borderline personality disorder, substance use disorder and ADHD overlap significantly those of hypomania/ mania, and some reports suggest that patients with these conditions often get misdiagnosed with bipolar disorder. These conditions also are often comorbid with bipolar disorder which make the diagnosis of this condition often challenging (42).

Validated self-report instruments, such as the Mood Disorders Questionnaire (MDQ) may be used as a screening tool to flag patients for whom a more detailed assessment is needed. It is important to note however that such tools have poor sensitivity and specificity, especially in community or highly comorbid populations and will thus have an elevated risk of also flagging

those with borderline traits (43). As such, tools such as the MDQ should be used only as an adjunct for screening clinical populations and not diagnostic or treatment planning purposes.

To improve the accuracy of diagnosis, it is important that clinicians strictly adhere to diagnostic criteria rather than relying on heuristics (44). It is important to complete a careful psychiatric history, including in first degree relatives, with attention paid to any suspected periods of increased activity, irritability, or other change in behaviors. Collateral information from friends and family members should be included wherever possible. Ongoing monitoring of symptoms, such as mood charting can also help detect bipolarity that may only become apparent over time. Confirmation of the diagnosis can then be made more confidently when episodes are prospectively observed.

Comorbidities and Mimics

As described in Section 6, patients diagnosed with bipolar disorder very commonly have one or more comorbid psychiatric diagnoses, with substance use disorders, impulse control disorders, anxiety disorders, and personality disorders (especially cluster B disorders) particularly common (45). The presence of comorbidity increases the complexity of the illness and can make an accurate diagnosis even more difficult.

In addition to differentiating bipolar disorder from other psychiatric diagnoses; alternative causes of mood symptoms such as personality disorders, medical or neurological conditions, substance use, and medications must be considered in the differential diagnosis (Table 2.4).

Suicide Risk

It is important for clinicians to frequently monitor suicidal ideation and risk in patients with bipolar disorder. Suicide is one of the leading causes of death in bipolar disorder, with approximately 6-7% of identified patients with bipolar disorder dying by suicide; thus suicide risk is substantially higher in bipolar disorder than that in the general population (10.7 per 100,000 per year) (46, 47). The fatality of suicide attempts is also higher in the BD than the general population (48, 49). Worldwide, approximately 43% of patients with BD report suicidal ideation, 21% a plan, and 16% a suicide attempt (6). Men are at a higher risk of death by suicide, with an estimated rate of 0.366 per 100 person years, compared to 0.217 for women (47).

As reviewed in the ISBD Task Force on Suicide in Bipolar Disorder (50), a number of sociodemographic and clinical risk factors need to be considered in determining the level of suicide risk (Table 2.5). Factors reported to be significantly associated with suicidal attempt include female sex, younger age of illness onset, depressive polarity of first illness episode, depressive polarity of current or more recent episode, comorbid anxiety disorder, comorbid substance use disorder, comorbid cluster B/borderline personality disorder, first-degree family history of suicide, and previous suicide attempts. Only male sex and first degree family history of suicide have been significantly associated with suicide deaths (50, 51). The period during and following hospital admission further represent times of particularly high risk- with 14% of suicides occurring during an inpatient stay and another 26% within 6 weeks of discharge (47, 52).

A comprehensive assessment for suicide risk should occur during all clinical interactions. Risk stratification using assessment tools is not sufficiently accurate for prediction of suicide risk in clinical use; instead clinical assessment should focus on modifiable risk factors that could be targeted to reduce the risk (53). The ISBD has developed clinical tips and patient information sheets (translated into several languages) that can be useful tools for clinicians , patients and families to develop a comprehensive approach to suicide prevention (http://www.isbd.org/Files/Admin/Knowledge-Center-Documents/Suicide-Prevention-Tip-Sheet.pdf).

The association between various treatments and suicide risk has been reviewed by the ISBD Task Force, and others which suggest that lithium (54)and, to a lesser extent, anticonvulsants may contribute to preventing suicide attempts and deaths; although more data is needed to determine their relative efficacy. There was limited data on both antipsychotics and antidepressant agents (47). As the most common method of suicide in this population is self-poisoning, the potential benefits of various treatments should be considered against their risk of toxicity and lethality. One small Canadian study indicated higher rates of lethal doses of antipsychotics (32%), opioids (29%), benzodiazepines (27%), carbamazepine (21%) and diphenhydramine (15%) compared to lithium (3%) in 34 self-poisoning deaths (55).

Chronic Disease Management

Due to the chronic, relapsing and remitting nature of BD, a long-term, multidisciplinary approach to management is needed. The Chronic Disease Management Model (56), outlines several important principles to enhance long term care for these individuals and their families

(Table 2.6). After basic clinical management including attention to diagnosis, comorbidity, and medical health has been established, patient health education and pharmacotherapy should be the initial and foundational steps for all patients. Ideally, the patient will be connected to a health care team which includes at least one other health care professional (typically a nurse) in addition to the psychiatrist for psychoeducation, ongoing monitoring, psychosocial support, and referral to community resources(57). All patients should have access to a primary care provider to attend to mental and physical health needs. If the patient is stable and discharged to primary care, the mental health care system should provide support directly to the primary care provider with attention to continuity of care (58). Additional psychosocial treatments (described below) should also be selected to fit the specific needs and preferences of the patient.

A strong therapeutic alliance is central to improve treatment adherence and outcomes (59, 60). Providers should encourage individuals to actively participate in treatment planning, using a shared decision-making approach (61, 62). Whenever possible, family members or key friends should be included as part of the care team. There is evidence that specialised, team-approach based interventions combining pharmacotherapy and psychoeducation are more effective than standard community care (63).

Regular, ongoing monitoring of mood symptoms and other measures related to the patient's own individual recovery, such as sleep, cognition, functioning, and quality of life is encouraged (18). For many patients, daily recording of mood symptoms such as through a mood diary or NIMH-Life Chart Method- Self Rating Scale can help identify early warning signs of relapse, as well as outline relationships between mood and treatment or lifestyle factors such as diet, exercise, or stress (64). While many patients will agree with the value of completing a mood diary, and this

strategy has been shown to improve treatment, for many regular completions can be a burden (65) . Online solutions such as mobile apps may improve adherence (66)- such as the Self-Monitoring and Psychoeducation In Bipolar Patients smartphone app (SIMPLE) which provides weekly and daily mood tests, with reminders to take medication or see their doctor (67-69).

Dealing with Stigma

Stigma is an important issue that will impact individuals with bipolar disorder, as well as their family members, potentially preventing individuals to seek or engage in treatment or conceal their illness- reducing social support, functioning and quality of life (70). Linked to stereotypical negative attitudes that mental illness is due to personal weaknesses or decisions, or associated with violent or criminal behavior, stigma can be perceived or experienced with interactions with others, including health care providers; or internalized (self-stigma). Specific strategies to reduce stigma, particularly self-stigma, by enhancing coping skills through improvements in self-esteem, empowerment, and help-seeking behavior can improve outcomes in this population (71).

Psychosocial Interventions

While pharmacotherapy is essential and forms the foundation for the successful treatment of bipolar disorder, adjunctive psychosocial interventions may also be useful for acute depressive episodes, as well as in maintenance treatment to prevent relapse as well as restoring quality of life to the individual and family (72, 73). No evidence exists, and hence there are no recommendations, for specific psychosocial interventions in acute mania. Psychoeducation, Cognitive Behavioural Therapy (CBT), Family-Focused Therapy (FFT), Interpersonal and Social-Rhythm Therapy (IPSRT), and Peer Support have each been found to have positive

evidence in the maintenance phase of bipolar disorder and are included as recommended adjunctive treatment options, with additional studies needed before conclusions can be drawn regarding other strategies such as Family/ Caregiver Interventions, Dialectical Behavioural Therapy (DBT), Mindfulness Based CBT (MBCBT), Cognitive and Functional Remediation, and Online Interventions (Table 2.7).

In general, provision of psychoeducation to all patients and family members is an evidence based recommendation for prevention of relapse, particularly early during illness; with selection of any additional psychosocial therapies to be based on individual concerns/presentations or deficits.

Psychoeducation

Psychoeducation broadly includes provision of information about the nature of the illness and its treatments, and key coping strategies to the patient and family (74). Current psychoeducational models for BD teach skill development in detecting and managing prodromes of depression and mania, ongoing stress management, problem solving, how to diminish the effects of stigma and denial of the illness, and provide tips on enhancing medication adherence and developing healthy lifestyles (e.g. minimizing the use of alcohol, tobacco, drugs, stimulants such as caffeine; getting regular exercise; and regulating sleep and wake times). A key goal is the creation of personalized coping strategies to prevent mood relapse.

Psychoeducation may be delivered individually or in group settings. Empirical models of psychoeducation involve face-to-face interaction with a therapist, but new models are being tested that involve online tools, smartphone apps, and workbooks (75). Consistent with broader theories of learning, it is believed that psychoeducation is enhanced when it features active

learning, with attention to monitoring the development of understanding, active skill development, and homework between sessions. Peer support and group learning are also postulated to add efficacy to psychoeducation. Regardless of the type of model and content included, priority should be given to maximize the therapeutic alliance, convey empathy, and consistently monitor symptoms (76).

Two models of psychoeducation, both delivered in group format to individuals who are well (euthymic), have published manuals and have substantial research support. These programs, the Barcelona Bipolar Disorders Program (77) (21 sessions over 6 months) and the Life Goals Program (78) (Phase I is 6 weekly sessions) also have tools to aid implementation with workbooks and handout materials, and both are first line psychoeducational interventions based on level 2 evidence for the prevention of relapse. Individual psychoeducation based on these manuals would likely be effective, and when individual trials utilizing several different approaches to psychoeducation are combined in a meta-analysis, individual psychoeducation of at least 5 sessions would still be a first line intervention for relapse prevention, based on level 2 evidence (75, 79, 80). One large study demonstrated that the 6 session Life Goal psychoeducational intervention was equivalent in relapse prevention to 20 sessions of individual CBT, at far lower cost (81), with probable shared mechanisms (82). Furthermore, that study demonstrated that integration of best practices in medication and psychotherapy simultaneously produced striking overall improvement in course of illness (83). Psychoeducation does not have any significant evidence of utility in either acute depressive or manic episodes.

Cognitive-Behavioral Therapy

CBT in bipolar disorder is supported by several published manuals and typically is given in 20 individual sessions over six months, often with additional booster sessions. Despite evidence of efficacy for CBT for MDD and psychosis, the results of CBT trials for bipolar disorder have been mixed. One large RCT supports it use for acute bipolar depression (84) in a trial that compared the efficacy of up to 30 (mean 14 sessions) CBT sessions against FFT, IPSRT, and a 3-session control intervention, but it was not possible to identify whether the benefits came from changes in the medications prescribed or the psychosocial treatments. The efficacy of CBT in relapse prevention was observed in one RCT (85), but not in another larger RCT- at least in patients that had multiple mood episodes (86). From meta-analyses, effects on either depressive symptoms or on relapse remain uncertain due to important methodological problems and study selection factors (87-89). A promising new direction in CBT has been established by a pilot study of "recovery-focused CBT" where 33 subjects received the novel CBT intervention, with evidence of reduction of relapse in the intervention group (90). Group CBT in euthymic BD is also a new direction and has shown to increase time in remission (91).

In MDD, CBT, interpersonal psychotherapy (IPT) and behavioural activation have been explored in multiple randomised controlled trials and in general display similar efficacy (92). Based on this and that of the study by Miklowitz and colleagues in acute bipolar depression (84), CBT is still recommended as an adjunctive second line treatment for acute bipolar depression (Level 2). The recommendation is also second line for maintenance treatment (Level 2) for patients with fewer episodes and less severe form of illness. No evidence exists, and hence no recommendation is made, for CBT in mania.

Family Focussed Therapy (FFT)

Family focused therapy (93) presumes that bipolar disorder outcomes may be enhanced with the support and cooperation of family or significant others, particularly in families characterized by high levels of expressed emotion. FFT focuses on communication styles between patients and their families or marital relationships with the goal of improving relationship functioning and is delivered to the family and patient in 21 sessions over 9 months.

For acute bipolar depression in adults, an intensive FFT (up to 30 sessions, mean 14) out-performed a 3 session control condition (94); although this study is limited by the caveats identified for CBT and IPSRT. Given that the original creation of FFT targeted factors related to depression, it may have specific antidepressant activity, which is also suggested by reduced depression relapse in maintenance studies. For relapse prevention, four significant RCTs of varying sizes have been conducted, delivered to a mixed audience of young adults and adolescents (95). In these studies, FFT demonstrated efficacy in reducing recurrence of new episodes of depression, not mania. Overall, FFT is recommended as adjunctive second line treatment for acute depression (Level 2) and for maintenance (Level 2). No evidence exists, and hence no recommendation is made, for FFT for mania.

Interpersonal and Social Rhythm Therapy (IPSRT)

IPSRT expands on the IPT focus on grief, interpersonal role transition, role dispute, and interpersonal deficits by including regulation of social and sleep rhythms, specifically targeted to the bipolar population. It is typically delivered in 24 individual sessions over 9 months. (96, 97).

Few controlled trials of IPSRT have been done, with limited evidence of acute efficacy. The first, large trial (98) showed no effect of IPSRT compared to a control condition but did show benefit for reduction of relapse and improved occupational functioning. An acute bipolar depression study (84) showed intensive IPSRT (up to 30 sessions, mean 14) out-performed a 3 session control condition, but it is impossible to state whether the performance was related to the intensity and number of sessions, changes in medication use or specific attributes of IPSRT. Two small studies failed to demonstrate specific benefits of IPSRT compared to control conditions (99, 100). Other open studies have shown some pre-post benefits in very small samples (101-103). Again, since many BD psychosocial treatments share a common core of elements that may be psychoeducational, it is possible that the relapse prevention aspects of psychoeducation may also result from IPSRT interventions, mediated by the same therapeutic processes (104).

Overall, IPSRT is recommended as an adjunctive third line treatment for acute depression and for maintenance, based on limited (effect size and small sample size) level 2 evidence in each phase. No evidence exists, and hence no recommendation is made, for IPSRT for mania.

Peer Interventions

Peer interventions, such as peer groups or one-on-one supports, are an important strategy believed to reduce the self-stigma and isolation in bipolar disorder, and help improve engagement in treatment (105). Some caution is needed when applying this strategy, however- as there may be risks if the peers delivering the intervention are not adequately trained or

supported, and if they promote a viewpoint that does not support treatment compliance or promotes substance use.

Reviews of peer interventions for persons with serious mental illnesses, usually incorporating a small but significant number of individuals with bipolar disorder, have demonstrated modest evidence from RCTs and other controlled studies suggesting that there are important improvements in self-efficacy and reduction in self-stigma (106-109). The largest peer intervention study involving bipolar disorder allocated 153 individuals to attend 21 weekly group psychoeducation events, with another 151 assigned to attend 21 weekly group peer support events. Both programs achieved similar outcomes in terms of time to relapse, and increased knowledge about bipolar disorder, although psychoeducation was more acceptable to the subjects and worked more effectively at preventing relapse in a subset of people with fewer previous episodes(110).

A significant source of peer support is emerging from online resources, particularly through the websites of Peer Advocacy organizations like the Depression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=peer_landing), the Mood Disorders Association of Ontario (https://www.mooddisorders.ca/), the research and advocacy group CREST.BD (http://www.crestbd.ca/), MoodSwings (www.moodswings.net.au/), and Revivre (http:/wwww.Revivre.org). YouTube is also emerging as an important source of Peer Support, along with other social media (111, 112).

Overall, Peer Interventions receive a third line treatment recommendation (Level 2) as an adjunctive maintenance therapy.

Other Psychosocial Interventions

Various other approaches have been tried in bipolar disorder, with a variety of aims, modalities, and outcome targets. None of the other interventions have been specifically targeted for bipolar depression or for mania. Some have been designed in part to reduce episode recurrence, but none have been successful in providing substantial evidence of efficacy. Because CANMAT recommendations are for the treatment of acute depression and mania, and maintenance treatment to prevent them, we do not make specific recommendations regarding these treatments. However, some of these approaches have been helpful in ameliorating some important symptoms in individuals with bipolar disorder, for example residual mood symptoms or anxiety, and so we will describe them briefly. Although somewhat like FFT, Family / Caregiver Interventions constitute a distinctly different psychosocial intervention in that the intervention is given to the family / caregiver, not the person with bipolar disorder; and evidence exists that such interventions improve clinical outcomes in the patient (75, 113). Clinical wisdom and common practice, however, support the importance of family or caregivers being included in at least some sessions with the patient (particularly for psychoeducation), both to reduce symptom burden on the individual with BD as well as to reduce burnout and emotional burden on the caregiver. Validated caregiver resources are available online, such as www.bipolarcaregivers.org (114).

Dialectical Behavior Therapy, which includes distress tolerance training, has several small studies showing its utility in reduction in some depressive symptoms and particular utility in addressing suicidality (75). One RCT of Mindfulness Based Cognitive Therapy (MBCT) involving 95 patients did not demonstrate any difference in relapse prevention compared to a treatment-as-usual group, but did reveal fewer anxiety and depressive symptoms in the MBCT

arm (115). Coupled with other smaller studies, MBCT may have a role for anxiety reduction in BD (75, 116) While not reviewed here, given that individuals with bipolar disorder may have histories of childhood abuse, comorbid personality disorders, and experience various sequelae such as shame or conflict due to behaviours experienced during acute bipolar episodes; all of these may rightly be a target for psychosocial intervention in a very individualized manner.

Cognitive and Functional Remediation

Functional impairment as well as cognitive deficits are found in many individuals with bipolar disorder, not just during an acute episode but even between episodes, prompting the evaluation of various psychosocial and biological strategies to address these problems. One intervention, "Functional Remediation for Bipolar Disorder" involves a 21-session group intervention over six months. In a large RCT, Functional Remediation (FR) was shown to have substantial impact on functioning, in comparison to treatment-as-usual(117). Coupled with other small studies involving other interventions, there is considerable hope in addressing cognitive and functional deficits in BD (118). Computer based cognitive remediation, though, may show positive effects on cognition but not on functioning (119).

Online and Digital Strategies

Modern trends to rely on the internet and apps, along with access problems in mental health, have led to the study of various online tools and mobile phone apps (120). Such strategies also build on strong traditions of self-monitoring and self-management developed formally in traditional psychoeducational interventions. In reviews, such internet and mobile health interventions have shown good adherence to validated psychological health principles, good

acceptability to patients, ease of access, and ease of use. However, research is mostly limited to pilot studies and the relatively few larger studies have not shown unequivocal benefit (121, 122).

Section 3: Acute Management of Bipolar Mania

Presentations of Mania

The DSM-5 (5) made a change to "criterion A" for mania which now requires a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy present most of the day, nearly every day for at least one week (or less time if hospitalization is necessary). In addition, a diagnosis of a "manic episode" requires at least three (or four if the mood is only irritable) of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure of speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increased goal-directed activity or psychomotor agitation, or excessive involvement in activities with a high potential for painful consequences (Table 2.1). The mood disturbance must lead to marked impairment in functioning, require hospitalization, or be accompanied by psychotic features.

Unlike in DSM-IV, the DSM-5 allows a diagnosis of bipolar I disorder in patients with major depression whose mania emerges during (e.g., medication, ECT) and persists at a fully syndromal level beyond the physiological effect of the treatment.

The DSM-5 has eliminated the categorical "mixed episode" specifier, replacing it with the more dimensional "mixed features". The DSM-5 also includes other specifiers that can accompany a manic episode: anxious distress, rapid cycling, mood congruent or mood incongruent psychotic

features, catatonia, peripartum onset, and seasonal pattern (Table 2.2). The utility of several of these specifiers in selecting treatment options for mania is discussed later in this section (See Clinical Features that Help Direct Treatment Choice).

Management of Agitation

Agitation is common in mania, and is particularly frequent in patients who have mixed features (123). Defined in the DSM-5 as "excessive motor activity associated with a feeling of inner tension" (5), agitation can manifest as pacing or fidgeting in mild cases to uncooperative, threatening, or aggressive behaviours in severe cases. Severe symptoms of agitation require prompt attention in order to reduce distress, mitigate potentially dangerous behaviour, and allow for an assessment and evaluation of underlying manic symptoms (124).

A key step in treating agitation is preventing it, or at least mitigating its severity by rapidly treating the causative manic episode. When addressing agitation in patients with bipolar disorder, clinicians need to be aware that akathisia may present as agitation and therefore, this must be excluded before implementing the general principles of management of acute mania described in Step 1 (See Pharmacological Treatment of Manic Episodes). Since agitation in this context is a manifestation of mania, it is assumed that effective interventions for treating mania that have rapid onset of efficacy would be effective in reducing agitation. Therefore, if the patient is agreeable to taking oral medications, antimanic agents with rapid onset of efficacy should be considered first.

When agitation persists despite administration of antimanic treatments, additional rapidly-acting pharmacotherapy may be often needed. The evidence for specific efficacy of various agents in

short-term treatment of agitation is summarized in Table 3.1. Some of these agents are either not available or rarely used in North America (e.g. midazolam, promethazine). We further note that the dose ranges in Table 3.1 are based on the doses studied in the trials, and would likely be appropriate in most situations. However, a comprehensive evaluation of the agitated patient is necessary (i.e. medical conditions, treatments, drugs, intoxication, etc) to determine a safe and adequate dose.

As can be seen from the table, the highest level of evidence available in short-term treatment of agitation for oral formulations of any agent is Level 3, and Level 2 for intramuscular (IM) or inhaled formulations. In this context, it is important to remember that the absence of evidence doesn't constitute lack of efficacy. Indeed, clinical experience suggests that agitation in many patients with acute mania responds well to the oral medications. Thus, a loading dose of valproate, oral formulations of atypical antipsychotics, conventional antipsychotics such as haloperidol or loxapine, and/or benzodiazepines such as lorazepam may be appropriate. If a patient indicates willingness to take oral treatment but there is a suspicion that the patient might « cheek » the medication, then either orally dispersing tablets, those that rapidly melt, oral liquid, or oral inhalation forms should be considered. In countries where inhaled loxapine is available, this should be considered if there are no contraindications.

If oral preparations are ineffective or if the agitation is severe and if the patient is refusing oral medications, or when oral therapy cannot be safely or reliably administered, then IM formulations should be considered (125). Because of the strength of evidence for efficacy in alleviating agitation in this population, aripiprazole IM (Level 2), (126, 127), lorazepam IM (Level 2) (126, 128), loxapine inhaled (Level 1) (129, 130) and olanzapine IM (Level 2) (128,

131-134) are recommended as the first line option. Sublingual asenapine (Level 3) (135), haloperidol IM (Level 3) (132, 136, 137), haloperidol IM + midazolam IM (Level 3) (132, 138), haloperidol IM + promethazine IM (Level 3) (132, 138, 139), risperidone ODT (Level 3) (137), or ziprasidone IM (Level 3) (132, 138, 140) are recommended as a second line treatment. Haloperidol PO (Level 4) (141, 142), loxapine IM (Level 4) (clinical opinion), quetiapine PO (Level 4) (142), or risperidone PO (Level 4) (141) are included as a third line options (Table 3.1).

Pharmacological Treatment of Manic Episodes

There are a range of strategies that have been investigated for use in mania; including lithium, divalproex, other anticonvulsants, typical and atypical antipsychotics, and other agents and therapies. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1.1) as well as safety and tolerability (Section 8). The evidence for efficacy and the recommendations for treating acute mania are summarized in Table 3.2.

As stated previously, the first and second line agents are listed hierarchically taking into consideration not only their efficacy for acute mania but also based on their efficacy in preventing mania or depression, treating acute bipolar depression, safety/tolerability and the risk of treatment emergent switch. The implication of this hierarchical recommendation is that those listed higher up in the table should be considered first before moving onto the next on the list unless other factors such as history of previous non-response or patient's preferences preclude such strategy in a given patient.

Monotherapy and combination therapy are listed separately as first line treatments for acute mania in the table. This does not mean that all monotherapy agents should be tried first before considering combination therapy for acute mania. We suggest that the treating clinician make a decision as to whether to treat a given patient with monotherapy or combination therapy. That decision is typically based on the rapidity of response needed (eg. combination treatments tend to work faster), whether patient had a previous history of partial response to monotherapy, severity of mania, tolerability concerns with combination therapy, and willingness of patient to take combination therapy. Once a decision is made whether to treat the patient with monotherapy or combination therapy, then hierarchy related to mono or combination therapy could be followed. We also suggest that clinicians evaluate the efficacy and tolerability at the end of week 1 and 2 and modify treatment options accordingly.

Step 1: Review General Principles and Assess Medication Status

Examination of a patient presenting in a manic state should include an immediate assessment for risk of aggressive behaviour, violence and safety threat to others, suicide risk especially in those with mixed features, degree of insight and the ability to adhere to treatment, comorbidity (including substance use that may be aggravating or contributing to clinical presentation), and availability of a psychosocial support network. A physical examination with lab investigations (described in Section 8) should be conducted, but may be deferred for patients who are uncooperative. Results of the overall assessment should be used to establish the most appropriate treatment setting (e.g. ambulatory or inpatient).

Before initiating pharmacological treatment for a manic episode, it is imperative to rule out symptoms secondary to drugs of abuse, medications, other treatments, or a general medical or a neurological condition (although, even in these cases, symptomatic treatment may be applied on a short-term basis). Steps should be taken to rule out any other factors that may be perpetuating symptoms such as prescribed medication, illicit-drug use/abuse or an endocrine disorder. Any patients presenting with mania who have been taking antidepressants should have these medications discontinued. If there is a previous diagnosis of bipolar disorder, it is appropriate to immediately commence antimanic agents. If this is the first emergence of manic symptoms, clinicians are advised to confirm the diagnosis of bipolar disorder by monitoring patients for a period of time after antidepressant discontinuation and obtain collateral information to confirm whether symptoms remain and antimanic treatment is necessary. Patients should also be supported to discontinue stimulant use, including caffeine and alcohol. Current and prior therapies should be assessed, including appropriateness of medications, dosing, and trough serum levels (where indicated), as well as past response; and this should be used to direct subsequent therapeutic choices. Attention should be paid to managing withdrawal symptoms that may occur in manic patients with histories of substance abuse.

When the symptoms of mania have remitted, behavioural and educational strategies should be applied to promote ongoing medication adherence, reduce residual symptoms, help identify early signs of relapse, and support functional recovery (see Section 2).

Step 2: Initiate or Optimize Therapy and Check Adherence

It is recommended that for all patients (including those who are untreated as well as those receiving a non- first-line treatment), therapy should be initiated with one of the available first-line monotherapy or combination treatments.

First Line Monotherapy. Approximately 50% of patients will respond to monotherapy with significant improvement in manic symptoms within 3 to 4 weeks (143). Lithium (Level 1), quetiapine (Level 1), divalproex (Level 1), asenapine (Level 1), aripiprazole (Level 1), paliperidone (Level 1 for doses>6mg), risperidone (Level 1), and cariprazine (Level 1) are all recommended as first line treatment options. Overall, these agents show comparable efficacy (Cohen's d 0.32-0.66; small to medium effect size) (144).

Although they have comparable efficacy for treating acute mania, we recommend that the agents listed first in th text and placed higher in Table 3.2 be tried first, in the order listed, unless there are patient specific reasons for choosing an agent lower down in the order (see Clinical Features that Help Direct Treatment Choices). For instance, lithium should be considered first for acute mania unless there are specific reasons such as mixed features or comorbid substance use or previous non-response to lithium.

Carbamazepine, olanzapine, ziprasidone and haloperidol also have Level 1 evidence for efficacy but they are down-graded to second line options due to safety/tolerability risks with these agents.

First Line Combination Therapy. Combination therapy with the atypical antipsychotics quetiapine (Level 1), aripiprazole (Level 2), risperidone (Level 1), or asenapine (Level 2) and

lithium or divalproex are also recommended as first line treatment options with greater efficacy than monotherapy with lithium or divalproex alone, especially in those with higher index severity (145).

In general, combination therapy is preferred to mood stabilizer monotherapy because clinical trials suggest that on average about 20% more patients will respond to combination therapy (143, 146, 147). There is also some evidence to suggest the benefit of combination therapy compared to atypical antipsychotic monotherapy, although there are fewer trials. Specifically, lithium plus quetiapine showed superiority to quetiapine alone (148). While there is also Level 1 evidence for olanzapine combination therapy over olanzapine monotherapy, this is also downgraded to second line due to tolerability/safety concerns with olanzapine.

The decision to treat with one or a combination of available first line agents should be informed by current and prior medication use, with treatment previously shown to be successful in managing symptoms preferred. Safety and tolerability factors for each medication and clinical features predictive of better response (see Clinical Features that Help Direct Treatment Choices) should also be considered. In general, combination therapy is associated with more adverse events than monotherapy. Whenever possible, options should be discussed with the patient and/or their caregiver and their preferences considered prior treatment selection.

If symptoms are not controlled using monotherapy or combination therapy with first line agents, dosing should be optimized, issues of non-adherence identified and addressed, and considerations made for possible substance use (Section 4) prior to adding or switching therapies (Step 3). Given that almost all antimanic agents separated from placebo within one week, some

therapeutic response is expected with antimanic agents within one to two weeks. If no response is observed within 2 weeks with therapeutic doses of antimanic agents, and other contributing factors for non-response are excluded, then switch or add-on strategies must be considered at this stage.

Step 3: Add-on or Switch Therapy (Alternate First Line Agents)

If therapy with one or a combination of the first-line agents (lithium, divalproex and/or an atypical antipsychotic) at optimal doses is inadequate or not tolerated, the next step is to switch to or add-on an alternate first- line agent. An exception is that despite Level 1 evidence for monotherapy with paliperidone and ziprasidone, we do not recommend combination therapy with these agents due to lack of evidence for additional efficacy (see No Specific Recommendation/ Agents which Require Further Study, below). Because there are multiple first line agents with substantial efficacy data and relative safety and tolerability, the use of second and third line agents is only recommended after unsuccessful trials of multiple first line strategies.

Step 4: Add-on or Switch Therapy (Second Line Agents)

Second Line. In patients who are inadequately responsive to first-line agents, second line choices include monotherapy with olanzapine (Level 1), carbamazepine (Level 1), ziprasidone (Level 1), and haloperidol (Level 1) (144) or combination therapy with olanzapine plus lithium or divalproex (Level 1) . While each of these strategies has strong support for their efficacy, as indicated above, safety and tolerability concerns relegate them to second line options. Although widely used in clinical practice, the combination of lithium and divalproex is also recommended

as a second line choice, as evidence supporting its efficacy is limited to uncontrolled trials (Level 3) (149-152).

Electroconvulsive therapy (ECT) is also recommended as a second line option (Level 3) (153); and although the number of controlled trials is limited there is evidence to suggest that up to 80% of patients will show marked clinical improvements (154). Brief pulse therapy, with two or three treatments per week has been used. Bifrontal electrode placement is preferred over bitemporal as it is associated with faster treatment response and fewer cognitive side effects (155-157).

When all first line agents have failed, the hierarchy should be applied to second line agents as well. Hence, olanzapine which is highest in the hierarchy amongst second line agents as first choice before moving down the list in Table 3.2

Step 5: Add on or Switch Therapy (Third Line Agents)

Third Line. Agents recommended as third line options for treatment of acute mania include monotherapy with chlorpromazine (Level 2) (158), clonazepam monotherapy (Level 2) (159) monotherapy or adjunctive therapy with clozapine (Level 4) (160-163), and tamoxifen (Level 2) (144). Tamoxifen is downgraded because of risk of uterine cancer and lack of clinical experience despite higher level of evidence for efficacy. Combination treatments with carbamazepine or oxcarbazepine (Level 3) (164), haloperidol (Level 2) (165) (145), or tamoxifen (Level 2) (166) plus lithium or divalproex are also included as third line. Repetitive transcranial magnetic stimulation (rTMS) in the right prefrontal cortex at 110% motor threshold (Level 3) (167)can also be considered in combination with pharmacotherapy.

The third line agents should only be used if a patient has not responded to adequate trials with all first and second line agents alone and in combinations. Given that the evidence is very limited for third line agents, it was not possible to list them in any hierarchical order and they are thus listed alphabetically (Table 3.3).

Agents Not Recommended for the Treatment of Acute Mania

Antimanic efficacy has not been demonstrated for allopurinol (Level 1-ve)(168), eslicarbazepine/licarbazepine (Level 2-ve) (169), gabapentin (Level 2 -ve), lamotrigine (Level 1-ve)(144), omega-3 fatty acids (Level 1-ve) (170), topiramate (Level 1-ve) (144), valnoctamide (Level 2 -ve) (171, 172), or zonisamide (Level 2 -ve) (173) (Table 3.3).

No Specific Recommendation/ Agents which Require Further Study

Trials with paliperidone (Level 2 -ve) and ziprasidone (Level 2 -ve) adjunctive therapy to lithium or divalproex showed lack of efficacy (145). This is surprising given that all other atypical antipsychotic agents which showed efficacy in monotherapy have also been shown to offer additional benefit when combined with lithium or divalproex. It is likely that methodological problems have contributed to failure in these studies; hence further studies are needed before specific recommendations can be made about the use of these combinations for mania.

Studies of olanzapine (Level 2-ve) (174) or risperidone (Level 3-ve) (175) plus carbamazepine have been negative, although this is probably due to enzyme inducing effects of carbamazepine. While this may be overcome dosing adjustments, because such interactions are unpredictable and effective doses have not been established we are unable to provide a specific recommendation.

Nutraceuticals such as branched chain amino acids (Level 3) (176), folic acid (Level 2)(177), and L-tryptophan (Level 3)(178), as well as other experimental agents such as medroxyprogesterone (Level 3) (179, 180), memantine (Level 4) (181), mexiletine (Level 4) (182), levetiracetam (Level 4) (183) and phenytoin (Level 3) (184) have all shown indications of efficacy when used adjunctively with other antimanic agents; as have glasses which block blue light (Level 3) (185). Larger controlled trials are needed, however, before a recommendation for their use in mania can be made. While an initial small RCT did not show anti-manic efficacy for verapamil (186), there is some evidence that it may work as an adjunctive therapy (Level 4)(187) or as monotherapy in women (Level 4)(188). Larger studies are needed before a conclusion can be made.

Clinical Features that Help Direct Treatment Choices

Clinical features, including DSM-5 specifiers, may assist in making treatment choices between first and second line treatment options.

In general, lithium is preferred over divalproex for individuals who display classical euphoric grandiose mania (elated mood in the absence of depressive symptoms), few prior episodes of illness, a mania-depression-euthymia course (189-191), and for those with a family history of bipolar disorder, especially with a family history of lithium response. Divalproex is equally effective in those with classical and dysphoric mania. Further, divalproex is recommended for those with multiple prior episodes, predominant irritable or dysphoric mood and/or comorbid substance abuse or those with history of head trauma (189, 192-196). Because of its teratogenic potential, however, caution should be taken when prescribing divalproex to women of childbearing age. Patients specific factors such as a history of head trauma, comorbid anxiety and

substance abuse, schizoaffective presentations with mood-incongruent delusions, or negative history of bipolar illness in first-degree relatives may respond to carbamazepine (197).

Combination therapy with lithium or divalproex and an atypical antipsychotic are recommended when response is needed faster, in patients that had a previous history of partial acute or prophylactic response to monotherapy or in those with more severe manic episodes (146).

Anxious distress. Symptoms of anxiety frequently co-occur during a manic episode, and are a predictor of poor outcome- including greater severity of manic symptoms (198) a longer time to remission (198, 199) and more reported side effects of medication (199). There have been no studies specifically examining the efficacy of any agents in reducing symptoms of anxiety during a manic episode, although these symptoms do tend to improve concurrently with mood disturbance. Post-hoc analyses suggest that divalproex, quetiapine, and olanzapine may have specific anxiolytic benefits (200) and carbamazepine may be useful as well (197).

Mixed features. Depressive symptoms co- occur alongside mania in 10-30% of cases (201, 202), with studies suggesting mixed features are indicative of a more severe and disabling course, as well as a higher rate of suicide (202, 203). Evidence supports the preferential use of atypical antipsychotics and divalproex in these cases, with combination therapy frequently required (196, 204). Atypical antipsychotics such as asenapine, aripiprazole, olanzapine and ziprasidone have been shown to be equally effective in treating manic symptoms in those with classical mania as well as in mixed mania or in manic patients with mixed features (197) (205, 206).

Psychotic features (mood congruent or incongruent). At least half of manic episodes are characterized by the presence of psychosis (207), and theories suggest that it is a nonspecific

feature which improves alongside underlying manic symptoms (208). While the prognosis for patients experiencing mood-congruent psychotic features may not differ from those with an absence of psychotic symptoms, limited evidence does suggest those with mood incongruent features have a more severe illness with poorer long term prognosis (208-213)). There is no evidence of superiority of any first line monotherapy treatment in comparison to other monotherapy options in treating patients with psychotic features. Similarly, there is no evidence that any first line combination therapy of lithium or divalproex plus an atypical antipsychotic is more effective than other first line combination therapy (175, 214, 215) (194). However, clinical experience suggests that combination of lithium or divalproex plus an atypical antipsychotic is more appropriate for manic patients with mood incongruent psychotic features (i.e. other than grandiose delusions). Similarly, in patients where the diagnostic possibility of schizoaffective disorder with manic symptoms is considered, either use of an atypical antipsychotic or combination of an atypical with a mood stabilizer is more appropriate.

Rapid cycling. Rapid cycling, or a course of illness that includes four or more mood episodes a year, affects up to one third of patients with bipolar I disorder (216-219). Hypothyroidism, antidepressant use and substance abuse are often associated with rapid cycling; thus assessing thyroid function, and discontinuation of antidepressants, stimulants, and other psychotropic agents that are contributors to cycling is imperative. Consideration should be given to gradually withdrawing substances in order to prevent withdrawal, but this needs to be balanced against the severity of mood cycling and the need for rapid mood stabilization. As there is no evidence for the superiority of any first line treatment in addressing acute manic symptoms in patients with a rapid cycling course (220), appropriate pharmacotherapy should be selected primarily based on

effectiveness in the maintenance phase if known (see Section 5). It is likely that combinations of mood stabilizing drugs may be more often necessary than monotherapies when rapid cycling is present (221), but triple mood stabilizer therapy has not demonstrated superiority to double mood stabilizer therapy in a single RCT (222), though methodological weaknesses most likely limited interpretability of the findings.

Seasonal pattern. While some individual patients may show a pattern, Canadian data is mixed as to whether episodes of mania or depression in bipolar disorder follow a consistent seasonal variation (223). There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

Section 4: Acute Management of Bipolar Depression

Presentations of Bipolar Depression

The DSM-5 criteria for bipolar depression are unchanged from the DSM-IV. Depression is characterized by a minimum of 2 weeks of depressed mood and/or anhedonia and at least four other symptoms that include changes in sleep, appetite/weight, energy, psychomotor activity, concentration, thought content (guilt, worthlessness), and suicidal intent. For many patients with bipolar disorder, the depressive polarity is often more pervasive and more debilitating than manic states, with estimates that depressed mood accounts for up to two thirds of the time spent unwell, even with treatment (12, 224, 225). Subsyndromal depressive symptoms, which persist despite treatment, are particularly common and a major source of functional impairment in these patients (226-230). They should be treated aggressively.

The DSM-5 includes several specifiers that may accompany depressive episodes: anxious distress, mixed features, rapid cycling, melancholic features, atypical features, mood congruent or mood incongruent psychotic features, peripartum onset, and seasonal pattern (Table 2.2). The utility of several of these specifiers in selecting treatment options for depression is discussed later in this section (See Clinical Features that Help Direct Treatment Choices).

Diagnostic and Treatment Challenges

Misdiagnosis and Delayed Diagnosis

Patients with depression occurring in the context of bipolar disorder are frequently misdiagnosed as having major depressive disorder (MDD) since the presence of mania or hypomania (particularly mild or moderate episodes which do not require hospitalization) may be challenging to establish retrospectively. This is especially true in the absence of a comprehensive diagnostic interview or collateral information, as patients may often lack basic knowledge of what hypomania/ mania is, and/or have limited insight into these symptoms and thus may not disclose this information unless specifically asked. Alternatively, patients who will ultimately present with hypomanic or manic episodes may only have experienced episodes of depression. Thus, clinicians must be vigilant for a diagnosis of bipolar disorder, and routinely ask for symptoms of a previous manic / hypomanic episode in every patient presenting with a major depressive episode. A diagnosis of MDD should be made only after excluding the possibility of a bipolar disorder.

In addition to overt manic/hypomanic symptoms, there are numerous features which increase the likelihood of a diagnosis of bipolar disorder in depressed individuals. These include earlier age

of illness onset (before 25 years), brief, highly recurrent depressive episodes, a family history of bipolar disorder, depression with psychotic features, atypical features such as reverse vegetative symptoms of hypersomnia and hyperphagia, leaden paralysis, psychomotor agitation, postpartum depression or psychosis, as well as antidepressant-induced irritability, manic symptoms or rapid-cycling (38, 39)(Table 2.3).

Individuals with depression who are at high risk for bipolar disorder, particularly those with a strong family history of bipolar disorder, should be closely monitored for emergence of manic or mixed symptoms. Consideration should also be given to applying the bipolar disorder depression treatment algorithm amongst those at very high risk rather than risk potential iatrogenic effects of antidepressant monotherapy- although this recommendation is based on clinical experience as there is a lack of sufficient research addressing this issue. As discussed in Section 2, there are also several useful psychosocial interventions, such as individual and family psychoeducation and family focused therapies that have been shown to have some benefit in this population.

Suicide Risk

Principles related to management of suicidal ideation and risk (see Section 2 and (47) are of utmost importance during depressive episodes, as more than 70% of suicide deaths and suicide attempts in patients with bipolar disorder occur during this phase (231, 232). Depressive episodes with mixed features, while less predominant than typical depressive episodes, are a particularly dangerous period associated with even higher short-term risks of suicide attempts or death (233). Overall, it is imperative for clinicians to review risk factors (Table 2.6) and determine an appropriate treatment setting to address any safety issues. All patients at risk should

be encouraged to develop and share a written safety plan listing coping strategies and sources of support which may be applied during times of crisis. As described in Section 2, the most common method of suicide in this population is self-poisoning, and as such potential benefits of various treatments should be considered against their risk of toxicity and lethality. One study found that there were fewer deaths due to lethal lithium levels compared to carbamazepine, and that opioids and benzodiazepines were the most common medication classes ingested at lethal levels – noteworthy given the lack of efficacy of these agents in the disorder (55).

Cognitive and Functional Impairment

Part of the impact of acute and subsyndromal depressive symptoms on functional impairment is thought to be mediated through cognitive performance, which is both subjectively and objectively impaired in bipolar depression and linked to poor psychosocial function (234-237).

Because of the important link between cognition and functioning (238) attention should be paid to avoiding treatments which may further exacerbate cognitive difficulties (239) (See Section 8). Although evidence for their efficacy is limited, cognitive enhancement therapies can be considered experimental in this population (72, 240, 241).

Psychological Interventions for Acute Bipolar I Depression

While pharmacotherapy is essential and forms the foundation for successful treatment of bipolar disorder, adjunctive psychosocial interventions may also be useful for acute depressive episodes. As described in Section 2, there are no first line psychosocial treatment options for acute bipolar

depression. Selecting between second line options such as CBT (Level 2), and FFT (Level 2), as well as the third line options IPSRT (Level 3) should be based on individual strengths and needs.

Pharmacological Treatment for Acute Bipolar Depression

Lithium, anticonvulsants, atypical antipsychotics, and other agents such as antidepressants have all been investigated for efficacy in managing bipolar depression. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1.1) as well as safety and tolerability (Section 8). Recommendations are summarized in Table 4.1.

Step 1: Review General Principles and Assess Medication Status

Examination of a patient presenting in a depressed state should include an assessment of the nature and severity of depression and associated symptoms, risk of suicide/ self-harm behavior, ability to adhere to a treatment plan, availability of a psychosocial support network and functional impairment. Lab investigations (described in Section 8) should also be completed. Results of the overall assessment should be used to establish the most appropriate treatment setting (eg ambulatory or inpatient), with consideration given to management of safety risks. Before initiating pharmacological treatment for a depressive episode, it is imperative to rule out symptoms secondary to alcohol/drug use, medications, other treatments, or a general medical condition. Patients should be supported to discontinue stimulant use and limit nicotine, caffeine and alcohol use. Course of illness and treatments used in current and prior episodes should be assessed, including past response and tolerability to specific medications and doses, and used to direct subsequent therapeutic choices. Consideration should be given to restarting medications if their recent discontinuation appeared to coincide with a depressive relapse.

Psychoeducation and other psychosocial strategies should also be offered alongside pharmacological treatment to promote ongoing medication adherence, reduce residual symptoms and suicidal behavior, help identify early signs of relapse, and support functional recovery (see Section 2).

Step 2: Initiate or Optimize Therapy and Check Adherence

It is recommended for all patients, that pharmacotherapy be initiated with one or more of the available first-line agents. Choice of agent or agents to manage an acute bipolar depressive episode should be discussed with the patient and their supporters (as appropriate) and take into account current and prior medication use and response, personal preference, safety and tolerability of each agent, as well as clinical features that may influence prognosis (See Clinical Features that Help Direct Treatment Choices).

First Line. Quetiapine (Level 1) (242-244), lithium (Level 2)(245-247), lamotrigine (Level 2) (243, 248, 249) and lurasidone (Level 2)(250) are all recommended as first line treatment options with evidence for efficacy as monotherapy.

Lurasidone (Level 1)(250, 251) and lamotrigine (Level 2)(252, 253) are also recommended as first line adjunctive treatments (Figure 4.1). Although quetiapine and lithium have not been assessed for efficacy as adjunctive treatments for acute bipolar depression, clinicians may choose either to treat depression in patients that continue to remain depressed despite optimization of treatment with other treatments (Level 4).

Figure 4.1: Why are lithium and lamotrigine recommended as first line for bipolar depression? Reconciling Conflicting Data

Lithium

In the only large double blind placebo controlled trial conducted to date, lithium was not more effective than placebo for treating acute bipolar depression(254). So, how does one justify recommending lithium as a first line agent?

The mean serum lithium levels in this study was only 0.61 mEq/L and this may account for lack of efficacy as a previous study demonstrated that lithium monotherapy was as effective as lithium plus paroxetine in those with serum lithium levels of ≥0.8 mEq/L (247).

Further, several small crossover trials demonstrated significantly higher response rates to lithium than placebo in patients with acute bipolar depression (245). As well, the STEP-BD study suggested that mood stabilizers which include lithium are as effective as mood stabilizers plus antidepressants in treating acute bipolar depression, although the durable recovery rate was modest, and there was no sub analysis focusing on lithium versus other antimanic drugs (246). Thus, the findings of these studies justify a Level 2 rating of efficacy for lithium.

Given that lithium also has clearly demonstrated efficacy in preventing mood episodes and in treating acute mania, our hierarchical rating thus justifies lithium as an important first line agent for bipolar depression, and based on overall evaluation of available studies, it is our opinion that a trough lithium serum level of 0.8-1.2 mEq/L would be needed for clinical effectiveness.

Lamotrigine

Lamotrigine monotherapy was not superior to placebo in four double blind placebo controlled trials of acute bipolar depression on the primary outcome(255). However, a meta-analysis conducted on the response rates from these studies as well as a BDII trial showed superiority of lamotrigine (248). Moreover, methodological issues with the trials likely led to the effect of lamotrigine being underestimated- including the relatively low final dose (200mg in most trials, which is lower that usually used in clinical practice (256) and short trial duration (8 weeks in most trials) which, coupled with the slow titration of lamotrigine, resulted in participants being on the final dose for only a short period. Further, lamotrigine was superior to placebo on MADRS in one of the studies (249), and changes in symptoms on this scale have since been used to demonstrate the efficacy of other agents for acute bipolar depression. Finally, the addition of lamotrigine to lithium (253) was superior to adding placebo to lithium and there was a trend for superiority of addition of lamotrigine to quetiapine vs placebo add on (252) in treating bipolar depression. It is likely that these beneficial effects are due to the direct effect of lamotrigine and not due to pharmacokinetic interaction between lamotrigine and concomitant medications. Furthermore, trial design issues, especially the fact that the six-week dose titration phase took up most of the 8 week trials, is likely to compromise efficacy signals. Lastly, the short and long-term tolerability of lamotrigine is a major benefit. Taken together, we believe these data justify at least a Level 2 rating for lamotrigine for acute bipolar depression.

In addition to this Level 2 rating for bipolar depression, lamotrigine also has demonstrated efficacy in maintenance treatment and an excellent tolerability profile- features which qualify it to be a first line treatment for bipolar depression.

Our recommendations as to which first line treatment should be considered first is outlined in our hierarchy, unless other considerations such as previous history of response/non-response and

specific clinical features suggest otherwise. For instance, if a patient presents with an acute bipolar depressive episode and is not taking any treatment and has not been treated for this episode, that patient should be commenced on quetiapine monotherapy if there is no previous history of non-response or tolerability concerns with quetiapine. However, if a patient had been taking lithium and either had a breakthrough acute bipolar depressive episode or did not respond to monotherapy with lithium, then lurasidone or lamotrigine or quetiapine add-on or switch to quetiapine monotherapy or lurasidone monotherapy might be more appropriate in that order given that lurasidone and lamotrigine adjunctive therapies have demonstrated efficacy in lithium non-responders. Similarly, in non-responders to lithium monotherapy, adjunctive lamotrigine could be another option.

Clinicians are advised to appropriately dose these medications for adequate period of time before concluding lack of efficacy. Clinical trials have shown that there is no difference in efficacy between daily doses of quetiapine 300 mg and 600 mg. Lower doses of quetiapine have not been studied in clinical trial for bipolar depression. Therefore, clinicians are advised to consider a target dose of 300 mg per day for quetiapine. For, lithium, we suggest that serum lithium levels should be maintained between 0.8 to 1.2 meq/L while for lamotrigine, the target should be at least a minimum of 200 mg/day.

Step 3: Add-on or Switch Therapy (Alternate First Line Agents)

Across several different medications for bipolar depression, early improvement (after 2 weeks) has been found to be a reasonable predictor of overall response, whereas lack of early improvement is a more robust predictor of non-response (257). Lamotrigine is the exception to

this rule given a necessary slow titration initiating the medication. In the case of non-response, dosing should be optimized and issues of non-adherence identified and addressed (see Section 2) prior to adjusting treatment strategies.

When determining whether an agent should be switched or another first line agent be added-on to any current treatment, the effectiveness of each of the medications needs to be understood in context of all the goals of managing bipolar disorder. It is often the case that a medication may be selected to address several goals, for instance, lithium could be added for acute depression with the belief that it will also bolster anti-manic prophylaxis. In this scenario, if lithium is ineffective in the individual patient for an acute bipolar depression but is also being used over the long-term for anti-manic prophylaxis, then and "add-on" intervention should be the next treatment for the acute bipolar depression. If, for instance, the anti-manic prophylaxis is already being fully provided by an atypical antipsychotic, then the new medication could replace lithium via a switch strategy. Decision-making must also address efficacy for comorbid conditions, as well as tolerability concerns. In principle, all things being equal, a switch is preferred over add-on to limit the degree of polypharmacy, but the clinical reality is that medications may be helpful for some but not all components of the illness, and using rational polypharmacy via add-on treatments is often required. For situations in which patients experience a depressive episode while already receiving an adequately dosed antidepressant, strong consideration should be given to discontinuing or switching the class of antidepressant, unless clear benefits are apparent in reducing the severity or frequency of depressive episodes. Switch of medications should be done in an overlap and taper manner unless there is medical necessity for abrupt discontinuation (258).

All first line options should be tried in adequate doses for adequate duration of time before considering second line options either as an add-on or switch strategy.

Step 4: Add-on or Switch Therapy (Second Line Agents)

Second Line. In patients who are inadequately responsive to first-line agents, monotherapy with divalproex (Level 2) (243, 259) is included as a second line option.

Adjunctive use of antidepressant (SSRIs or bupropion) therapy with lithium/divalproex or an atypical antipsychotic may also be considered as a second line add-on treatment. While some individual studies have failed to demonstrate the efficacy of adjunctive antidepressant therapy, a recent meta-analysis (Level 1) supports efficacy albeit with a small effect size (260).

This is a key aspect of decision-making regarding antidepressants, since historically much of the focus has been on risk of manic switch or rapid cycling, and an underappreciation for the relatively weak efficacy data. This new appreciation, exemplified by the small benefit seen in the above meta-analysis, led to the change from the last CANMAT guidelines, which previously gave add-on SSRIs/ bupropion antidepressants a first line recommendation. As per the ISBD Antidepressant Task Force recommendations (261), antidepressants should ideally be avoided, or used cautiously if necessary, in patients with a history of antidepressant-induced mania or hypomania, current or predominant mixed features, or recent rapid cycling. Patients and caregivers (as appropriate) should receive education regarding early warning symptoms of mood switching or cycle acceleration, and antidepressants should be discontinued if these emerge. Antidepressant monotherapy should NOT be used for the treatment of bipolar I depression.

ECT (Level 2) is also a second line treatment, and should be considered particularly for treatment-refractory patients and those for whom rapid treatment response is needed, such as severe depression with imminent suicidal risk, catatonia, psychotic depression, and/or when rapid response is important for medical stabilization. Data supports efficacy for brief pulse right unilateral placement, although there is insufficient data to guide decision of unilateral or bilateral placement for bipolar depression (262). Additional second line options include cariprazine, with efficacy demonstrated through a large RCT (263) and a pooled analysis of a failed RCT and a positive RCT (264) (Level 2), although there is less clinical experience supporting its use. Olanzapine-fluoxetine combination (Level 2) (265, 266) is effective and is also recommended as a second line option.

Similar to the approach for treatment of a manic episode, multiple first and second line agents and combinations should be trialled before considering initiating third line agents in Step 5.

Step 5: Add-on or Switch Therapy (Third Line Agents)

Third Line. Third line options are listed alphabetically in Table 4.2. In patients who fail to respond to multiple first and second line agents, third line choices include monotherapy with carbamazepine (Level 2) (243) or olanzapine (Level 1) (243).

Agents which may be applied adjunctively include aripiprazole (Level 4)(267, 268), armodafinil (Level 4) (269, 270) (Figure 4.2), asenapine (Level 4) (271), levothyroxine (Level 3) (272, 273), modafinil (Level 2)(269)(Figure 4.2), and pramipexole (Level 3) (274, 275). rTMS targeted at the left or right dorsolateral prefrontal cortex (Level 3) (276) may also be used in addition to medication. Other classes of antidepressants (SNRIs, and MAOIs) could be used adjunctively but

clinicians need to ensure adequate anti-manic prophylaxis in such situations as SNRIs and MAOIs have a higher propensity than other antidepressants to induce manic switch and cause mood destabilization (Level 2) (277-279).

Ancillary treatments such as adjunctive eicosapentaenoic acid (EPA) (Level 2) (170, 280, 281), N-acetylcysteine (Level 3) (282), and light therapy (Level 3) (283)- including bright light delivered mid-day (Level 3)(284), are also recommended as a third line treatment options to use adjunctively to other medications. There may be additional benefits to using light therapy in combination with total sleep deprivation (Level 2), although there is little clinical experience with this technique. While there is evidence from several small studies that intravenous ketamine (Level 3) (285) is a highly effective and fast acting antidepressant; due to its invasive nature, short duration of effect, and lack of long-term safety data, it has been relegated to a third line treatment; with recommendations that it be reserved for patients with severe symptoms or significant suicidal ideation for whom other treatments have been unsuccessful. In clinical situations that prioritize rapidity of response to treatment, ketamine may be considered earlier in the treatment algorithm, although clinicians need to be aware that the data for efficacy is limited and the effects do not appear to last longer. Further, there are case reports of manic switch but the clinical trial data has not provided any confirmatory evidence (285). As well, clinicians need to be aware of potential abuse of ketamine, especially in domiciliary use situations (286).

Figure 4.2: Why are armodafanil and modafanil third line treatments for bipolar I depression?

Armodafanil adjunctive therapy was assessed in three double blind RCTs. Of these, one was positive (270) but in the other two studies, it failed to separate from placebo on the primary efficacy measure (287, 288)although in one of the trials several secondary outcomes were positive(288). Furthermore, in a fourth trial, there was also suggestion of efficacy based on some secondary measures (289). Therefore, although two trials were negative on the primary efficacy measure, based on one positive trial and some positive secondary outcomes in two trials, this was given a Level 4 rating (expert opinion), and recommended as a third line.

Although modafanil has been shown to be efficacious in the only trial (269), it was also recommended a third line in light of the three negative trials for armodafanil.

Agents Not Recommended for the Treatment of Acute Bipolar Depression

Antidepressants should not be used as monotherapy in patients with bipolar I depression, as available trials do not support their efficacy and there are concerns about their safety in terms of mood switching (Level 2-ve) (261, 290) (291, 292).

Aripiprazole monotherapy failed to separate from placebo in two bipolar depression trials (293). Although the pooled analysis reports separation (294), the mean difference in MADRS change score was only 1.12 points which is not clinically meaningful and is thus not recommended (Level 1-ve). Ziprasidone monotherapy or adjunctive therapy (Level 1-ve) (243, 295), lamotrigine in combination with folic acid (Level 2-ve)(252), and mifepristone (adjunctive) (Leve 2-ve)(296) are also not recommended due to evidence for lack of antidepressant efficacy (Table 4.2).

No Specific Recommendation/ Agents which Require Further Study

There are insufficient data to make a recommendation regarding the use of aspirin (adjunctive) (Level 3-ve)(297), celecoxib (adjunctive) (Level 3-ve)(298), gabapentin (monotherapy) (Level 3-ve) (299), leviteracitam (adjunctive) (Level 3-ve)(300), lisdexamphetamine (adjunctive) (Level

3-ve)(301), memantine (adjunctive) (Level 3)(302), pioglitazone (adjunctive) (Level 3) (303, 304), riluzole (Level 4-ve)(305), and risperidone (adjunctive) (Level 3) (306). Although adjunctive therapy with pregnenolone separated from placebo at week 6, the change in depressive symptoms was not significantly different from week 8 to week 12 between the two groups (Level 2) (307).

Clinical Features that Help Direct Treatment Choices

There are limited data on predictors of treatment response in bipolar depression. However, clinical features of a depressive episode including DSM-5 specifiers may assist clinicians in choosing among recommended treatment options.

Need for rapid response. Amongst the first line options recommended, quetiapine and lurasidone have separated from placebo in clinical trials at as early as week 1 (250, 308, 309). Thus, these medications may be preferable when rapid response is required, for example patients at increased risk of suicide or have medical complications including dehydration. While ECT is recommended as a second line option, this may also be used earlier when rapid response is imperative. Second line options such as cariprazine and olanzapine-fluoxetine have also separated from placebo at as early as week 1 and may also be considered when rapid response is desirable but this needs to be balanced against the potential side effects. Lamotrigine administration requires slower titration due to risk of skin rashes, Steven-Johnson syndrome, and toxic epidermal necrolysis; and is thus not ideal for patients requiring rapid response. Lamotrigine, however, is well tolerated, and there is some evidence that its effectiveness may be more pronounced in patients experiencing depressive cognitions and psychomotor slowing (310).

Previous treatment response. Adjunctive antidepressant use may be appropriate in those with prior antidepressant response if there was no history of treatment emergent switch (311).

Anxious distress. Symptoms of anxiety are often experienced during a depressive episode, and are predictive of more persistent depressive symptoms (312) and increased suicidal ideation (313). A pooled analysis of two double-blind RCTs demonstrates that quetiapine is more effective than placebo in relieving symptoms of anxiety co-occurring alongside bipolar depression (314), and olanzapine-fluoxetine combinations have also been shown to be effective (315). In a post-hoc analysis, lurasidone was effective in improving depressive as well as anxiety symptoms in patients with MDD who had mixed features and anxiety (316). The anxiolytic effects of divalproex, risperidone, and lamotrigine appear to be limited (317),(200) .

Mixed features. Many patients with bipolar depression will also experience at least subsyndromal hypomanic or manic features, and this presentation is associated with more severe depressive symptoms, as well as a higher rate of substance use, and cardiovascular disease (318). For many of these patients, combination therapy will be necessary to adequately address symptoms (319). Pooled analysis indicates that atypical antipsychotics show a class effect in alleviating mixed features in bipolar depression, with olanzapine-fluoxetine combination, asenapine, and lurasidone, all demonstrating efficacy (320). Lurasidone has further been shown to have efficacy in treating both depressive and hypomanic symptoms in major depressive disorder with mixed features (321). The ISBD Task Force recommends avoiding antidepressants in patients with mixed features (261) and the CANMAT/ISBD group concurs with such recommendation.

Melancholic features. No specific studies assessed predictive ability of melancholic features; however, clinical experience suggests that ECT is very effective in this population.

Atypical features: There is some evidence for efficacy of tranylcypromine in patients with anergic bipolar depression (322). However, given the risks of potential manic switch, this agent should only be used in conjunction with lithium or divalproex or an atypical antipsychotic. Clinicians also must also consider adverse events of this agent related to its interactions with food and other medications.

Psychotic features (mood congruent or incongruent). Up to 20% of inpatients experience psychosis in the context of an acute bipolar depressive episode (323).The relative efficacy of various medications to treat these features in this phase of illness has not been examined, although clinical experience suggests that ECT and antipsychotics are highly effective for this population.

Rapid cycling. As described in Section 3, hypothyroidism, antidepressants and substance abuse may be associated with rapid cycling; thus making assessment of thyroid function and discontinuation of antidepressants, drugs of abuse, stimulants and other psychotropic agents imperative. As there is no evidence to support any specific agent to treat acute depression during a rapid cycling phase, appropriate pharmacotherapy should be selected based on effectiveness in the acute and maintenance phase. Lithium, divalproex, olanzapine, and quetiapine all appear to have comparable maintenance efficacies in these patients (220).. In contrast, lamotrigine did not separate from placebo in maintenance treatment in patients with rapid cycling bipolar I disorder

(324). Antidepressants are not recommended, as they have been shown to destabilize patients, even with concurrent mood stabilizer use (325).

Seasonal pattern. While some individual patients may show a pattern, Canadian data is mixed as to whether episodes of mania or depression in bipolar disorder follow a consistent seasonal variation (223). There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

Section 5: Maintenance Therapy for Bipolar Disorder

Need for Long Term Strategies

Almost all individuals with bipolar disorder require maintenance treatment to prevent subsequent episodes, reduce residual symptoms, and restore functioning and quality of life. There is increasing evidence to suggest that bipolar disorder may be a neuroprogressive disease in which recurrences are associated with reductions in brain grey and white matter volumes, worsening cognitive impairment, a decrease in inter-episodic recovery and functioning, higher rate and severity of relapse, and reduced rate of treatment response to both pharmacotherapy and psychotherapy in a subgroup of patients (326). As such, it is important that comprehensive treatment be initiated even after a first episode (63). Effective maintenance treatment, early in the course of illness has been shown to reverse cognitive impairment and preserve brain plasticity, particularly in those that remain episode free (327, 328) and may therefore lead to improved prognosis and minimization of illness progression (329). There is preliminary data that after a first episode, lithium might be superior to quetiapine in both volumetric and cognitive outcomes (330, 331).

With treatment, 19-25% of patients will experience a recurrence every year, compared to 23-40% of those on placebo (332). Risk factors for recurrence include younger age of onset (333), psychotic features (213), rapid cycling (332), more (and more frequent) previous episodes (334), comorbid anxiety (335), and co-morbid substance use disorders(336) . Persistent subthreshold symptoms also increase risk for subsequent mood episodes (335, 337, 338) and as such presence of residual symptoms should be an indicator of a need for further treatment optimization. Availability of psychosocial support and lower levels of stress are also protective against recurrence (338, 339).

Treatment Adherence

Concordance between clinician and patient views of illness and treatment is a crucial determinant of adherence (340), and reinforces the need for a collaborative approach to the treatment alliance(341). Asking about adherence behaviour and attitudes in a non-judgemental manner and exploring the reasoning behind poor adherence is an important part of treatment (342), as up to half of patients do not take their medications as prescribed (343-345). Unrecognized treatment non-adherence can lead physicians to believe that the patient is non-responsive; resulting in unnecessary dose increases (especially problematic for drugs with narrow therapeutic index), medication switches, or adjunctive medications (342). Treatment withdrawal may precipitate recurrence; 50-90% of patients discontinuing lithium experience a recurrence within 3 to 5 months (346, 347); with rapid lithium discontinuation associated with greater recurrence risk than gradual discontinuation (348). Withdrawal of other mood stabilizers also predicts recurrence (349, 350). Risk for hospitalization, suicide, and lost productivity are also increased with non-adherence or discontinuation (351-353). A variety of patient, disorder,

and treatment related risk factors for non-adherence or partial adherence are outlined in Table 5.1 (354).

Meta-analyses suggest that interventions aimed at engaging patients in treatment may more than double adherence compared to treatment as usual or other control groups (355). Brief psychoeducational interventions focusing specifically on medication adherence can be integrated into clinical practice (355). Flexible and collaborative engagement to address individual risk factors for non-adherence is recommended to optimize acceptability of pharmacological therapies (354, 356-358).

Psychosocial Interventions for Maintenance Therapy

Although pharmacotherapy is the foundation of maintenance treatment of bipolar disorder, it is often insufficient to prevent recurrence. Over the last two decades, several controlled trials have examined the efficacy of adjunctive psychosocial treatments in reducing recurrence in bipolar disorder. On average, adjunctive psychosocial treatments reduce recurrence rates by about 15%. Therefore, adjunctive psychosocial interventions are an important component of management of bipolar disorder and should be offered for all patients.

As described in more detail in Section 2, psychoeducation is the only first line psychosocial intervention for the maintenance phase (Level 1) which should be offered to all patients. Additional second line options such as CBT (Level 2), FFT (Level 2), and third line options such as IPSRT (Level 2) and peer support (Level 2) should be offered based on individual strengths and needs.

Efficacy Ratings for Pharmacological Agents Used as Maintenance Therapy: Importance of Naturalistic and Cohort Studies

Evidence from randomized clinical trials (RCTs) is at the core of the recommendations in these guidelines. Nonetheless, RCTs are not the only source of clinically useful information, particularly when evaluating maintenance therapy. RCTs offer relatively limited follow-up time frames while, for some patients, maintenance therapy may extend across decades. Furthermore, new medications are often assessed in studies with an enriched design (which includes only patients which have responded to the medication under study in the acute phase), limiting the generalizability of positive findings to patients who responded to the medication acutely.

Useful data can be obtained from large, often whole population databases obtained from electronic medical records or electronic patient registries with large numbers of patients that would be difficult to obtain in RCTs. In some instances, they allow comparisons of multiple treatments (359-361). These large numbers make it possible to evaluate differences in rates of rare events such as less common side effects or suicide (362, 363).

Patient cohorts followed in a specific setting provide another source of informative data. Their main advantage usually is the length of observation, in some instances reaching several decades (364-366). This comes at the cost of generalizability, both in terms of patient selection and non-random treatment allocation.

Pharmacological Treatments for Maintenance Therapy

As with earlier sections, pharmacological treatments for maintenance therapy have been evaluated using the criteria for strength of evidence for efficacy (Table 1.1) as well as safety and tolerability (Section 8). Results are summarized in Table 5.2.

Step 1: Review General Principles and Assess Medication Status

Many agents recommended for management of acute manic or depressive episodes have prophylactic efficacy. Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase. However, there are exceptions to this: the efficacy of adjunctive antidepressant therapy has not been examined systematically in large double blind placebo controlled trials; hence long term antidepressant use is not recommended especially in light of the concerns about potential risk of manic/hypomanic switch and mood instabilitiy. However, patients who have responded to combination treatment and are stable, preliminary evidence suggests that withdrawl of antidepressants may contribute to destabilization (367).

Clnical trials have shown that many atypical antipsychotics have been shown to be effective in preventing relapse of mood episodes; with many agents, this effiacy is related to prevention of manic episodes but not depressive episode. However, many of these trails have been conducted in patients with an index manic epsiode and given that the polarity of an index episode predicts the polarity of relaspe, depressive relapse rates in placebo groups in such studies have been low thus compromising the statistical power to test their effiacy in prvention of depressive relapses. Thus, the efficacy of many of these agents in preventing depressive relapses remains unknown. .

For patients who are currently not receiving or responding to a pharmacological treatment, a careful history including details of clinical course, response (or lack thereof) to previously used medications, and family history should be collected. Other variables to be considered include psychiatric comorbidity (ioncluding substance use), the predominant illness polarity, as well as polarity of the most recent episode.

Ongoing clinical monitoring, including medication blood levels as appropriate, is also a crucial part of maintenace treatment that should be used to support enhanced medication adherence, detection of early symptoms of recurrence, and monitoring of side effects (See Section 8).

Step 2: Initiate or Optimize Therapy and Check Adherence

The choice of agent or agents used in maintenance treatment should be discussed with the patient and their caregivers (as appropriate) and based on knowledge of current and prior medication use and response, safety and tolerability of each agent, predominant episode polarity, as well as clinical features that may influence prognosis (See Clinical Features that Help Direct Treatment Choices). As with treatment for mania and acute depression, we recommend that treatment choices for maintenance treatment of bipolar disorder should follow the hierarchy listed in Table 5.2 unless patient preference or other considerations such as previous response/non-response, tolerability, predominant polarity etc. justify other choices. Similarly, as a general rule, if a patient has been treated for an acute mood episode and responded to a first line maintenance treatment, we recommend continuing that treatment for maintenance even if lower down in the hierarchy. As an example, if a patient responded to asenapine in an acute manic episode, asenapine should be continued, even if it is lower down in the hierarchy for maintenance

treatment. It may be necessary to lower the dose to some degree once in maintenance treatment as patients often experience more side effects once out of the acute episode.

There is evidence the risk of recurrence is reduced when an antipsychotic is combined with lithium/divalproex. When a combination therapy of an atypical antipsychotic with lithium/divalproex was used to treat acute mania, continuing the atypical antipsychotic for the first 6 months following response offered clear benefit in reducing risk of mood episode recurrence (Level 2) (368) but the benefits beyond 6 months remain uncertain. Therefore, clinicians are advised to re-evaluate risks and benefits after 6 months sustained response to determine whether maintenance combination therapy with an atypical antipsychotic is justified.

First Line. Lithium (Level 1) (369, 370), quetiapine (Level 1) (370, 371) , divalproex (Level 1) (370, 372, 373) (Figure 5.1) and lamotrigine (Level 1) (370, 374) monotherapies have best combination of clinical trial, administrative data, and clinical experience to support their use as first line therapies for maintenance treatment of bipolar disorder. Recent data suggests that asenapine (Level 2) (375) is effective in preventing both manic and depressive episodes, and thus is recommended as a first line treatment. Finally, aripiprazole oral (Level 2)(376, 377) or once monthly (Level 2) (378) is also recommended as a first line monotherapy in view of its efficacy in preventing any mood episode and manic episode as well as its safety/tolerability profile; although it has not been shown effective in preventing depression.

Additional combination therapies included as first line include quetiapine adjunctive therapy with lithium/divalproex (Level 1) (379, 380), which has demonstrated efficacy in preventing any

mood episode, manic episode and depressive episode. Aripiprazole plus lithium/divalproex (Level 2)(381) should also be considered as a first line option.

For patients who experience a recurrence or who remain symptomatic while on a first line agent or a combination, dosing should be optimized and issues of non-adherence identified and addressed prior to moving to Step 3.

Figure 5.1: Why is valproate recommended as a first line maintenance treatment for bipolar I disorder?

In the only large double-blind placebo controlled RCT of valproate monotherapy (373), it was not more effective than placebo in preventing relapse of mood episodes i.e. time to any mood episode. However, in this trial, lithium which has been shown in many other studies to be effective in relapse prevention, was also found to be no more effective than placebo. Thus, these results suggest that this trial was a failed trial and not a negative trial.

Most modern studies of maintenance therapy use enriched design, meaning that those that responded in acute phase to the medication being tested are randomized to continuation of the same drug or replacement with placebo. This practice to a large extent mirrors clinical practice as clinicians are likely to continue the medication that worked in the acute phase for maintenance treatment. Interestingly, in the valproate RCT, some but not all patients that were randomized into the double-blind phase were valproate responders. In a post-hoc analysis of this study, in this enriched subgroup of patients that responded to valproate during the acute phase and randomized to continuation of valproate vs switch to placebo, valproate was more effective in preventing relapse of mood episodes compared with placebo.

Further, valproate was superior to placebo on a number of other secondary efficacy measures such as lower rates of discontinuation for any mood episode or a depressive episode. Surprisingly, there was also a trend for superiority of valproate relative to lithium in time to any mood episode.

Other RCTs have shown that valproate is as effective as lithium (221) in preventing relapse of mood episodes.

As well, two meta-analysis have concluded that valproate is effective in preventing relapse of mood episodes (370, 372), and a population based cohort study in the UK showed that there were no differences in efficacy between valproate, quetiapine and olanzapine in the maintenance treatment of bipolar disorder(359).

Taken together, we believe these efficacy data support our rationale for a Level 1 rating. This along with clinical experience, real world cohort data, and safety, justify our recommendation of valproate as a first line maintenance treatment.

Step 3: Add-on or Switch Therapy (Alternate First Line Agents)

If therapy with one or a combination of the first-line agents at optimal doses is inadequate or not tolerated, the next step is to switch to or add-on an alternate first- line agent. Because there are multiple first line agents with substantial efficacy data and relative safety and tolerability, the use of second -line agents is only recommended after unsuccessful trials of multiple first line strategies.

Step 4: Add-on or Switch Therapy (Second Line Agents)

Second Line. Although olanzapine (Level 1) (382, 383) is effective in preventing any mood episodes, manic episodes and depressive episodes, it is considered second line treatment because of safety issues such as metabolic syndrome. Biweekly long acting injectable risperidone mono- (Level 1) (384) or adjunctive therapy (Level 2) (385) has demonstrated efficacy in preventing any mood and manic episodes, but have no clear efficacy in depressive prevention in these trials. Further, there was a trend for superiority of oral risperidone adjunctive therapy at 6 months in preventing any mood episode and in preventing mania but not depression (368). Carbamazepine (Level 2) has not been assessed in any large placebo controlled trials but active comparator trials support its efficacy (386). Paliperidone (Level 2) was more effective than placebo in preventing any mood episode and manic episode but less effective than olanzapine (387).

Ziprasidone oral adjunctive therapy (Level 2) (388) has been shown effective in preventing any mood episode and manic episode, although there are conflicting (positive and negative) data for acute treatment (see Section 3 and 4). There was a trend for superiority of lurasidone adjunctive therapy in preventing any mood episode (but not manic or depressive episodes individually) in a

controlled trial with significant separation from placebo in preventing mood episodes in those with an index depressive episode(389). Thus, lurasidone adjunctive therapy may be appropriate for those who responded to this medication during an index depressive episode.

Step 5: Add-on or Switch Therapy (Third Line Agents)

Third Line. Third line agents are listed alphabetically in Table 5.3. There was a trend for superiority of adjunctive aripiprazole with lamotrigine (Level 2) (390) compared to lamotrigine monotherapy in preventing mania; thus this combination may provide additional prophylaxis for patients on lamotrigine monotherapy in preventing manic relapses. Clozapine (Level 4)(163), and gabapentin (Level 4)(391) may also be useful adjunctive treatments for those who incompletely respond to first or second line therapies. The olanzapine/fluoxetine combination appears to maintain mood stability over a 6 month time period in patients with bipolar depression who respond acutely to this combination (Level 2)(392).

No Specific Recommendation/ Agents which Require Further Study

We do not provide specific recommendations for the use of cariprazine, as there is currently only evidence for efficacy in acute manic and depressive episodes (263, 393) but not yet for maintenance treatment (Level 4). While a small RCT suggests a lack of efficacy for fluphenixol as maintenance treatment, larger studies are needed before definite conclusions can be drawn (Level 3-ve) (394). Likewise, oxcarbazepine adjunctive therapy requires further evaluation (Level 4) (395-397). No recommendation is made for topiramate as it there is an absence of controlled data supporting its efficacy in maintenance (Level 4-ve), and a lack of efficacy in

acute mania (382); however, it's use may be indicated as it has efficacy for many syndromes that are often comorbid with bipolar disorder (Section 7).

Agents Not Recommended for Maintenance Treatment

Perphenazine is not recommended for maintenance based on evidence that patients treated with perphenazine and a mood stabilizer following an episode being more likely to have emergent depressive symptoms or intolerable side effects, compared to those maintained on the mood stabilizer alone (Level 2-ve) (398). Maintenance tricyclic antidepressant mono or adjunctive maintenance therapy is not recommended due to increased risk of manic switch (Level 2-ve) (399-401) (Table 5.3).

Clinical Features that Direct Treatment Choices

Clinical trials tell us how efficacious one drug is in comparison with another (or placebo) in groups of patients. To determine the degree of long term response in an individual patient requires a different evaluation and may take a considerable amount of time. Few patients manage a lifetime of bipolar disorder with monotherapy- most will require short or long-term combination therapies to address acute or subsyndromal symptoms as well as to reduce rates of recurrence. Some (360, 402, 403), but not all (404, 405), reports suggest that long term treatment becomes less effective with longer duration of untreated illness, an argument for finding an effective treatment as early as possible.

In most instances, it is difficult to differentiate nonspecific correlates of good prognosis of the illness from factors specific to the response to a particular mood stabilizer. Available data come

mostly from naturalistic / cohort studies and few randomized trials (406). Nevertheless, several tentative predictors are emerging from the available data.

Factors associated with overall good prognosis of bipolar disorder include good treatment adherence, lack of early adversity, intermediate age at onset, good social support, and the absence of spontaneous rapid cycling (407, 408) or features of a personality disorder (409).

In general, lithium is the gold standard for maintenance treatment, as it is effective in preventing both manic and depressive episodes (magnitude of prophylactic efficacy greater against mania vs depression) and appears to have a degree of anti-suicidal effects (353, 370, 410-414). Patients who respond well to lithium treatment usually have an episodic remitting pre-treatment clinical course, family history of bipolar disorder (especially bipolar disorder responsive to lithium), low rates of comorbidity (especially anxiety and substance abuse disorders), and pattern of mania-depression-euthymia in biphasic episodes, as well as a typical clinical presentation (415-417). Responsiveness may also be a familial trait, with a study showing that patients who have a lithium responsive relative have a 67% likelihood of also being lithium responsive, versus 35% those without a responsive relative (418). Among biological measures, lack of EEG abnormalities, higher brain lithium concentration, increased N-acetyl aspartate and lower myo-inositol peaks on magnetic resonance spectroscopy, as well as several variants in candidate gene studies may predict response(419), but these studies require confirmation. Response to lithium in particular seems to be quite specific, as shown in a study of neurons derived from induced pluripotent stem cells. The neurons from people with bipolar disorder were hyperexcitable and their activity was selectively modified by in vitro lithium in accordance with clinical response (420).

Responders to lamotrigine have predominantly depressive polarity as well as comorbid anxiety (421, 422). Lamotrigine monotherapy is not appropriate for patients with frequent manic episodes, as it has limited efficacy in preventing mania.

Quetiapine has been shown to be effective in preventing manic, depressive and mixed episodes in patients with index manic, depressive and mixed episodes, and thus may be particularly valuable in those with mixed features (423). Asenapine appears to be effective in preventing both mania and depression although the magnitude of prophylactic efficacy is greater for mania relative to depression. In a randomized open trial of carbamazepine versus lithium (MAP Study), responders to carbamazepine were more likely to suffer from an atypical illness, bipolar II disorder or schizoaffective disorder (406).

Data to differentiate anti-psychotic medication responders from non-responders are lacking.

Overall, some of these possible predictors can have clinical utility, but not all are practical. For instance, it is difficult to evaluate a pre-treatment course in patients who started their treatment after one or two episodes (practice recommended by most treatment guidelines), and biomarkers are intriguing but lack sufficient replication and are not readily available.

In patients with a history of rapid cycling course, as indicated in previous sections, factors associated with rapid cycling must be addressed. These include discontinuation of stimulants and antidepressants and treating hypothyroidism if present. With regard to treatment options, the evidence suggests that monotherapy with a single mood stabilizer is often ineffective and patients may require combination of mood stabilizers for achieving mood stability.

Treatment Refractory Bipolar Disorder

Treatment refractoriness may be related to non-adherence to oral medications, failure to optimize evidence based oral medication therapy/therapies, comorbidities complicating therapeutic response or true resistance to pharmacotherapy. Clinicians are advised to make a comprehensive assessment to determine factors responsible for treatment refractoriness. Adequate doses of first and second line agents should be employed for adequate period of time (eg. this is typically individualized based on the previous course of mood episodes in each patient) to assess prophylactic response. Comorbidities should be addressed with pharmacological or psychological strategies as appropriate. While genotyping for cytochrome P450 enzymes such as 2D6 and 3A4 which metabolize most psychotropic drugs is not routinely recommended, clinicians are advised to consider this in patients with refractory bipolar disorder who had not responded to high doses of various first, second, and third line treatments or their combinations in order to exclude the possibility of ultra rapid metabolic status contributing to poor response.

In non-adherence patients, psychosocial strategies such as psychoeducation should be used to improve treatment adherence. If ineffective, long acting injectable medications should be offered. Risperidone long acting injectable in monotherapy (384) or adjunctive therapy (Level 2) (385) once every two weeks or aripiprazole once monthly injectable monotherapy (Level 2) (378) have been shown to be effective in preventing relapse of mood episodes in patients with bipolar disorder.

There is dearth of clinical trial data to inform treatment options for management of patients with refractory bipolar disorder. Clozapine adjunctive therapy has been shown to be effective in reducing symptoms and total medication use in treatment resistant bipolar patients (163).

Section 6: Bipolar II Disorder

Presentation of Bipolar II Disorder

Bipolar II disorder (BDII) is a distinct disorder from bipolar I disorder (BDI), with similar Canadian prevalence (0.67% compared to 0.87% for BDI) (7). The diagnosis of BDII requires one or more episodes of hypomania, one or more episodes of depression, and an absence of manic episodes. The DSM-5 criteria for hypomania are similar to those for mania (Table 2.1), with symptoms being uncharacteristic of the individual, observable by others, and lasting at least 4 consecutive days. In contrast to mania, they cannot be severe enough to cause marked impairment or require hospitalization, and there must be an absence of psychosis. Further, the DSM-5 has added mixed features specifier to hypomania as well. The diagnosis of BDII is generally stable over time although there may be a higher risk of conversion to BDI early in the illness, suggesting that BDII may be a risk factor or prodrome of BDI in some patients (424).

Although hypomania is, by definition, less severe than mania, the disability associated with BDII is comparable to BDI (14, 425) and the economic burden of BDII is up to four times greater (426, 427). This is because BDII patients spend as much time symptomatic as BDI patients, with mood symptoms predominantly in the depressive phase (428, 429). Rates of attempted and completed suicide are similar in BDI and BDII, with approximately one third of BDII patients

attempting suicide over the course of their illnesses (430) and one in twenty-five completing suicide (431).

Pharmacological Treatment of Bipolar II Disorder

General Considerations for Interpreting Recommendations

The treatment of BDII has been understudied relative to BDI. This is likely due to the long-standing but discredited impression of BDII as a less severe form of bipolar disorder. The number of RCTs in BDII is substantially smaller than in BDI, and those studies that do exist are frequently under-powered. It also remains common for trials to enroll BDII and BDI patients without reporting results separately, making it difficult to determine if there are clinically meaningful differences in treatment response between the two illnesses. This is important because while clinical experience and the results of many studies suggest that response to mood stabilizers and antipsychotics is similar in BDII and BDI, there are enough exceptions to suggest this should not be taken for granted (249, 406, 432). That is also the case for antidepressants, which may have a more favorable risk-benefit ratio in BDII (reviewed below). Therefore, in formulating our recommendations, studies that enrolled BDII and BDI patients but did not report results for BDII separately are assigned level 4 status (expert opinion) if they enrolled fewer than 50% BDII patients.

The relative paucity of large, methodologically sound clinical trials in BDII create challenges in formulating evidence-based guidelines. As will be seen, there are fewer treatments with high-quality evidence in BDII compared to BDI and fewer first line treatment recommendations. The limitations of the evidence base necessitate an awareness of the nuances of the available studies,

and a greater reliance on clinical experience. We thus have endeavored to be clear in outlining the rationale for selecting first, second, and third line treatments for hypomania, depression, and maintenance treatment of this important illness. There is clearly a pressing need for adequately-powered trials in BDII across all illness phases.

Acute Management of Hypomania

The general principles for assessing manic patients apply to those with hypomania. For some patients, hypomania causes no-to-minimal functional impairment and may even be associated with brief periods of above-normal functioning. However, prolonged, relatively severe, or mixed or irritable hypomania may be impairing (424). Treatment should include discontinuing agents that can worsen or prolong symptoms, including antidepressants and stimulants and initiating appropriate pharmacotherapy.

Unfortunately, many standard medications for mania, including lithium and most atypical antipsychotics, have not been studied in hypomania. There are four placebo-controlled trials that investigated divalproex (Level 4)(433), N-acetylcysteine (Level 4) (434), and quetiapine (Level 4) (435, 436) ; and one open-label study of risperidone (Level 4) (437) in acute hypomania. The studies generally suggested efficacy but all had significant weaknesses, including one or more of: 1) small sample sizes, 2) mixed samples with BDI, BDII, and BDNOS; 3) mixed samples with hypomania and mania, and 4) positive findings on some but not all outcomes. The small N's and mixed samples mean that even the placebo-controlled trials only met criteria for Level 4 evidence (Table 1.1)

These methodological limitations, coupled with the lack of clinical trial evidence for many medications, make it difficult to make specific suggestions for the treatment of hypomania. Clinical experience suggests that all anti-manic medications are also efficacious in hypomania. Thus, when hypomania is frequent, severe, or impairing enough to require treatment, clinicians should consider mood stabilizers such as lithium or divalproex and/or atypical antipsychotics. N-acetylcysteine may also be of benefit, but further studies are needed.

Acute Management of Bipolar II Depression

The general principles for assessing depression in patients with BDI apply to BDII. First, second, and third line treatment options are listed below and shown in Table 6.1. Specific considerations regarding each treatment are highlighted in the relevant sections.

First Line. Quetiapine is the only recommended first line treatment for BDII depression (Level 1). Pooled analyses of five identically designed trials demonstrated that quetiapine was superior to placebo, and moreover was equally effective for acute depression in BDI and BDII (244, 438). The latter finding must be reconciled with the fact that quetiapine beat placebo in only three of the five individual trials in patients with BDII, compared to all five in patients with BDI (254, 439, 440),(291, 441). This is likely because the smaller sample of BDII patients- only about half as many BDII as BDI patient were enrolled in each of the trials- providing less statistical power for BDII. Finally, open-label studies also suggest efficacy for adjunctive quetiapine (Level 4) (442, 443).

Second Line. Second line treatments include lithium, ideally at a serum level of 0.8-1.2mEq/L (Level 2) (Figure 6.1), and the antidepressants bupropion (adjunctive) (Level 2) (277), sertraline

(Level 2) (427) and venlafaxine (Level 2) (444, 445), mainly for patients with pure (non-mixed) depression (Figure 6.2). Lamotrigine (Level 2) is also recommended as a second line agent despite conflicting evidence; with the rationale for this provided in Figure 6.3.

Figure 6.1: Why is lithium recommended as a second line agent for bipolar II depression? Reconciling Conflicting Data

In a 16-week double blind RCT, lithium was as effective as sertraline and lithium + sertraline combination (427) which qualifies lithium for Level 2 evidence. Additional supporting data come from a single-blinded trial which showed that lithium was as effective as lamotrigine in treating BDII depression over 6 weeks (446). However, neither of these studies had a placebo arm. Positive placebo- controlled data come from 4 small placebo-controlled crossover studies conducted in the 1960s and 1970s, in which lithium was effective in a mixed sample of BDI and BDII depressed patients (447-450). Results were reported separately for BDII in 2 of the studies and were identical to BDI (pooled response rate = 65% for both)(447).

In contrast, in the only modern a placebo-controlled parallel group study, lithium was not superior to placebo in BDII depression (254). Further, lithium was less effective than venlafaxine in a 12-week RCT (451).

A potential explanation might have to do with trough serum lithium levels. Lithium levels ranged from 0.8-1.3 mEq/L, and were often at the high end of that range in the older placebo-controlled RCTs while in the negative placebo-controlled RCT, the mean serum lithium level was lower (<0.61 mEq/L in the combined BDI + BDII sample, not reported separately for BDII). Thus, the optimal serum level for treating bipolar II depression is unclear. However, based on the placebo-controlled BDII trials, as well as placebo-controlled studies in BDI (247), a serum level of 0.8-1.2 mEq/L appears most likely to be beneficial.

In addition to the evidence for efficacy in acute depression, lithium also has efficacy in preventing mood episodes in BDII (400, 452-454). Therefore, in balance, we believe the evidence, though mixed, justifies recommending lithium as a second line agent for BDII depression.

Figure 6.2: Should antidepressants be used in Bipolar II Depression? Addressing the Controversy

The question of whether, and if so when and how, to use antidepressants in BDII remains controversial due to concerns regarding both safety (particularly the possibility of hypomanic switch, mixed symptoms, and increased cycling) and efficacy.

With respect to safety, a meta-analysis that compared rates of antidepressant-associated mood elevations in BDII, BDI, and MDD reported that they were significantly less frequent in BDII than BDI, and occurred almost exclusively into hypomania rather than mania (455). Switch rates were low even during antidepressant monotherapy and with antidepressants associated with high switch rates in BDI (tricyclics, venlafaxine). An ISBD task force report on antidepressants also concluded that their risk-benefit ratio was more favorable in BDII (261, 450).

The issue of efficacy is less clear due to limited evidence. RCTs have shown that sertraline monotherapy was as effective as lithium and lithium+ sertraline combination, and that venlafaxine monotherapy was more effective than lithium, sufficient for level 2 evidence for these agents. In an a RCT of BDI and BDII patients, bupropion was shown to be as effective as sertraline and venlafaxine(277). Open-label data also suggest efficacy for fluoxetine, and there are maintenance data for venlafaxine and fluoxetine in preventing relapses. These positive findings should be balanced against the fact that paroxetine and bupropion were not better than placebo for acute depression in patients taking concomitant mood stabilizing medications. Moreover, it is important to bear in mind that 1) there are no placebo-controlled acute-phase trials of antidepressant monotherapy in BDII, 2) many antidepressants have not been studied at all (and we do not believe it is warranted to extend positive findings from sertraline/venlafaxine - or for that matter negative findings from paroxetine/bupropion - to “antidepressants” generally), 3) the existing trials enrolled people with pure (non-mixed) depression, and their efficacy/safety in the broader spectrum of BDII patients is unclear, and 4) many of the existing trials have significant weaknesses, including one or more of: low dosing of the antidepressant; sub-therapeutic dosing of comparator medications; and lack of replication.

All of this makes it particularly difficult to make evidence based recommendations regarding antidepressants in BDII. We have restricted our recommendations to the specific agents that have been studied, and we recommend bupropion, sertraline, and venlafaxine monotherapy as second line treatments; and fluoxetine as third line. We further recommend that any antidepressant, especially in monotherapy, be reserved for patients with pure depression and avoided in those with mixed symptoms or a history of antidepressant-induced hypomania (261). Whether antidepressants should also be avoided in patients with rapid cycling is unclear, since some studies report poorer outcomes in rapid-cycling patients (456) while others do not (451, 457-459). Patients prescribed antidepressants must be educated regarding early-warning signs of hypomania and carefully monitored for them. Finally, there is a pressing need for further studies of other antidepressants in BDII, in both monotherapy and combination therapy.

Figure 6.3: Why is Lamotrigine a Second Line Recommendation for Bipolar II Depression? Reconciling Conflicting Data.

Lamotrigine monotherapy was studied in two trials in BDII depression: one in which 221 BDII patients received 200 mg/day or placebo for 8 weeks, and a second in which 206 BDI or BDII patients (N=84 with BDII) received 100–400 mg/day for 10 weeks (255). Both produced negative results. A meta-analysis confirmed that lamotrigine was not superior to placebo in BDII depression, although it did separate from placebo in BDI (248). Several methodological shortcomings likely resulted in the studies underestimating the drug's effect, including 1) a slow titration which resulted in subjects being on the target dose for a short time, 2) a target dose lower than that often used in clinical practice and in successful maintenance studies (256, 324), and 3) higher placebo response rates. In contrast, a single-blind RCT with a relatively high dose (final peak dose=300mg) and a longer duration (16 weeks) found that lamotrigine monotherapy was as effective as adequately-dosed lithium (mean final serum level=1.1 mEq/L) in N=98 BDII patients (446). Two large RCTs in BDI+BDII and a 12-week open-label trial in patients with BDI+BDII+BDNOS also reported that adjunctive lamotrigine was effective, but did not report results separately for BDII (252, 253). Finally, lamotrigine has robust efficacy in preventing depressive relapse in BDI and BDII (324, 460). Taking all of these factors into consideration we recommend lamotrigine as a second line treatment, particularly for patients who can tolerate a slow titration and delayed effect.

Third Line. The third line options include monotherapy with divalproex (Level 4) (259, 461, 462) (463-467), fluoxetine (mainly for patients with pure depression) (Level 3) (468-470) tranylcypromine (Level 3) (279), or ziprasidone (solely for patients with depression and mixed hypomania) (Level 3) (471, 472). Adjunctive agomelatine (Level 4) (473), eicosapentaenoic acid (EPA) (Level 4) (474-476), N-acetylcysteine (NAC) (Level 4) (477), pramipexole (Level 3) (275), or thyroid hormones (Level 4) (273) may also be considered.

ECT (Level 3) (262) and intravenous ketamine (Level 3) (478, 479) are important options for patients in need of rapid response, those who are severely ill, and/or are treatment refractory.

No Specific Recommendation/ Agents which Require Further Study. A number of agents do not have sufficient data to warrant specific recommendations for BDII depression, including cranial electrotherapy stimulation (CES) (480), dextromethorphan + quinidine (481), light therapy (482-486), lisdexamphetamine (adjunctive) (301), olanzapine (487), pioglitazone (303), adjunctive

pregnenolone (307), celecoxib (298), levetiracetam (488), adjunctive lisdexamphetamine (301), s-adenosylmethionine (489-491), acetyl-L-carnitine + alpha-lipoic acid (492), adjunctive modafinil (269), rTMS (276, 493, 494), and memantine (495).

Agents Not Recommended for the Treatment of Acute BDII Depression. Based on negative placebo-controlled data, we do not recommend paroxetine (Level 2 -ve) (246).

Maintenance Treatment

Maintenance treatment is important to prevent relapse, reduce subsyndromal symptoms, and improve quality of life. As with BDI, selection of an agent should be informed by acute phase treatment. Recommended agents and their evidence ratings are listed in Table 6.2.

First line. Monotherapy with quetiapine (Level 1) (496), lithium (Level 2) (400, 452, 453), and lamotrigine (Level 2) (324) are first line options.

Quetiapine: In two 52-week maintenance studies, patients with BDII who achieved remission from depression with quetiapine monotherapy continued it or switched to placebo (496). A pooled analysis reported that quetiapine-treated patients had a significantly longer time to relapse into any mood episode (HR 0.33, or a 67% reduction in the risk of relapse) and into depression (HR=0.28 or a 72% risk reduction). Time to relapse into hypomania was not significantly greater (HR=0.65 or a 35% risk reduction). The latter finding may be related to the low base rate of hypomania, which occurred in only 10% of all study participants. Quetiapine was at least as effective in BDII as BDI, for which the risk reductions were 42% for any relapse, 48% for depression, and 30% for mania. Adjunctive quetiapine was also studied in a 6-month

single-blind trial which randomly assigned patients with either BDI or BDII to lithium or quetiapine added to treatment-as-usual. They were equally effective in preventing relapse (454). Results were not presented separately for BDII, but BDII patients responded better to both treatments than did BDI patients.

Lithium: In 3 placebo-controlled RCTs conducted in the 1970s and 1980s (duration=11-25 months), lithium decreased the frequency and/or severity of hypomanic and depressive episodes (400, 452, 453). Serum lithium levels were 0.8-1.2 mEq/L. A number of active comparator studies also support lithium. As noted above, lithium was as effective as quetiapine in preventing relapse in a 6-month single-blind trial (454). A 20-month study comparing lithium and divalproex in rapid cycling BDI+BDII found both drugs to be equally effective in preventing relapses (497). The authors noted that findings were similar for BDII and BDI, but results were otherwise not reported separately for BDII. In a 2.5-year study in BDII+BDNOS, lithium and carbamazepine were equally effective on most outcomes, although a numerical advantage favored carbamazepine for reducing clinical + subclinical recurrence (406). In contrast, head-to-head comparisons with antidepressants (reviewed below) found that lithium was not as effective in preventing depressive relapse as fluoxetine or venlafaxine (470, 498). This may be explained by the mean lithium levels which were 0.7mEq/L in both studies, while the fluoxetine trial was also enriched for fluoxetine responders.

Long-term naturalistic data also provide strong support for lithium. In a 6-year study of patients with either BDI or BDII (39% with BDII), lithium reduced time in hypo/mania by 61% and time in depression by 53% in the entire sample, compared with the period before lithium treatment

was initiated (499). The authors noted that the proportion of time with mood symptoms was significantly lower for BDII than BDI patients.

Lamotrigine: In a 6-month placebo-controlled RCT of lamotrigine monotherapy in rapid-cycling BDI+BDII, post-hoc analysis showed that significantly more lamotrigine-treated than placebo-treated BDII patients were stable without recurrence into any mood episode (324) although lamotrigine was not superior to placebo in BDI. In a large 52-week RCT in BDI+BDII patients, adjunctive lamotrigine was superior to placebo for improving depression severity and remission rates. However, results were not presented separately for BDII (252). Open-label trials and retrospective chart reviews also support lamotrigine (249, 500-503).

Second Line. Monotherapy with venlafaxine (Level 2) or fluoxetine (Level 3) are second line options.

Venlafaxine: In a small 6-month RCT in BDII patients who responded acutely to venlafaxine or lithium without hypomanic switch, there was a trend for lower rates of relapse into depression for patients treated with venlafaxine. Further, the rate of sustained response was significantly greater in those who continued venlafaxine compared to those who continued lithium (504).. No hypomanic episodes occurred in either group.

Fluoxetine: In a 50 week RCT, the mean time to relapse into depression was significantly longer for fluoxetine than for lithium or placebo. Patients had responded acutely to open-label fluoxetine, making the sample enriched for fluoxetine response. Hypomanic episodes occurred in a similarly low frequency in the three groups (470). In a separate small 6-month placebo-controlled trial, there was a statistical trend for lower relapse rates with fluoxetine compared to

placebo (505). Finally, a post-hoc analysis of a large 12-month placebo-controlled trial found that response rates to fluoxetine were similar in BDII and MDD (469). However, it did not report whether fluoxetine was superior to placebo in BDII.

Third line. Divalproex (Level 4) (506), carbamazepine (Level 3) (406), escitalopram (Level 3) (507), other antidepressants (Level 3) (456), and risperidone (mainly for prevention of hypomania) (Level 4) (437) may be considered as third line options.

No Specific Recommendation/ Agents which Require Further Study. There is insufficient data to make a recommendation regarding olanzapine (508).

Section 7: Specific Populations

Management of Bipolar Disorder in Women at Various Stages of the Reproductive Cycle

Pre-conception, Psychoeducation and Contraceptive Counselling

The importance of pre-conception counselling should be raised with all women of child bearing age. It should be provided for all patients at least three months prior to considering pregnancy or immediately for those already pregnant. The issues most frequently raised are fear of adverse effects of medications on the fetus, fear of illness recurrence, and genetic transmission to offspring (509). Other important topics to review include the effect of bipolar disorder on risk for gestational hypertension, antepartum hemorrhage, induction of labor, increased risk for C-section, instrumental delivery and preterm delivery, and neonatal size (510, 511). Discussion of modifiable risk factors is critical in pre-conception management of BD. For instance, pregnant women with bipolar disorder are more often overweight, more often smoke tobacco during

pregnancy, have poorer diet quality, and present more often with a history of drug and alcohol misuse in pregnancy (511). Modification of these risk factors may have significant positive impact on outcomes for both the mother and child.

Decisions should be made collaboratively on whether medications should be continued, discontinued, or switched; and whether any dosage changes are needed. Conventional antipsychotics and risperidone may need to be discontinued to increase the likelihood of conception, as these medications often increase serum prolactin levels and thus interfere with ovulation and decrease fertility (512). For women who wish to have a medication free pregnancy, it might be appropriate to have one or more psychotropic medications gradually tapered off prior to conception provided they have been clinically stable for a minimum of 4-6 months and are considered at low-risk of relapse. Information regarding potential teratogenic effects of different psychotropic medications, as well as limitations of the scientific evidence, should be discussed and carefully considered. The decision to stop medications pre-conceptually should ideally occur only after careful individualized risk- benefit analysis for a given patient(513-515). If pharmacotherapy is required, monotherapy at minimum effective dose is recommended whenever possible (516, 517).

Contraceptive counselling, including emphasis on the effectiveness of consistent use in reducing the likelihood of unintended pregnancies, should be included as part of a comprehensive treatment plan for women with bipolar disorder.

Several anticonvulsants, including carbamazepine, topiramate, and lamotrigine can affect the pharmacokinetics of oral contraceptives and some might significantly reduce the effectiveness of

oral contraceptives and this should be considered when making treatment decisions(518, 519). Oral contraceptives might also have effects on the efficacy of lamotrigine via reduction in lamotrigine levels (518).

While folic acid supplementation is protective against spontaneous spina bifida, there is not enough evidence to indicate that folic acid, even in high doses, protects against spina bifida following the use of anticonvulsants (520). In addition, Health Canada recommends that "Valproate products (valproic acid, divalproex sodium) should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. Health Canada also recommends that women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of valproate products during pregnancy, and in women planning to become pregnant every effort should be made to switch to appropriate alternative treatment prior to conception (521)

Regardless of treatment decisions made prior to or following conception, it is also important to work with the patient to develop and agree upon a monitoring schedule and treatment plan to be implemented should clinically significant symptoms emerge. Education on risks of psychotropic medications is critical, and careful discussion is needed regarding the magnitude of risks and benefits and limitations with the data. It is important to acknowledge the patient's desire to do what is right for the child and support the decision made. Whenever appropriate, involve partners in the discussion and review the decision and supporting evidence for it directly or through educational materials (522).

Screening for Bipolar Disorder during Pregnancy and Postpartum

All women with depressive symptoms should be screened for bipolar disorder during pregnancy and the postpartum period (523, 524). Standardized screening tools such as the Mood Disorder Questionnaire alone or in conjunction with the Edinburgh Postnatal Depression Scale are useful (523-526). Importantly, a screening should be followed by a clinical interview to confirm or exclude a diagnosis of bipolar disorder. Women should also be assessed for other psychiatric disorders that commonly co occur with BD such as anxiety disorders or obsessive compulsive disorder (527).

Pharmacological Management of Bipolar Disorder during Pregnancy

Given the complexity and risks associated faced by women with BD in pregnancy and puerperium, it is good clinical practice to encourage liaison between the mental health and Ob/Gyn teams. A longitudinal study conducted in a tertiary care centre found a high risk of recurrence during pregnancy: 85% of pregnant women with bipolar disorder who discontinue a mood stabilizer and 37% of those who are maintained on one or more mood stabilizers experience a mood episode -predominately depressive or mixed- during pregnancy. For nearly half of the patients, recurrence occurred in the first trimester- with the median time for recurrence for those abruptly discontinuing treatment being 2 weeks, compared to 22 weeks for those who were gradually tapered off (513). However, studies from primary care, as well as obstetric centres found relatively lower rates of relapse or hospitalizations in pregnancy (528).

The algorithms presented throughout these guidelines should be followed for management of the various phases of bipolar disorder, with considerations given to specific risks associated with the

use of each medication using the most up to date information available from the US Food and Drug Administration (FDA) website (http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm117976.htm).

Table 7.1 includes a brief overview of medications commonly used in bipolar disorder and the risk categories. This list should not be viewed as complete or comprehensive. Further, the FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final Rule (PLLR) with narrative sections and subsections. For instance, for pregnancy, the information for each medication will be provided using the following sub-headings: Pregnancy Exposure Registry, Risk Summary, Clinical Considerations, and Data. The last 3 sub-sections apply to medication risks during lactation. The FDA has not finalized and published the data for all medications as of completion date of these guidelines (November 2017), and new data appear to suggest that risks may have been overestimated for some medications such as lithium (529). Thus, clinicians are strongly advised to use all the current data including the FDA PLLR information if available in collaboration with patient and family members to make final treatment decisions.

Wherever possible, psychosocial strategies should be preferred over medications in the first trimester as this period holds the highest risk for teratogenicity. When medications are deemed necessary, preference should be given to monotherapy using the lowest effective dose.

Each pregnancy should be closely monitored and appropriate screening tests (e.g. fetal ultrasound if lithium is used in the first trimester) should be performed (530). Divalproex should

be avoided during pregnancy due to elevated risk of neural tube defects (up to 5%), even higher incidences of other congenital abnormalities, as well as evidence of striking degrees of neurodevelopmental delay in children at 3 years of age and loss of an average of nine IQ points (531-533). Because of changes in physiology in the second and early third trimesters, such as increased plasma volume, hepatic activity, and renal clearance; patients may require higher doses of medications towards the later part of the pregnancy. Prenatal vitamins, including high dose (5mg/d) folic acid are also recommended preferably even before conception and continuously through pregnancy; and preparations containing choline have recently been recommended as possibly preventive of the later development of schizophrenia (534). While it is important to note that folic acid may reduce the effectiveness of lamotrigine (252), the anti-teratogenic effects of folate may outweighthe potential for this loss of effectiveness. However, recent concerns have been raised regarding potential association between very high plasma levels of maternal folate and risk of autism spectrum disorders (535).

Pharmacological Management of Bipolar Disorder during the Postpartum Period

The postpartum period is a time of elevated risk for recurrence – with 66% of women who were medication free during pregnancy and 23% of those on treatment experiencing a mood episode following the delivery (536). The risk of postpartum relapse is highest in women who also experienced a mood episode during pregnancy and those who are not on prophylactic treatment (537). Despite the high prevalence of postpartum episodes, there is a dearth of studies investigating the efficacy of medications during this period. There is evidence of efficacy of benzodiazepines, antipsychotics and lithium for postpartum mania (537), and quetiapine for

postpartum bipolar depression (Level 4) (538). There are no studies of psychotherapy in the acute or preventative treatment of bipolar postpartum depression (539).

Patients should be encouraged to initiate or optimize maintenance treatment as soon after giving birth as possible, with preference given to medications which have previously shown to be successful. Near delivery close monitoring is essential for early detection and management of symptoms that might signal pregnancy onset of major postpartum mood or psychotic episodes(540). If an acute mood episode emerges in the postpartum period, the algorithm for non-postpartum episodes should be followed, but because most psychotropic medications are excreted in breast milk, treatment choice should take into consideration safety in breastfeeding when applicable.

The FDA website mentioned in the previous section as well as Table 7.1 also include information on lactation. The FDA PLLR should be consulted for further information about medication risks as many are secreted in milk if breast feeding is being considered.
The potential risks and benefits of taking medications while breastfeeding should be discussed with the patient. Education on early recognition of drug toxicity and requirement of ongoing monitoring of infants is also critical (541). A recent systematic review suggested quetiapine and olanzapine as preferred choices for breastfeeding considering their relatively lower infant dosages (542). The impact of medication on the infant can be reduced by scheduling medication administration after breastfeeding (543).

Replacing or supplementing breast milk with formula can also be considered. Although there are many benefits to breastfeeding, associated sleep disruption may increase the risk of mood episodes in women with BD. If possible, bottle feeding at night by the woman's partner or a support can be beneficial to allow the woman to maintain a better sleeping schedule. In women with postpartum psychosis or mania breastfeeding may be more risky, and therefore not indicated, as the mother may be too disorganized to safely breastfeed(544).

As childbirth can be a trigger for first onset of hypomania/mania in women with major depressive disorder, antidepressants should be used cautiously, especially in women with a family history of bipolar disorder (545). Women with first onset of depression in the postpartum period, or those who have onset of depression during the early postpartum period may also be at a high risk of switching to BD following treatment with antidepressants(539).

Impact of the Menstrual Cycle on Symptoms

Despite the paucity of large, well-designed research studies examining the impact of the menstrual cycle on mood symptoms in bipolar disorder, accumulating evidence suggests that hormonal changes can impact the course of illness. Several case reports and prospective studies suggest that women who experience premenstrual symptom exacerbation are more likely to have a highly symptomatic and relapse prone illness (546, 547). One of the largest studies (n=1,099 found that women who met DSM-5 provisional criteria for premenstrual dysphoric disorder (PMDD) had an earlier illness onset, more co-morbid Axis-I disorders, higher number of hypo/manic and depressive episodes, and higher rates of rapid cycling (548). In this study, there was a closer gap between BD onset and age of menarche in women with comorbid PMDD,

which suggests that sensitivity to endogenous hormones may influence the onset and the clinical course of bipolar disorder. Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) also occur more frequently in women with bipolar disorder (549, 550). Importantly, an accurate diagnosis of co-morbid PMDD in women with bipolar disorder is conducted during clinical remission (euthymia), with a minimum of two months of prospective symptom charting (551).

Menopause

For many women, stress and hormonal changes associated with the transition to menopause may increase or trigger mood symptoms (552-554). A post-hoc analysis of the prospective Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed increased rates of depressive, but not manic episodes during menopause transition (555). However, due to the paucity of clinical trials in this area, more data is needed before treatment recommendations can be made (556).

Management of Bipolar Disorder in Children and Adolescents

Presentation and Diagnosis

As the following section comprises only a brief overview of the epidemiology, phenomenology, and differential diagnosis of bipolar disorder in children and adolescents, the reader is referred to more detailed reviews for further information (557-562).

Between one-third (community samples) and two-thirds (clinical samples) of patients with bipolar disorder experience their first mood episode during childhood or adolescence, with an

earlier onset related to a more severe illness characterized by increased symptom burden and comorbidity (563, 564). In contrast to the controversies of as recently as a decade ago, there is now far greater consensus in the field that although there are developmental differences in the manner in which symptoms manifest themselves, the actual diagnosis of bipolar disorder in children and adolescents should be made based on the same set of symptoms applied to adults (565). When defined rigorously according to DSM-5 criteria, the course of illness in childhood and adolescence is characterized by eventual high rates of symptomatic recovery, but also high rates of recurrence, even in the context of naturalistic treatment (566). While the concepts of "over diagnosis" and "over treatment" in pediatric bipolar disorder have received substantial attention (567), representative population studies demonstrate that adolescent bipolar disorder is characterized by low rates of treatment, alongside high rates of suicidality and comorbidity (568, 569). As such, risks of incorrectly diagnosing and treating bipolar disorder in a child or adolescent should thus be carefully weighed against the risk of incorrectly or not diagnosing or treating (570)- keeping in mind the duration of treatment delay has been shown to be an independent risk factor for a poor outcome in adulthood (571).

Distinguishing early onset mania or hypomania from other psychiatric disorders is important as there is a high level of symptomatic overlap for multiple conditions including but not limited to ADHD, oppositional defiant disorder (ODD), disruptive mood dysregulation disorder (DMDD), substance abuse, personality disorders and generalized anxiety disorder (557, 572) (Table 7.2). The discrete episodes of mania/hypomania and the non-overlapping symptoms can facilitate accurate diagnosis. When a comorbidity is present, such as ADHD, overlapping symptoms (e.g. distractibility, hyperactivity) should only count toward a diagnosis of mania or hypomania if they

intensify during intervals of elation or irritability. Notably ADHD is an ongoing condition where as bipolar disorder is episodic; and decreased sleep, hypersexuality, hallucinations or delusions, and homicidal or suicidal thoughts and actions occur with childhood mania, but are rare or absent in uncomplicated ADHD.

It is important to note that while chronic irritability with episodic behavioral outbursts or rages can be seen in multiple pediatric psychiatric disorders (including emerging personality disorders, substance abuse, ODD, pervasive developmental disorders, and major depressive episodes); such irritability and explosiveness is not sufficient to make a diagnosis, even when severe. The recent DSM-5 diagnosis DMDD- which includes chronic irritability as a defining feature- lists bipolar disorder as an exclusion criterion. However, the DMDD phenotype is evident in about 25% of adolescents with episodic bipolar disorder, and is associated with factors such as greater family conflict and ADHD comorbidity (573). As such, classical bipolar disorder and chronic irritability are not mutually exclusive, the non-specific nature of the latter notwithstanding.

A significant minority of children or youth with MDD will eventually go on to develop bipolar disorder, with an average rate of 28% being reported (574, 575). Risk factors for switch to mania following a depressive episode include a family history of mood disorders, emotional and behavioural dysregulation, subthreshold manic symptoms, cyclothymia, atypical depression and psychosis (574). A recent meta-analysis suggested that the most potent predictors were family history, an earlier age of onset and the presence of psychotic symptoms (576). There is an increased prevalence of bipolar disorder among offspring of parents with bipolar disorder (577-579). Although there is no uniform strategy for managing depression (or ADHD, anxiety, etc.) in the child of a parent with bipolar disorder, increased caution is warranted when prescribing

antidepressant or stimulant medications as these have the potential to precipitate mania/hypomania (580). Patients and their parents should be informed of the potential switch risk and close monitoring for treatment emergent manic/hypomanic switch should be instituted.

Self-report and/or parent-reported questionnaires can be informative and can raise the index of suspicion for bipolar disorder (581). However scores on such questionnaires as the Child Behaviour Checklist (CBCL) "dysregulation phenotype", previously described as "bipolar disorder phenotype" have poor capacity for differentiating bipolar disorder from other complex and severe symptomatic presentations (582). Questionnaires can be used as screeners, but do not substitute for a thorough diagnostic evaluation. Longitudinal rating by parents may be most helpful in diagnosis and assessment of treatment response. An online program for weekly parental ratings (of depression, anxiety, ADHD, oppositional behaviour, and mania) of children aged 2-12 is available at www.bipolarnews.org, click on Child Network (583).

Pharmacological Management

General Principles

The general principles for managing adults with bipolar disorder also apply to children and youth. In youth, themes of comorbidity and tolerability are accentuated. Comorbid ADHD is more common in children and adolescents as compared to adults with bipolar disorder. Moreover, ADHD symptoms often do not improve following mood stabilization, and may require concurrent ADHD treatment. In addition, due to elevated risk for accelerated atherosclerosis and early cardiovascular disease in this population, cardiovascular risk factors should also be assessed regularly and intervention implemented. Lifestyle management including

attention to diet, substance use, smoking and physical activity should be implemented alongside any psychological or pharmacological interventions (584). Relatedly, children and adolescents are more susceptible than adults to the metabolic side-effects of psychiatric medications, particularly the atypical antipsychotics that are considered first line treatments (585). Taken together, these distinguishing features underscore the importance of ensuring that polypharmacy, as often required, is judicious and informed by a balance of factors including mood symptom burden, global functioning, and physical health.

Acute Management of Mania

First line. Lithium (Level 1) (585-587), risperidone (Level 1) (586, 588), aripiprazole (Level 2)(589), asenapine (Level 2) (590), and quetiapine (Level 2) (585, 591) are recommended as first line treatment options. Risperidone may be preferable to lithium for non-obese youth, and youth with ADHD (586).

Second Line. Due to safety and tolerability concerns, olanzapine (Level 2)(592) and ziprasidone (Level 2)(593) should be considered second line options. Quetiapine adjunctive therapy (Level 3)(594) is also recommended as a second line treatment.

Third Line. Despite low response rates in two RCTs, on the basis of a long history of use among adults with bipolar disorder, combined with positive findings in open-label studies, there are grounds for considering divalproex as a third line option for youth who do not respond to or tolerate first or second line agents (Level 4) (595).

Not Recommended. Oxcarbazepine was not superior to placebo in a large RCT (Level 2-ve) (596).

Acute Management of Bipolar Depression

The data in pediatric samples is very limited, and complicated by extremely high placebo-response rates in RCTs. As such, these recommendations are to a greater extent informed by clinical experience and studies in adults than the above acute mania recommendations (see Figure 7.1).

First line. A recently published RCT found that lurasidone was superior to placebo (Level 2) (597) in improving depressive symptoms in children and adolescents with acute bipolar depression; however, there is comparatively little clinical experience in this population . Nevertheless, given its efficacy in adult bipolar depression and clinical experience, lurasidone is recommended as a first line treatment.

Second line. Although lithium and lamotrigine were recommended as first line agents for bipolar depression in adults, there is only open-label data for lithium (Level 4) (598) and lamotrigine (Level 4) (599) in children and youth. Despite limited RCT data, there is, however, substantial clinical experience with these agents as they are widely used in clinical practice. For this reason, together with the strength of evidence in adults, lithium and lamotrigine are recommended as second line, rather than third line agents (see Figure 7.1).

Third line. There is a positive RCT of olanzapine-fluoxetine combination among youth with bipolar depression (Level 1) (600); however, metabolic concerns regarding olanzapine, and

limited clinical experience with olanzapine-fluoxetine combination in youth with bipolar disorder, lead to the positioning of this option as third line. Despite negative findings in pediatric samples, quetiapine (Level 2-ve)(601, 602) is also recommended as third line for this population due to the abundance of evidence from adult studies, combined with substantial clinical experience, and alongside several methodologic concerns (see Figure 7.1).

Despite limited knowledge regarding the precise risks of antidepressant-induced mania in youth with bipolar disorder, observational pharmaco-epidemiology studies support the conclusion that antidepressants should be used with caution in bipolar I and II disorder, and in combination with mood stabilizing medication (Level 4) (580, 603).

Not Recommended: A large RCT found that oxcarbazepine was not superior to placebo (Level 2-ve) (596) although is was effective in the youngest group of patients but not the older adolescents.

Figure 7.1: Reconciling the paucity of RCT data with abundant clinical experience in determining level of recommendation for treatment of pediatric bipolar depression

Aside from lurasidone, which has positive RCT data (597) alongside good tolerability, options include either treatments with substantial tolerability concerns (olanzapine-fluoxetine combination) or treatments with no RCT data (eg. lithium, lamotrigine) or without positive RCT data (eg.quetiapine). In this instance, clinical experience combined with tolerability considerations and adult data informed the ranking of recommendations. Lithium and lamotrigine have not been tested in RCTs in pediatric bipolar depression. However, there is abundant clinical experience with these agents in treating depression in the pediatric group alongside positive open trials. Further, these agents are recommended for treating acute bipolar in adult populations, and they have good tolerability. Thus, despite lack of RCT data, they are recommended as second line agents for treating acute bipolar depression in pediatric population.

In terms of quetiapine, of the two negative RCTs (601, 602), one had a dose range of 300-600mg/day but was limited to 32 participants and had a 67% placebo response rate. The other study was dosed at only 150-300mg/day and had a 55% placebo response rate. One can argue that the quetiapine studies have been failed, rather than truly negative, studies. Therefore, given its demonstrated efficacy in adult bipolar depression and methodological problems in studies of pediatric bipolar depression and based on clinical experience, it is recommended as a third line option.

Ultimately, treatment decisions in general, but particularly in the context of empirical uncertainty, should be informed by a thorough discussion of comparative risks and benefits of competing options. Risk-benefit ratios may differ across patients depending on factors such as BD subtype, comorbid anxiety, and sleep disturbance.

Maintenance Treatment

The data in pediatric samples are very limited. As such, these recommendations are informed by clinical experience and studies in adults to a greater extent than the above acute mania recommendations.

First Line. Preferred maintenance treatment options for this population are aripiprazole (level 2)(604, 605), lithium (Level 2) (606) and divalproex (Level 2) (606, 607). However, it should be noted that follow-up duration for the aripiprazole study was only 30 weeks, and the sample size in the 18-month maintenance study of lithium vs. divalproex was only 30 participants. It is important to note that few patients continued to do well upon the switch to either lithium or divalproex monotherapy and the majority re-responded when the combination was re-instated. Further, other studies have also suggested the efficacy of combination therapy (eg. risperidone

plus lithium or divalproex) (586) (eg. lithium plus divalproex or carbamazepine)(608) to achieve and maintain remission Adjunctive lamotrigine may also be considered for those age 13+ (Level 2) (609)

Second Line. No treatments with Level 3 or higher evidence are available to recommend as second line options for maintenance.

Third Line. Although there has been far less experience with asenapine than with other medications discussed in this section, a recent open-label extension study suggests continual reduction in manic symptoms over 50 weeks (Level 4)(610). Further, a recent RCT in adults confirmed it's efficacy in preventing relapse of mood episodes (375). Although there have not been maintenance studies for quetiapine, risperidone, or ziprasidone in this population; clinical experience and open label studies indicate that continuation and maintenance treatment with these medications is another option- particularly for those patients who have responded well to acute treatment (Level 4) (593, 611, 612). Further, there is evidence that oral quetiapine and long acting injectable risperidone mono and adjunctive therapy and oral ziprasidone adjunctive therapy are effective in preventing mood episodes in adults with bipolar disorder (370, 371,384, 385, 388).

Treatment of Comorbid Conditions

ADHD. Stimulants may also be used for comorbid ADHD in stable/euthymic youth taking optimal doses of anti-manic medications. Adjunctive mixed amphetamine salts (Level 3) (613) and methylphenidate (Level 3) (614) have both been shown to be effective in addressing attention symptoms and are well tolerated overall within the RCTs completed to date, theoretical

and epidemiological data regarding risks of induction of mood elevation notwithstanding (615). Although open trials suggest potential benefits of atomoxetine (Level 4) (616, 617), the possibility of inducing mania or hypomania remains (618), suggesting the need for RCTs before clinical recommendations can be made.

Substance Use. Comorbid substance use should be treated concurrently to mood symptoms, with inpatient hospital or community residential treatment employed as clinically indicated. A small study suggests that lithium may be effective for reducing substance use in this population (Level 3)(619), and family focused therapy should also be considered (Section 2). Positive trials of N-acetylcysteine (NAC) for cannabis use disorders among adolescents (620), smoking(621), and bipolar depression among adults (282) suggest that NAC may benefit adolescents with comorbid bipolar and substance use disorders; however, studies examining this hypothesis have not yet been completed (Level 4).

Management of Bipolar Disorder in Older Age

Presentation and Course

Because of the aging population in Canada and many countries around the world, knowledge on pertinent issues related to the management of older adults is becoming increasingly important. Approximately 6% of geriatric psychiatry outpatients and 10% of inpatients have bipolar disorder (622), and proportionally this population is one of the highest users of psychiatric and physical health services (623). Approximately 25% of the patients with BD in the United States in 2005 were over the age of 60 (624), and by 2030 >50% of patients with BD are expected to be aged >60 (625).

The lifetime prevalence of late-life bipolar disorder is about 1%-2% with a one year prevalence of 0.1% to 0.7% in general population. About 90-95% of older adults with bipolar disorder have their initial episode prior to age 50, although there is a minority who will have a later onset (626, 627). Late onset is often related to neurological or physical comorbidity (628), and may carry a negative prognosis (629); although this is not a consistent finding (630).

While symptoms of mania or hypomania are generally less prominent in older adults, depressive and cognitive symptoms are more often observed; and hyperactivity, aggression, insomnia, impulsivity, and self-neglect may pose a significant risk to the patient and others (631, 632). Psychiatric comorbidity is also generally lower than in younger patients, with anxiety and substance use being the most common (633). Compared to younger patients, older adults are less likely to utilize inpatient, outpatient, and emergency room services and more likely to use case-management and conservator services (634).

Cognitive dysfunction is a significant concern for this population, with more than 30% showing significant deficits across all mood states, including euthymia (635). This cognitive dysfunction is relatively stable, is related to the number of mood episodes earlier in life and does not appear to exceed normal aging in 2-5 year follow-up (636-638). Lithium use has been associated with lower rates of cognitive disorders in BD (639), and higher lithium levels in drinking water may be associated with lower dementia risks (640, 641); although prospective trials are required to definitively assess this. Standardized instruments, such as the Montreal Cognitive Assessment (MoCA) should be used to quantify cognitive dysfunction. Because of the link between cognition and functioning in bipolar disorder (636, 642), the impact of medications (particularly those with a high anticholinergic burden) on cognition should be considered when making treatment

decisions. Furthermore, improvement of modifiable risk factors such as diet, exercise, and mental stimulation should also be promoted in order to further diminish the risk of cognitive decline.

Medical Comorbidity

Older adults with bipolar disorder have an average of three to four medical comorbidities; with metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine abnormalities being the most common (633, 643). Together, this contributes to a reduction in life expectancy of 10-15 years in bipolar disorder compared to non-psychiatric populations (644). Because of these high rates of comorbidities, assessment of an older adult with bipolar disorder should include a thorough physical and neurological examination, including clinical laboratory tests. Neuroimaging should also be applied as indicated, particularly in the presence of focal neurological signs and symptoms, abrupt late onset, or the presentation is different from prior episodes. Coordination with other health care providers is also imperative, as this can optimize physical health (645), as can smoking cessation.

Pharmacological Treatment

The data supporting efficacy of medications in various mood states in this population is limited- with only a single RCT exclusively of geriatric patients completed to date- comparing lithium vs. divalproex for the treatment of mania/hypomania (646). Despite this, open-label trials, naturalistic studies, and post-hoc analyses of mixed aged RCT's suggest that medications efficacious in adults will also be effective in older adults although additional considerations regarding medication tolerability and age-related changes in pharmacokinetics and

pharmacodynamics must be made. Because of the high number of medical comorbidities as well as physical changes related to the aging process, strict attention must be paid in these patients to potential pharmacokinetic issues, drug-drug interactions, side effects, and the need for ongoing monitoring (See Section 8).

Amongst other effects, lithium has been associated with adverse neurological effects (647) and renal disease (648). Divalproex has been associated with motor side effects (647) and metabolic effects (weight gain, diabetes mellitus) (649). Carbamazepine induces CYP 450 enzymes and can reduce the levels of divalproex and other medications (650). Regarding antipsychotics, which are now very commonly used in geriatric bipolar disorder, dose reduction may be beneficial in some aging patients to lower the risk of motor, sedation, metabolic syndrome, and cognitive effects (651). There is an association between mortality and antipsychotics in dementia patients (652) but it is unclear how this should be managed for people with bipolar disorder. Recently there has also been data linking antipsychotics with acute kidney injury (653).

In particular, when lithium is used in this population, lithium level and renal monitoring should occur at least every 3-6 months, as well as 5-7 days following a lithium dose adjustment or adjustment of non-steroidal anti-inflammitory drugs (NSAIDs), antiontensin II receptor blockers (ARBs), angiotensin- converting enzyme inhibitors (ACEIs), or thiazide diuretic dosing (654). Special considerations also need to be made to dose selection. A post hoc analysis of the STEP-BD study found that while on average, older patients required a similar number of medications as younger patients to achieve recovery, lower doses were used. In that sample, over twice as many older patients as younger ones recovered using lithium alone (42% vs 21%)(655). In general, starting at a lower dose (e.g. 150 mg nightly for lithium) is recommended, with gradual

adjustments to reach the lowest end of the therapeutic range for adults, with subsequent titration based on tolerability and effectiveness; keeping in mind some geriatric patients will require adult blood levels for remission. Further discussion, including clinical guidance and more detailed treatment recommendations, can be found in the ISBD Task Force report (656). In light of very limited international guidelines for maintenance treatment of older adults with bipolar disorder (OABD), the International Society for Bipolar Disorders (ISBD) task force on OABD is currently undertaking a Delphi survey of international experts and clinicians are advised to consult these as results become available in the future. (Shulman K, personal communication).

Pharmacological treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1.1) in older adults as well as safety and tolerability (Section 8). Unfortunately, there is a dearth of literature for efficacy of treatments in older adults. However, clinical experience supports the notion that treatments known to work in adults are also effective in older adults. Tolerability may be different and this is an important consideration in treatment selection in older adults. General principles for management of acute episodes described in Sections 3 and 4 also apply to this population.

Acute Mania. Monotherapy with lithium (Level 2)(646) or divalproex (Level 2) (646) is recommended as a first line treatment. Quetiapine (Level 2) (657) can be considered as second line. Asenapine (Level 4)(658, 659), aripiprazole (Level 4)(660), risperidone (Level 4) (661), or carbamazepine (Level 4) (656) may be applied as third line treatments. For treatment resistant episodes, clozapine (Level 4)(662), and ECT (Level 4) (656) should also be considered.

Bipolar Depression. There are no RCTs of any agents in older adults with acute bipolar depression. Post-hoc analyses of RCTs suggest efficacy of quetiapine (Level 2) (663) and lurasidone (Level 2)(664) monotherapy and hence, these are recommended as first line options. However, in older adults, given the concerns about side effects of atypical antipsychotics, clinicians may wish to try lithium or lamotrigine first based on their efficacy in adult populations although the evidence of efficacy is limited in older adults (lithium -Level 4; lamotrigine -Level 4) (665, 666). Divalproex (level 4), aripiprazole (Level 4) (660), or carbamazepine (Level 4) (667) are third line options. ECT (Level 4) (656) is an important option that should be considered in treatment-resistant cases, for suicidal patients, or patients with inadequate food or fluid intake.

While the use of antidepressants in bipolar disorder remains controversial (261, 427) and there have been no studies in older age bipolar disorder; antidepressants are frequently used in this population (>40% of patients (668)). Antidepressants with relatively lower manic switch potential (e.g. SSRI and bupropion) (261) used in combination with mood stabilizers may be beneficial in selected patients who cannot tolerate/do not respond to other agents with a stronger geriatric evidence base. Possible medication interactions with ongoing medications for non-psychiatric conditions must always be considered.

Maintenance. Choice of agents should be based on what has been effective in the acute phase, with recommended options with geriatric efficacy data being lithium (Level 2)(669, 670), lamotrigine (Level2)(670),and divalproex (Level 3)(669)

Management of Comorbid Conditions in Bipolar Disorder

Comorbid Psychiatric Disorders

Epidemiology

Most patients diagnosed with BD will also have at least one comorbid psychiatric diagnosis. The most common comorbid conditions are substance abuse/ dependence, anxiety disorder, personality disorder, and impulse control disorder (such as ADHD, ODD, and CD) (45). Comorbidity impacts the course of bipolar disorders by increasing the likelihood of treatment resistance and suicide risk, and also by increasing the time spent with impairing symptoms (34, 50, 671, 672).

When treating comorbid conditions, determining which disorder to address first requires careful consideration. Some comorbid disorders may be managed with the same treatment employed to manage bipolar symptoms (eg. quetiapine for comorbid anxiety and bipolar disorder), while other comorbid disorders (e.g. ADHD) may require distinct treatments. Importantly, some treatments for comorbid disorders may lead to bipolar symptom destabilization- for instance, an antidepressant employed to treat an anxiety disorder may provoke mood elevation.

Safely and effectively managing co-morbid conditions often necessitates the implementation of a hierarchical approach, depending on each patient's individual needs and preferences. In general, the disorder or symptom associated with the greatest morbidity and mortality- such as acute mania, psychosis, or suicidal ideation- should be managed first. Substance misuse/ abuse/dependence may be addressed concurrently or sequentially, depending on its severity and contribution to mood instability. Once mood stability is established, the treatment of additional

co-morbid conditions, such as ADHD or metabolic disorders, should follow based on their impact and the patient's preference.

There is a dearth of research to guide the best management of bipolar disorder in the context of co-morbid conditions. There have been few trials designed with co-morbid symptoms as the primary target for mood stabilizing treatments- evidence is mainly derived from secondary analysis of published data. Thus, the limited research informing the treatment of comorbidities constrains our ability to make definitive recommendations. However, because comorbidity is so common and burdensome for patients, appropriate management is a challenging daily reality in clinical practice. Therefore, CANMAT decided to provide a brief overview of relevant clinical issues and the evidence base for pharmacological treatments for treating comorbid populations. The reader is advised to consult the following for the role of psychological treatments in managing comorbidity (673-675).

Substance Use Disorders

Two recent reviews indicated that the prevalence rate of comorbid substance use disorder (SUD) in bipolar disorder is about 33% in general population surveys (676) and approximately 45% in clinical settings (677). SUD can negatively impact the course of BD, resulting in lower rates of remission (408), a higher number of hospitalizations (678, 679), and an increased risk of suicide attempts (430) and perhaps suicide deaths (680).

Substance use should be addressed as early as possible, as it is likely to interfere with treatment for BD. However, the presence of substance abuse should not preclude an attempt to treat BD, which might result in an individual being more amenable to treatment. As the directionality of

the interaction between SUD and BD is rarely clear in the reality of clinical practice, it is recommended that both conditions be treated simultaneously.

A more detailed discussion on the impact of and the general principles of the treatment of substance use comorbidity can be found in a CANMAT Task Force publication (681), and other reviews and meta-analysis published on the topic since 2012 (675, 682, 683). Here we provide a brief update on the pharmacological treatments identified in the CANMAT Task Force publication. It is important to note that the criteria for level of evidence used here are more stringent than those applied to Task Force report.

The levels of evidence for treatment of comorbid SUD are low. This is because of 1) the paucity of data, 2) complexity of study designs (given the fact that many patients will be using more than one substance), and, most importantly, 3) inconsistency of the outcome variables used in these studies; hindering direct comparison of results. Nevertheless, some evidence-based recommendations are available for clinicians starting with general principles of treatment: if at all possible, avoid medications which could increase the risk of destabilizing the bipolar condition, and choose treatments which could help both conditions.

Alcohol Use Disorder

A combination of divalproex and lithium is the only treatment for alcohol abuse comorbid with bipolar disorder which meets criteria for Level 2 evidence (684, 685). In a small RCT, there was a significant reduction in the number of drinks per drinking day, as well as per heavy drinking day, in the combination group compared to lithium alone when adherence to treatment was added as a covariate. There is only Level 3 evidence for lamotrigine (686), and divalproex

monotherapy or add-on (687-689). While lithium may also show some benefits (Level 3) (619) it has to be used with caution in heavy drinkers because of potential electrolyte imbalance; and anticonvulsants warrant liver function tests and lipase levels before initiating treatment. Agents for primary alcohol use disorder may also show benefits in bipolar disorder, such as disulfiram (Level 3) (690-693), naltrexone (Level 3) (694-697) and gabapentin (Level 4) (698, 699). Furthermore, guidelines for the pharmacotherapy in alcohol dependence alone can offer some guidance in the absence of comorbidity specific trials (700).

Quetiapine is not recommended for the treatment of alcohol abuse comorbid to bipolar disorder because of lack of efficacy. Quetiapine add-on therapy was not more effective than placebo add-on in reducing the number of drinks per day or other alcohol related measures in patients with BDI (701) or BDI and BDII with alcohol dependence (Level 1 -ve)(702). In another RCT, quetiapine mono or add-on therapy to mood stabilizers was compared with placebo mono/add-on therapy in bipolar depressed patients with co-morbid anxiety and substance use disorders (703). They found no significant improvement in depressive or anxiety symptoms but did not report separately on the alcohol or substance use related outcomes.

No specific recommendations are given regarding acamprosate at this time. In a smaller RCT, acamprosate add-on was ineffective in improving drinking related outcomes in BDI/BDII patients with alcohol dependence (Level 3-ve)(704) but a post-hoc analysis showed a small decrease of the Clinical Global Impression scores for substance use severity toward the end of the trial. Further studies are needed.

Cannabis use disorder

About 20% of patients with bipolar disorder have cannabis use disorder at some point in their life (677). Cannabis use disorder is associated with younger age, manic/mixed episode polarity, presence of psychotic features, and comorbid nicotine dependence, alcohol use disorder, and other substance use disorders (705). Cannabis use is also associated with more time in affective episodes and rapid cycling (706).

There is limited research into treatment options for this frequent substance use disorder. Lithium and / or divalproex have Level 3 evidence (619, 684, 687-689). Quetiapine failed to provide any benefit in terms of mood and anxiety symptoms in a small subsample of highly comorbid bipolar patients with GAD (generalized anxiety disorder and cannabis use disorder)(703) (Level 3-ve). The effect of quetiapine on specific cannabis use related outcomes was not reported.

Stimulants: Cocaine, Amphetamine, and Methamphetamine Use Disorders

Citicoline adjunctive therapy had a positive outcome in two RCTs in patients with bipolar disorder with comorbid cocaine use disorder, although the benefits of citicoline decreased over time in the more recent study (Level 2) (707, 708).

Lithium or divalproex, either alone or in combination, were proven useful in small studies addressing cocaine use disorder (687-689, 709-711) (Level 4). Quetiapine in monotherapy or in combination with the on-going treatment shows evidence of efficacy for cocaine, amphetamine and methamphetamine use disorder (712-714)(Level 3). Risperidone has been studied alone and as an add-on agent for cocaine and for methamphetamine use disorders with Level 3 evidence for efficacy (714, 715).

Bupropion has anecdotal reports favoring efficacy in cocaine use disorders (Level 4) (716). Citicoline improved depressive symptoms in patients with methamphetamine dependence and bipolar depression (717).

Lamotrigine has been studied in a 10 week RCT of lamotrigine vs placebo added to ongoing medication. While results were negative on the a priori outcome variable (positive urine drug screens), they were positive on the secondary outcome of the amount of dollars spent per week on cocaine purchases (Level 2-ve) (718).

Opioid Use Disorder

While methadone has the most evidence of efficacy in comorbid bipolar disorder and opioid use disorder (Level 3) (719, 720), because of the lack of research in this space and increasing concern related to risk of overdose, clinicians should consult the Canadian Research Initiative in Substance Misuse (CRISM) national treatment guidelines on primary opioid use disorder when available (anticipated November 2017) for further advice on managing this comorbidity .

Others

Olanzapine add-on therapy was effective in decreasing manic symptoms and measures of substance use such as reduction in cravings in hospitalized inpatients (Level 2) (721). Aripiprazole has a Level 4 evidence to decrease craving of alcohol, but not consumption, and a Level 4 evidence to decrease cocaine use in polysubstance abusers (722).

Anxiety Disorders

Patients with bipolar disorder frequently experience symptoms of anxiety and comorbid anxiety disorders (GAD, panic disorder, PTSD and others). Clinical samples indicate that 24-56% of

bipolar patients meet criteria for one or more anxiety disorders, with the highest rates in women (723). Co-morbid anxiety symptoms and anxiety disorders are associated with a higher number of mood episodes and depressive symptoms including suicidality, sleep disturbance, and greater impairment of psychosocial functioning and quality of life (724). The presence of a comorbid anxiety disorder is also associated with high rates of antidepressant use (725), which should be employed with caution due to their potential for mood destabilization (Section 4).

While the CANMAT Task Force Report (723) described key studies and treatment recommendations in length, those recommendations have been updated below. However, it remains the case that there are few studies that focus exclusively on anxiety symptoms or disorders comorbid with BD, whether for treatment efficacy or safety. While there are treatment options, the limitations resulting from a paucity of data prevent the development of clear guidelines or treatment algorithms.

A "step-wise" approach was recommended in the 2012 CANMAT recommendations for managing comorbid anxiety. In general, mood stabilization is the priority before specific anxiety treatments are considered (Figure 7.2). Despite clinical experience, antidepressants, particularly serotoninergic agents, should be employed with caution due to their potential to provoke mood destabilization. While benzodiazepines are an important clinical tool because they can rapidly alleviate anxiety, clinicians should strive to prescribe them at the lowest possible dose for the shortest period possible, given the concerns about suicide risk, abuse and dependence. CBT continues to be an appropriate first line treatment for anxiety.

Figure 7.2: Primary Treatments for Anxiety Disorders- Should they be used to treat co-morbid anxiety in bipolar disorder?

There are no large RCTs that examined the efficacy of SSRIs, SNRIs, pregabalin or lorazepam in treating anxiety symptoms in BD patients with co-morbid GAD. However, several RCTs assessed the efficacy of these agents in patients with primary GAD and have been found to be effective (726). So, should clinicians employ these treatments in treating co-morbid anxiety symptoms in GAD? As with any clinical decision, CANMAT recommends assessing risk-benefit ratio.

Pregabalin is effective and is not associated with risk of mood destabilization and is well tolerated. Hence, pregabalin would be considered an appropriate option although this has not been tested in BD population with co-morbid anxiety. Lorazepam also does not cause mood instability but given the potential dependence with longer-term use, only short-term use of lorazepam may be appropriate. In the case of antidepressants, especially with SNRIs, the risk of manic/hypomanic switch is likely higher. Therefore, if antidepressants are being considered for treating anxiety symptoms, it is recommended to primarily use SSRIs. Further, if SSRIs are used, it is important to ensure adequate mood stabilization with one or more prophylactic antimanic agents (eg. lithium or valproate or an atypical antipsychotic).

Lorazepam and clonazepam do not provoke mood instability, they are rapidly effective for the acute management of anxiety and they may address early warning signs of mania by inducing sleep. While inappropriate prescribing may result in misuse and dependence and caution must be exercised when prescribing benzodiazepines to elderly patients in particular, the use of benzodiazepines may be appropriate for treating anxiety associated with bipolar disorder. Short-term use is desirable but some patients are unable to tolerate other anxiety treatments and experience significant symptomatic relief and functional improvement due to the judicious use of benzodiazepines.

Generalized Anxiety Disorder and Panic Disorder

Quetiapine was superior to placebo and divalproex in improving anxiety symptoms in patients with comorbid GAD and/or Panic Disorder (Level 2)(727). Further, secondary analyses from several RCTs indicate that quetiapine monotherapy significantly reduces symptoms of GAD and panic disorder in depressed bipolar patients (291, 314, 728). Negative trials include risperidone versus placebo in bipolar patients with GAD and/or panic disorder (729); and with ziprasidone versus placebo in a similar trial (730).

For euthymic patients treated with lithium, the addition of lamotrigine or olanzapine has demonstrated similar anxiolytic effects (Level 3) (731). In a secondary post-hoc analysis, combinations of olanzapine and fluoxetine (Level 3), and to a lesser extent olanzapine monotherapy, were effective in reducing anxiety in patients with bipolar depression ((315).

Gabapentin employed as an adjunctive therapy in open label studies reduced anxiety symptoms in patients with bipolar disorder (Level 4)(698),(732). Given its relatively benign side effect profile and efficacy in other primary anxiety disorders, gabapentin is an appropriate strategy.

Obsessive Compulsive Disorder

OCD was re-categorized in the DSM- 5 and is no longer characterized as an anxiety disorder; however, anxiety is a cardinal feature. OCD is a comorbid condition in 10-20% of patients with bipolar disorder (733-736) compared with 2-3% in the general population (737). However, the prevalence appears to vary widely, depending on the clinical setting and bipolar subtype (734). Co-morbid OCD may be more common in children and adolescents with bipolar disorder than in adults (734) and has been reported to co-occur more commonly with bipolar disorder than other anxiety disorders (738), although other studies have not found that association (739).

When diagnosed co-morbidly with bipolar disorder, OCD has been associated with an earlier onset of bipolar disorder; a higher number of previous mood episodes, rapid cycling, seasonality, substance misuse, and lower overall functioning (735, 740-745). Jeon et al recently conducted a comprehensive review of patients diagnosed with bipolar disorder and comorbid OCD and found twice the rate of pharmacological switch to mania or hypomania, but suggested this could be due to the more frequent use of antidepressants in that population (735). Other authors have raised similar concerns (746)

Symptoms of OCD may precede or follow mood symptoms and the severity of OCD symptoms tend to fluctuate with mood changes (747). The high rate of co-occurrence and the many shared clinical features of OCD and bipolar disorder suggest a shared neurobiology. Some researchers

have posited that the high rate of co-occurrence might reflect a distinct bipolar phenotype rather than separate disorders (739, 748).

OCD symptoms may remit during effective treatment of bipolar disorder; mood stabilizers alone or with atypical antipsychotics may be adequate to resolve co-morbid symptoms of OCD and antidepressants might not be necessary for the majority of patients (733, 739). If antidepressants are used clinical experience suggests that SSRIs are preferred, but because of the potential risk of manic switch clinicians need to optimize prophylactic antimanic agents before initiating. The CANMAT Task Force 2012 report included several small case reports indicating the potential benefit of lithium (746), anticonvulsants (746, 749), olanzapine (750, 751), risperidone (752, 753), quetiapine (754)) and aripiprazole (755) for the treatment of comorbid OCD (all Level 4 evidence).

Since the 2012 CANMAT publication, there is very limited new evidence regarding the treatment of comorbid BD and OCD. Two published case reports described successfully employing aripiprazole once monthly (756) and oral (757) for patients with intractable bipolar and OCD symptoms. Another case report described benefits of ECT (758), and a small trial also found benefits with adjunctive topiramate (Level 3)(759).

Personality Disorders

A meta-analysis indicates that 42% of patients with BD also have a comorbid personality disorder- and this feature can be both a diagnostic confound and predictor of poorer treatment response. The most prevalent was obsessive compulsive personality disorder (18%), followed by borderline (16%), avoidant (12%) paranoid (11%), and histrionic (10%) (760). Despite the high

prevalence of these comorbidities, research assessing the effectiveness of treatments is sparse. The CANMAT task force recommendations describe key issues in the management of personality disorders, including the relationship between personality and mood disorders, accurate diagnosis, and the effect on treatment response and clinical course (761).

The 2012 CANMAT task force recommendations for co-morbid personality disorder concluded that divalproex (Level 3) (467) and lamotrigine (Level 4) (762) may provide some symptomatic relief for comorbid borderline personality disorder. Psychoeducation might be of value, as one small RCT that included patients with any comorbid personality disorder (Level 3) (763) demonstrated. That study, along with another small trial that combined psychoeducation and skills training for patients with a mood disorder plus a personality disorder and suicidal ideation (Level 3) (764), showed a modest long-term benefit. Larger, more specific studies are needed. There is also data to support the utility of dialectical behavioural therapy (DBT) for the treatment of bipolar disorder, which has robust data for efficacy in the treatment of borderline personality disorder (75, 765, 766).

Since those CANMAT recommendations were published in 2012, few new studies have significantly contributed to our understanding of the appropriate treatment of these highly comorbid disorders. Alesiani and colleagues assessed that value of the Systems Training for Emotional Predictability and Problem Solving (STEPPS) Program for 32 subjects with personality disorder and mood disorder (half MDD and half BD, mostly type II), and history of suicide attempts or self-harm and emotional and behavioural dysregulation. Although results are preliminary due to small sample size and high-drop out rate, findings suggest such group treatment may improve symptoms, as well as reduce suicide attempts and hospitalizations (764).

ADHD

ADHD and bipolar disorder co-occur far more commonly than would be expected based on their individual prevalence in the general population. Approximately 10- 20% of patient with bipolar disorder meet the criteria for adult ADHD and up to 20% of adults with ADHD also meet the criteria for bipolar disorder (767). Bipolar disorder and ADHD have a high degree of symptom overlap, making the comorbid diagnosis difficult and requiring careful attention to childhood history and lifetime course of illness. Patients with comorbid ADHD often experience a more treatment refractory course, more mood episodes, greater functional impairment and a heightened risk of suicide (768).

The treatment of ADHD presenting comorbidity with bipolar disorder is discussed in detail in a previous CANMAT Task Force Recommendation paper (768). Recommendations were to treat bipolar symptoms first with mood stabilizers and or atypical antipsychotics and stabilizing mood before considering treatment for ADHD symptoms. Mixed amphetamine salts (Level 3) (613), methylphenidate (Level 3) (614), atomoxetine (Level 4) (617), bupropion (Level 4) (769), or lisdexamfetamine (Level 4) (770) add-on to mood stabilizing treatments have been reported to be efficacious in improving ADHD symptoms.

In a s Swedish national patient registry study of patients with bipolar disorder and ADHD, methylphenidate monotherapy significantly increased the risk of mania, while those patients treated concurrently with a mood stabilizer experienced a significantly reduced risk of mania when methylphenidate was employed (290).

Comorbid Metabolic Disorders

Epidemiology

While there is consistent evidence showing the high prevalence of comorbid medical conditions in BD (771-777) and the negative impact these diagnoses have on longevity (778, 779), these conditions frequently go undiagnosed or undertreated. In a large U.K. cross-sectional analysis of electronic data sets involving 1.7 million patients in primary care, those diagnosed with bipolar disorder, when compared with healthy controls, had lower rates of diagnoses (OR 0.59, 95% CI 0.54-0.63) and treatment of medical conditions, despite higher rates of one (O.R. 1.2, 95% CI 1.16 - 1.39) or multiple illnesses (O.R .1.44, 95% CI 1.3-1.64) (772).

Metabolic syndrome in particular is a highly prevalent comorbidity, present in 20-65% of patients with bipolar disorder (780). Defined as a cluster of clinical and biochemical features, including abdominal adiposity, hypertension, impaired fasting glucose or diabetes mellitus, and atherogenic dyslipidemia (781), metabolic syndrome not only greatly increases an individual's risk for cardiovascular disease, diabetes mellitus, and premature mortality (782) but also worsens bipolar clinical outcomes (783, 784). Increased BMI is an important contributor to metabolic syndrome, although metabolic dysfunction is not always accompanied by overweight/obesity, and as such patients with normal BMI should also receive regular monitoring (Section 8).

It has been hypothesized that bipolar disorder and metabolic syndrome share a set of common risk factors and overlapping pathophysiology (785-787). While medications used to treat bipolar disorder, particularly atypical antipsychotics, can also lead to metabolic dysfunction and weight problems, (Section 8) insufficient access to primary and preventative health care, low socioeconomic status, habitual inactivity, insulin dysfunction, peripheral inflammation and

neuroinflammation, oxidative stress, and childhood adversity are also important contributors (788).

Principles of Management

As noted in previously in these guidelines, older adults commonly have three or more medical comorbidities that contribute to the 10-15yr lower life expectancy compared to non-psychiatric populations (644). The most common medical comorbidities are metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine disorders (633, 643). This highlights the necessity for vigilance when treating all patients with BD, including regular assessments of their metabolic parameters.

Working collaboratively with other members of a patient's healthcare team is as essential aspect of good clinical care. Comprehensive management of comorbid medical conditions should include a multidisciplinary team based approach, including primary care, medical specialists, nurses, psychologists, and social workers as appropriate, with patients taking an active role in their care. Treatment strategies should focus both on the psychiatric symptoms, as well as medical issues and risk factors.

A promising strategy for improving the medical care of people with bipolar disorder is through "primary care-based medical homes" where those with a serious mental illness and at least one other chronic condition receive integrated care. While most studies do not separate bipolar disorder from other major mental illnesses in analyses, matched samples in the North Carolina Medical Homes program indicate that patients with bipolar disorder (n=13,406) in primary care medical homes had greater use of primary care and specialty mental health care compared with

propensity matched controls, and marginally lower use of emergency services. However, of three diagnostic groups studied (depression, schizophrenia, bipolar disorder), use of preventative services such as lipid screening and cancer screening was only greater in the depressed subgroup (789). At the same time, a cross–sectional Canadian study examining patient centred medical homes in naturalistic practice found that where rostering was elective, persons with bipolar disorder and psychosis were differentially excluded (RR 0.92,95% CI 0.90-0.93) (790)- suggesting that concentrated efforts should be made to ensure appropriate access to these services.

Treatment Recommendations

Treatment strategies that target metabolic disorders should include non-pharmacological lifestyle interventions. Replacing "high metabolic-risk" psychiatric medications with medications that have a more favorable profile is highly recommended if the therapeutic advantage of the high-risk agent over the alternative is minimal and metabolic/weight issues persist. Bariatric medicines should be considered following unsuccessful attempts at the aforementioned strategies if the individual has a BMI ≥27 with weight related morbidity or a BMI ≥ 30 without significant metabolic morbidity. Readers are referred to the CANMAT Task Force report (788) for further detailed discussion on foundational principles for managing metabolic conditions in patients with bipolar disorder.

While there is no evidence specifically regarding treatment of comorbid dyslipidaemia or hypertension in bipolar disorder, it is noteworthy that many of the medications used to manage these comorbid medical disorders have epidemiological or even clinical trial evidence that they may benefit mood. Examples include statins, aspirin and angiotensin antagonists (791-793) (794-

796). The implications are that clinicians should be actively engaged in the management of these disorders, and should select therapies from those agents that may have benefit in mood symptoms. This again is concordant with the notion of shared risk pathways for these non-communicable disorders.

Other Comorbid Medical Conditions

Two studies from a random sample of 1 million people, taken from a large population -based retrospective cohort in Taiwan, demonstrated a reduced risk of both stroke and cancer associated with lithium treatment for bipolar disorder. The lithium group was compared with propensity matched controls.

The first study reported a hazard ratio for stroke over 11 years of 0.39 (95% CI: 0.22-0.68) for those prescribed lithium even when adjusting for the risks associated with typical and atypical antipsychotics. The reduced risk was also correlated with a higher dose, longer treatment duration and a higher rate of exposure to lithium (797). In the second study, in a sample of 4729 patients diagnosed with bipolar disorder, lithium exposure was associated with a reduced risk of cancer, compared to a group prescribed anticonvulsant medications. (Lithium with or without anticonvulsant HR =0.735, 95%CI 0.55-0.97). The study also demonstrated a dose –response relationship (798). In a subsequent large BD cohort study (n= 9651) focusing on genitourinary cancer, however, lithium was not associated with any change in risk (799).

A recent meta-analysis suggests increased risk of dementia in those with bipolar disorder (800). There is some evidence that lithium in drinking water reduces risk of dementia in general population(640) as is the use of lithium in patients with bipolar disorder (801).

Section 8: Safety & Monitoring

Medical Evaluation and Laboratory Investigations

Complete medical history including assessment of Body Mass Index (BMI) and baseline laboratory investigations (Table 8.1) should be performed prior to initiating pharmacological treatment for bipolar disorder or, in the case of an acute clinical situation, as soon as the patient is cooperative. For more detail, readers are referred to comprehensive guidelines for safety monitoring in bipolar disorder (802). In women of child bearing age, pregnancy should be ruled out, and they should be counselled about the possibility of lamotrigine and carbamazepine affecting the efficacy of oral contraceptives before initiating pharmacotherapy.

For those on maintenance therapy with lithium, thyroid and renal function as well as plasma calcium (803) should be assessed at 6 months and at least annually thereafter or as clinically indicated. Menstrual history (to assess for polycystic ovary syndrome), haematology profile, and liver function tests should be obtained at 3 -6 month intervals during the first year, and yearly thereafter and as clinically indicated, in patients on maintenance treatment with divalproex. Patients initiated on lamotrigine or carbamazepine should be routinely educated about the risks of skin rashes and the potential for Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). They should be advised to contact the treating physician if they observe any type of skin rashes or mucosal ulcers as they require urgent medical evaluation to determine the nature of rashes/ulcers and implementation of most appropriate treatment options which might include discontinuation of these medications and instituting other therapeutic strategies to treat serious rashes and prevent destabilization of bipolar disorder. Further, prior to commencing carbamazepine, patients with ancestry in genetically at risk populations such as Han Chinese and

other asian patients should have a genotyping done to ensure that they do not have HLA-B*1502 allele which confers a high risk for SJS/TEN with carbamazepine (804). In addition, those on carbamazepine therapy should have serum sodium levels measured at least annually and as clinically indicated given the risk of hyponatremia with this compound. Patients on atypical antipsychotics should have their weight monitored monthly in the first 3 months and every 3 months thereafter. Blood pressure, fasting glucose and lipid profile should be assessed at 3 and 6 months, and yearly thereafter. Children under 10 years of age, seniors, medically ill patients, and patients on combination treatments should receive more frequent monitoring. Re-emergence of clinical symptoms, as well as signs of haematological, hepatic, cardiovascular, and neurological dysfunction, should also signal the need for additional investigations.

Patients receiving treatment should be regularly monitored for side effects, including weight changes and other adverse events such as extrapyramidal symptoms (EPS).

Monitoring Medication Serum Levels

Patients on lithium, divalproex, or carbamazepine need to have their serum medication levels monitored regularly. This is particularly important for those who may be non-adherent to treatment. Serum levels should be repeated at the trough point, which is approximately 12h after the last dose. It is recommended that two consecutive serum levels be established in the therapeutic range during the acute phase for lithium and divalproex, and then repeated every 3-6 months or more frequently if clinically indicated. For carbamazepine, serum level monitoring is mainly done to ensure that the levels are not in the toxic range and to check for treatment adherence as there is no established relationship between efficacy and serum levels; thus

monitoring for serum carbamazepine levels may be done at 6 to 12 monthly intervals and as clinically indicated.

The target serum level for lithium in acute treatment is 0.8-1.2 mEq/L (0.4-0.8mEq/L in older adults) while in maintenance treatment, serum levels of 0.6-1 mEq/L may be sufficient (805, 806); serum levels should be obtained about 5 days after the most recent dose titration. Clinicians may wish to consult the Lithiumeter schematic for further guidance (807)). It is important to avoid toxic levels as these are associated with an increased risk of kidney damage in the long term (808). The target serum level for divalproex is 350-700 mM/L (50 ug/ml-100 ug/ml) in the acute phase and should be obtained 3-5 days after the most recent dose titration. There is some evidence for a linear relationship between serum valproate levels and therapeutic efficacy in acute mania with higher levels associated with greater efficacy (809). It is currently unknown what levels of valproate offer optimum efficacy in maintenance treatment as no study to date has systematically assessed the relationship between serum valproate levels and the maintenance efficacy. Therefore, clinician are advised to maintain serum valproate levels within the accepted lab range values during maintenance treatment and carefully monitor patients for emerging mood symptoms and tolerability and adjust the dose of valproate as needed in order to achieve optimum efficacy and tolerability.

Patients who are treated with concurrent carbamazepine or other hepatic enzyme inducing agents should have serum levels of all psychotropic medications monitored, particularly in cases of inadequate or non-response, to determine whether efficacy has been compromised because of reduced serum levels.

Safety and Tolerability of Pharmacotherapy

Safety and tolerability issues, in addition to efficacy data, have been considered when determining recommendations for each phase of illness. The most notable concerns are described below and a summary of their potential impact on treatment selection is included in Table 8.2, as well as in treatment hierarchy tables in Sections 2-4. As medication side effects are an important contributor to medication non-adherence, these potential concerns should be discussed with patients receiving or considering treatment with various agents to help inform decision making.

Weight gain

As described in Section 6, despite normal weight at illness onset (810), it is common for patients with bipolar disorder to become overweight or obese, and several medications used to treat the illness may also exacerbate this effect. The likelihood of medications to cause weight gain should be carefully considered, as this is one of the most frequent treatment related factors of non-adherence; contributing to upwards of 60% of cases (811). The medications most commonly associated with weight gain are olanzapine, clozapine, risperidone, quetiapine, gabapentin, divalproex and lithium; with carbamazepine, lamotrigine, and ziprasidone being the safer or options associated with less weight gain (812). Recent reviews further suggest that asenapine and aripiprazole (longer term use)(813) also may lead to weight gain, but the impact of lurasidone on weight is minimal (814). All patients should be regularly monitored for weight changes.

Gastrointestinal Symptoms

Both lithium and divalproex are commonly associated with nausea, vomiting, and diarrhea- with 35-45% of patient experiencing these side effects (373, 815). For lithium, this is particularly pronounced during treatment initiation, or rapid dose increases (816). Gradual dose titration,

taking the medication at bedtime, taking medications with food, and slow release preparations may reduce nausea and other side effects (817).

Renal toxicity

Lithium has a well recognized potential for renal toxicity, including nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephropathy, and acute tubular necrosis, with NDI reported in 20%- 40% of patients (818-820). Upwards of 70% of patients on chronic lithium treatment will experience polyuria, which can cause impairment in work and daily functioning. This side effect is commonly underreported, unless it is directly inquired about (821). Long term administration (i.e 10-20+ years) is further associated with decreased glomerular filtration rate and chronic kidney disease (822). While long term lithium administration is likely an important risk factor for developing chronic kidney disease, factors which may increase susceptibility include higher plasma lithium levels, multiple daily lithium doses (vs. once daily), concurrent medications (e.g. NSAIDs, ARBs, ACEIs, diuretics), somatic illnesses (e.g. hypertension, diabetes mellitus, coronary artery disease) and age (823, 824). Instances of lithium toxicity will also greatly increase risk of renal dysfunction (825). Lithium use is associated with two-fold risk of chronic kidney disease in older adults (>66 years)(826). While the overall risk for progressive renal failure is low, plasma creatinine concentrations, and ideally estimated glomerular filtration rate (eGFR) for these patients should be measured at least every 3-6 months (802). Since 37% of patients aged >70 have an eGFR <60mL/min/1.73m^2 (827), a strict eGFR cut-off for lithium discontinuation is difficult. The UK NICE guidelines for chronic kidney disease (CKD) recommend nephrologist consultation if there is rapidly declining eGFR (> 5 ml/min/1.73 m^2 in

1 year, or > 10 ml/min/1.73 m^2 within 5 years, if the eGFR falls below 45 in two consecutive readings, or the clinician is concerned (648, 828).

Because of its narrow therapeutic window, acute lithium intoxication is also a complication, that though reversible, can lead to reductions in glomerular filtration rate (829, 830). Drugs which alter renal function and general medical conditions characterized by decreased circulating volume all contribute to increased risk (831).

Haematological

Carbamazepine may be a risk factor for leucopenia (832-834) although this finding is not robust (835). This side effect is generally reversible with dose reduction or discontinuation. There is also some concern about rapidly developing bone marrow suppression resulting from hypersensitivity, particularly in older patients (835, 836).

Clozapine carries the greatest risk for drug-induced changes in white blood cell counts; with approximately 0.18% of patients experiencing changes rated as probably or definitely drug induced (832). All patients started on clozapine should have a baseline haematological profile established and be enrolled in the clozapine monitoring programme that requires regular monitoring of haematological parameters- weekly at first and then every 2-4 weeks later in the course of treatment (837).

Cardiovascular

Lithium can increase the risk of abnormal QT prolongation or T-wave abnormalities ((838) an impact more pronounced with age, as almost 60% of older patients on lithium maintenance therapy having ECG abnormalities (839). Several antipsychotics, including risperidone,

olanzapine, ziprasidone and asenapine are also associated with arrhythmias, QTc prolongation, and other cardiovascular adverse events. Clozapine may increase the risk of several rare but serious events such as dilated cardiomyopathy, myocarditis, and pericarditis. Of the antipsychotics, lurasidone and aripiprazole are considered safe from a cardiac perspective; although aripiprazole may increase the risk for hypotension (814).

Endocrine

There is also a strong link between lithium maintenance treatment and hypothyroidism, which is also associated with increased risk of affective episodes, rapid cycling, and more severe depression (840, 841). As such, routine screening of thyroid function is recommended for all patients on lithium treatment. Since lithium can also cause hyperparathyroidism, routine monitoring for serum calcium is recommended, and if elevated, further investigations should be performed to evaluate for hyperparathyroidisim(842). Hypothyroidism is ordinarily not an indication for lithium cessation in a patient with good response, rather needs thyroid supplementation.

New onset oligomenorrhea or hyperandronism is more common in divalproex users (843). While there are reports of increased incidence of polycystic ovary syndrome (PCOS) in divalproex treatment, a recent meta-analysis did not support this (844). In those who develop PCOS on divalproex, there is evidence from a small sample that discontinuing divalproex results in remission of some of the aspects of PCOS (845).

Hyperprolactinaemia is common with some antipsychotics, and can have short-term and long-term adverse effects. Risperidone, amisulpride and paliperidone are more likely than other

compounds to cause it (846). Hyperprolactinaemia can induce amenhorrea, sexual dysfunction, and galacthorrea, amongst other effects. In the long-term, it can cause gynecomastia and osteoporosis (847). When such effects are seen, it may advisable to reduce the dose or switch to a different medication (848).

Cognition

While many patients experience cognitive impairment, these deficits may be attributable to the disease itself, with more pronounced effects in those with more severe or chronic illness (849). While a small study has led to suggestions that medicated patients who are euthymic do perform similarly to those not receiving treatment (850), other naturalistic trials point toward the potential negative impact of several medications; with the effects of antipsychotics being the most significant (849). Lithium can also lead to impairment in processing speed and memory, which patients may find distressing (851), although recent randomised controlled data suggest lithium is superior to quetiapine in this regard (330). Indeed, the effects of lithium on neurocognition are complex and further research is needed to fully elucidate its neurocognitive impact(852). Anticonvulsants, except for lamotrigine are also linked with subjective cognitive impairment (851). Given the importance of cognition on a patient's function and quality of life further studies are needed in this area.

Sedation

Sedation is a concern for many, and js reported by over half of patients as a reason for treatment non-adherence (811). Divalproex and atypical antipsychotics are most likely to lead to these effects, with 30-50% of patients on atypical antipsychotics experiencing sedation, compared to 8-13% with placebo (165, 215, 853-855) and 21-29% of patients on divalproex (856, 857). This is

not a concern with all antipsychotics, however- quetiapine, clozapine, and olanzapine will generally have higher rates of sedation compared to ziprasidone, risperidone, or aripiprazole (814). Lamotrigine and lithium have both been found to be less likely to cause sedation than divalproex (858, 859).

Neurological, including EPS

Tremor can be a significant cause of frustration for many patients; and is experienced by up to 10% of those treated with lithium or divalproex (670, 860, 861). New onset neurological symptoms in patients on divalproex should raise suspicion of hyperammonemic encephalopathy, which while rare, can be potentially fatal, and hence early detection and discontinuation of valproate is critical to prevent morbidity and mortality (862) Sustained release formulations and dose reductions may limit symptoms (806, 863, 864). While conventional antipsychotics such as haloperidol are often associated with EPS (including pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia) (865); this risk is either absent or low with atypical antipsychotic agents (866, 867). Among the atypical agents, risperidone, aripiprazole, cariprazine, ziprasidone and lurasidone are more likely to cause EPS particularly at higher doses (814). In older patients, impaired swallowing function and dysphagia have also been linked to atypical agents, particularly at higher doses (868, 869).

Although rare, neuroleptic malignant syndrome (NMS) is a potentially life threatening adverse event associated with antipsychotic agents. The risk with atypical agents was considered negligible initially; however, while the risk is very low, several atypical agents have nevertheless been associated with NMS (870). While generally unpredictable, patients are at greatest risk during the initial phase of treatment or change of dosage, intravenous or intramuscular

administration, high dosages or polypharmacy, when physically restrained, dehydrated, or in high ambient temperatures, as well as older age and medical or psychiatric comorbidities. Patients with previous history of NMS and/or a personal or family history of catatonia are also at higher risk (871). Antipsychotics may also impact thermoregulation, with case studies indicating the potential for both heat related illnesses (872) and hypothermia (873)- as such patients should be made aware and monitored for these risks during periods of extreme temperatures..

Dermatological reactions

Approximately 10% of patients being treated with lamotrigine will experience a non-serious rash, with 0.3-1% developing a serious rash such as toxic epidermal necrolysis and Stevens-Johnson syndrome (874), although for those initiated on a dose of 25 mg with a gradual titration increasing the dose by 25mg/ biweekly, the risk of developing serious rash may be as low as 0.02% or 1 in 5000 (875). In some cases, an even lower rate of titration may be used as 12.5 mg/day and the gradually increase per instructions. Carbamazepine is also be associated with increased risk of rash and Stevens-Johnson syndrome, especially in the first 8 weeks of therapy (876); although the baseline risk is extremely low. Similarly, while these can also occur with divalproex, the risk is extremely low. Nevertheless, it is important that patients be informed of these risks and told to report any rash immediately, and these treatments should be discontinued if a serious rash is suspected.

Lithium is also linked with a variety of potentially distressing skin conditions, including acne, psoriasis, eczema, hair loss, hidradenitis suppurativa, nail dystrophy and mucosal lesions, with overall estimates ranging from 3-45% depending on the criteria applied. Most cases can be managed without treatment discontinuation (877).

Metabolic Syndrome, Hyperglycemia, Type 2 Diabetes and Dyslipidemia

As described in Section 6, patients with bipolar disorder are already at elevated risk for these physical illnesses and this risk is further exacerbated by some atypical antipsychotic agents and mood stabilizers. Clozapine and olanzapine are associated with the greatest level of risk, followed by quetiapine (particularly in higher doses) and risperidone, with a more minimal impact by aripiprazole, ziprasidone, asenapine, and lurasidone (814). Lithium and divalproex are also associated with weight gain (794). All patients on atypical antipsychotics should be monitored for changes in blood glucose and lipid profiles as indicated previously in this section, and if disturbances are detected, the atypical antipsychotic should be discontinued if possible and appropriate treatment initiated if necessary.

Fracture risk

Some anticonvulsants, antidepressants, and antipsychotics may decrease bone mineral density and increase the risk of fracture in high risk patients (878, 879). This risk is increased by the presence of mood disorders, as well as known risks for mood disorders such as physical inactivity, smoking and poor diet quality (880). As such, screening for this population may be indicated (881)

Concluding Remarks

The diagnosis and management of bipolar disorders is complex, and effective, evidence based care requires knowledge of current research as well as lessons gained from years of clinical experience. Members of the CANMAT guidelines committee hope this document does an effective job at providing an easy to understand narrative of both, thus aiding both specialists and

primary care providers in delivering evidence based care to bipolar patients. As with previous editions of these guidelines, CANMAT will strive to provide regular updates capturing emerging trends and evaluating new evidence; and readers are encouraged to consult those as they become available to stay up to date in the field.

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References

1. Kusumakar V, Yatham LN, Haslam DRS, Parikh SV, Matte R, Sharma V, et al. The foundations of effective management of bipolar disorder. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 1997; 42:S69-S73.

2. Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disorders. 2006; 8:721-39.

3. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disorders. 2009; 11:225-55.

4. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disorders. 2013; 15:1-44.

5. Diagnostic and statistical manual of mental disorders : DSM-5. Fifth edition. Arlington, VA : American Psychiatric Publishing, [2013] ©2013; 2013.

6. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative. Archives of General Psychiatry. 2011; 68:241-51.

7. McDonald KC, Bulloch AGM, Duffy A, Bresee L, Williams JVA, Lavorato DH, et al. Prevalence of Bipolar I and II Disorder in Canada. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 2015; 60:151-6.

8. Bauer M, Glenn T, Alda M, Andreassen OA, Angelopoulos E, Ardau R, et al. Influence of birth cohort on age of onset cluster analysis in bipolar I disorder. European Psychiatry. 2015; 30.

9. Bellivier F, Etain B, Malafosse A, Henry C, Kahn JP, Elgrabli-Wajsbrot O, et al. Age at onset in bipolar I affective disorder in the USA and Europe. World J Biol Psychiatry. 2014; 15:369-76.

10. Joslyn C, Hawes DJ, Hunt C, Mitchell PB. Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. Bipolar Disorders. 2016; 18:389-403.

11. Sami M, Khan H, Nilforooshan R. Late onset mania as an organic syndrome: A review of case reports in the literature. Journal of Affective Disorders. 188:226-31.

12. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Archives of General Psychiatry. 2002; 59:530-7.

13. Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, et al. Long-term symptomatic status of bipolar I vs. bipolar II disorders. International Journal of Neuropsychopharmacology. 2003; 6:127-37.

14. Judd LL, Schettler PJ, Solomon DA, Maser JD, Coryell W, Endicott J, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. Journal of Affective Disorders. 2008; 108:49-58.

15. Gutierrez-Rojas L, Gurpegui M, Ayuso-Mateos JL, Gutierrez-Ariza JA, Ruiz-Veguilla M, Jurado D. Quality of life in bipolar disorder patients: a comparison with a general population sample. Bipolar Disorders. 2008; 10:625-34.

16. Bonnin CM, Sanchez-Moreno J, Martinez-Aran A, Sole B, Reinares M, Rosa AR, et al. Subthreshold symptoms in bipolar disorder: Impact on neurocognition, quality of life and disability. Journal of Affective Disorders. 2012; 136:650-9.

17. Maina G, Albert U, Bellodi L, Colombo C, Faravelli C, Monteleone P, et al. Health-related quality of life in euthymic bipolar disorder patients: Differences between bipolar I and II subtypes. Journal of Clinical Psychiatry. 2007; 68:207-12.

18. Michalak EE, Murray G, Crest BD. Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. Bipolar Disorders. 2010; 12:727-40.

19. Van Rheenen TE, Rossell SL. Objective and subjective psychosocial functioning in bipolar disorder: An investigation of the relative importance of neurocognition, social cognition and emotion regulation. Journal of Affective Disorders. 2014; 162:134-41.

20. Rosa AR, Gonzalez-Ortega I, Gonzalez-Pinto A, Echeburua E, Comes M, Martinez-Aran A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatrica Scandinavica. 2012; 125:335-41.

21. Oldis M, Murray G, Macneil CA, Hasty MK, Daglas R, Berk M, et al. Trajectory and predictors of quality of life in first episode psychotic mania. Journal of Affective Disorders. 2016; 195:148-55.

22. Michalak EE, Torres IJ, Bond DJ, Lam RW, Yatham LN. The relationship between clinical outcomes and quality of life in first-episode mania: a longitudinal analysis. Bipolar Disorders. 2013; 15:188-98.

23. Simonsen C, Sundet K, Vaskinn A, Ueland T, Romm KL, Hellvin T, et al. Psychosocial function in schizophrenia and bipolar disorder: Relationship to neurocognition and clinical symptoms. Journal of the International Neuropsychological Society. 2010; 16:771-83.

24. Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disorders. 2016; 18:440-50.

25. Gore FM, Bloem PJN, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10-24 years: a systematic analysis. Lancet. 2011; 377:2093-102.

26. Jin HJ, McCrone P. Cost-of-Illness Studies for Bipolar Disorder: Systematic Review of International Studies. Pharmacoeconomics. 2015; 33:341-53.

27. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015; 49:1087-206.

28. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. Acta Psychiatr Scand. 2017; 135:51-64.

29. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand. 2016; 134:91-103.

30. Berk M, Post R, Ratheesh A, Gliddon E, Singh A, Vieta E, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry. 2017; 16:236-44.

31. Kapczinski F, Magalhaes PV, Balanza-Martinez V, Dias VV, Frangou S, Gama CS, et al. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. Acta Psychiatr Scand. 2014; 130:354-63.

32. Alda M, Kapczinski F. Staging model raises fundamental questions about the nature of bipolar disorder. J Psychiatry Neurosci. 2016; 41:291-3.

33. Duffy A, Goodday S, Passos IC, Kapczinski F. Changing the bipolar illness trajectory. Lancet Psychiatry. 2017; 4:11-3.

34. Hirschfeld RMA, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: How far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. Journal of Clinical Psychiatry. 2003; 64:161-74.

35. Scott J, Leboyer M. Consequences of delayed diagnosis of bipolar disorders. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique. 2011; 37:S173-S5.

36. Knezevic V, Nedic A. Influence of misdiagnosis on the course of bipolar disorder. European Review for Medical and Pharmacological Sciences. 2013; 17:1542-5.

37. Altamura AC, Buoli M, Caldiroli A, Caron L, Melter CC, Dobrea C, et al. Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: A naturalistic study. Journal of Affective Disorders. 2015; 182:70-5.

38. Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RMA. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disorders. 2008; 10:144-52.

39. Schaffer A, Cairney J, Veldhuizen S, Kurdyak P, Cheung A, Levitt A. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. Journal of Affective Disorders. 2010; 125:103-10.

40. Gonzalez-Pinto A, Gutierrez M, Mosquera F, Ballesteros J, Lopez P, Ezcurra J, et al. First episode in bipolar disorder: misdiagnosis and psychotic symptoms. Journal of Affective Disorders. 1998; 50:41-4.

41. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry. 2008; 69:935-40.

42. Ghouse AA, Sanches M, Zunta-Soares G, Swann AC, Soares JC. Overdiagnosis of Bipolar Disorder: A Critical Analysis of the Literature. Scientific World Journal. 2013:5.

43. Cyprien F, Guillaume S, Jaussent I, Lopez-Castroman J, Mercier G, Olie E, et al. Impact of axis-I comorbidity and suicidal behavior disorders on sensitivity and specificity of the Mood Disorder Questionnaire in complex depressed inpatients. Compr Psychiatry. 2014; 55:876-82.

44. Meyer F, Meyer TD. The misdiagnosis of bipolar disorder as a psychotic disorder: Some of its causes and their influence on therapy. Journal of Affective Disorders. 2009; 112:174-83.

45. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Archives of General Psychiatry. 2007; 64:543-52.

46. Webb RT, Lichtenstein P, Larsson H, Geddes JR, Fazel S. Suicide, hospital-presenting suicide attempts, and criminality in bipolar disorder: examination of risk for multiple adverse outcomes. J Clin Psychiatry. 2014; 75:e809-16.

47. Schaffer A, Isometsa ET, Tondo L, Moreno DH, Sinyor M, Kessing LV, et al. Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Australian and New Zealand Journal of Psychiatry. 2015; 49:785-802.

48. Tondo L, Lepri B, Baldessarini RJ. Suicidal risks among 2826 sardinian major affective disorder patients. Acta Psychiatrica Scandinavica. 2007; 116:419-28.

49. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. Journal of the Royal Society of Medicine. 2014; 107:194-204.

50. Schaffer A, Isometsa ET, Azorin JM, Cassidy F, Goldstein T, Rihmer Z, et al. A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: Part II of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Australian and New Zealand Journal of Psychiatry. 2015; 49:1006-20.

51. Marangell LB, Bauer MS, Dennehy EB, Wisniewski SR, Allen MH, Miklowitz DJ, et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. Bipolar Disord. 2006; 8:566-75.

52. Keks NA, Hill C, Sundram S, Graham A, Bellingham K, Dean B, et al. Evaluation of treatment in 35 cases of bipolar suicide. Australian and New Zealand Journal of Psychiatry. 2009; 43:503-8.

53. Carter G, Milner A, McGill K, Pirkis J, Kapur N, Spittal MJ. Predicting suicidal behaviours using clinical instruments: systematic review and meta-analysis of positive predictive values for risk scales. The British Journal of Psychiatry. 2017; 210:387.

54. Smith KA, Cipriani A. Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. Bipolar Disord. 2017; 19:575-86.

55. Schaffer A, Sinyor M, Howlett A, Cheung A. Suicide by overdose in a bipolar disorder cohort. Bipolar Disorders. 2012; 14:122-.

56. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? Effective clinical practice : ECP. 1998; 1:2-4.

57. Parikh SV, Kennedy SH. Integration of Patient, Provider, and Systems Treatment Approaches in Bipolar Disorder: Where Evidence Meets Practice Reality. West Sussex, England: John Wiley & Sons Ltd; 2004.

58. Consensus statement on improving mental health transitions. . Institute of Health Economics. Alberta, 2014.

59. Sylvia LG, Hay A, Ostacher MJ, Miklowitz DJ, Nierenberg AA, Thase ME, et al. Association Between Therapeutic Alliance, Care Satisfaction, and Pharmacological Adherence in Bipolar Disorder. Journal of Clinical Psychopharmacology. 2013; 33:343-50.

60. Strauss JL, Johnson SL. Role of treatment alliance in the clinical management of bipolar disorder: Stronger alliances prospectively predict fewer manic symptoms. Psychiatry Research. 2006; 145:215-23.

61. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012; 27:1361-7.

62. Drake RE, Cimpean D, Torrey WC. Shared decision making in mental health: prospects for personalized medicine. Dialogues Clin Neurosci. 2009; 11:455-63.

63. Kessing LV, Hansen HV, Hvenegaard A, Christensen EM, Dam H, Gluud C, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. Br J Psychiatry. 2013; 202:212-9.

64. Denicoff KD, Ali SO, Sollinger AB, Smith-Jackson EE, Leverich GS, Post RM. Utility of the daily prospective National Institute of Mental Health Life-Chart Method (NIMH-LCM-p) ratings in clinical trials of bipolar disorder. Depression and Anxiety. 2002; 15:1-9.

65. van Bendegem MA, van den Heuvel S, Kramer LJ, Goossens PJJ. Attitudes of Patients With Bipolar Disorder Toward the Life Chart Methodology: A Phenomenological Study. Journal of the American Psychiatric Nurses Association. 2014; 20:376-85.

66. Lieberman DZ, Kelly TF, Douglas L, Goodwin FK. A randomized comparison of online and paper mood charts for people with bipolar disorder. Journal of Affective Disorders. 2010; 124:85-9.

67. Hidalgo-Mazzei D, Mateu A, Reinares M, Undurraga J, Bonnin Cdel M, Sanchez-Moreno J, et al. Self-monitoring and psychoeducation in bipolar patients with a smart-phone application (SIMPLe) project: design, development and studies protocols. BMC Psychiatry. 2015; 15:52.

68. Hidalgo-Mazzei D, Mateu A, Reinares M, Matic A, Vieta E, Colom F. Internet-based psychological interventions for bipolar disorder: Review of the present and insights into the future. J Affect Disord. 2015; 188:1-13.

69. Hidalgo-Mazzei D, Mateu A, Reinares M, Murru A, Bonnin CD, Varo C, et al. Psychoeducation in bipolar disorder with a SIMPLe smartphone application: Feasibility, acceptability and satisfaction. Journal of Affective Disorders. 2016; 200:58-66.

70. Hawke LD, Parikh SV, Michalak EE. Stigma and bipolar disorder: A review of the literature. Journal of Affective Disorders. 2013; 150:181-91.

71. Yanos PT, Lucksted A, Drapalski AL, Roe D, Lysaker P. Interventions targeting mental health self-stigma: A review and comparison. Psychiatr Rehabil J. 2015; 38:171-8.

72. Reinares M, Sanchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: What, for whom, and when. Journal of Affective Disorders. 2014; 156:46-55.

73. Murray G, Leitan ND, Thomas N, Michalak EE, Johnson SL, Jones S, et al. Towards recovery-oriented psychosocial interventions for bipolar disorder: Quality of life outcomes, stage-sensitive treatments, and mindfulness mechanisms. Clin Psychol Rev. 2017; 52:148-63.

74. Smith D, Jones I, Simpson S. Psychoeducation for bipolar disorder. Advances in Psychiatric Treatment. 2010; 16:147.

75. Salcedo S, Gold AK, Sheikh S, Marcus PH, Nierenberg AA, Deckersbach T, et al. Empirically supported psychosocial interventions for bipolar disorder: Current state of the research. Journal of Affective Disorders. 2016; 201:203-14.

76. Norcross JC, Wampold BE. Evidence-based therapy relationships: research conclusions and clinical practices. Psychotherapy (Chic). 2011; 48:98-102.

77. Colom, F, E V. Psychoeducation

manual for bipolar disorders. Cambridge University Press; 2006.

78. Bauer, M, L M. Structured

Group Psychotherapy for Bipolar Disorder. The Life Goals Program 2ed.: Springer; 2003.

79. Oud M, Mayo-Wilson E, Braidwood R, Schulte P, Jones SH, Morriss R, et al. Psychological interventions for adults with bipolar disorder: systematic review and meta-analysis. British Journal of Psychiatry. 2016; 208:213-+.

80. Bond K, Anderson IM. Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disorders. 2015; 17:349-62.

81. Parikh SV, Zaretsky A, Beaulieu S, Yatham LN, Young LT, Patelis-Siotis I, et al. A Randomized Controlled Trial of Psychoeducation or Cognitive-Behavioral Therapy in Bipolar

Disorder: A Canadian Network for Mood and Anxiety Treatments (CANMAT) Study. Journal of Clinical Psychiatry. 2012; 73:803-10.

82. Parikh SV, Hawke LD, Zaretsky A, Beaulieu S, Patelis-Siotis I, Macqueen G, et al. Psychosocial interventions for bipolar disorder and coping style modification: similar clinical outcomes, similar mechanisms? Can J Psychiatry. 2013; 58:482-6.

83. Parikh SV, Hawke LD, Velyvis V, Zaretsky A, Beaulieu S, Patelis-Siotis I, et al. Combined treatment: impact of optimal psychotherapy and medication in bipolar disorder. Bipolar Disorders. 2015; 17:86-96.

84. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: Results from a 9-month Randomized controlled trial. American Journal of Psychiatry. 2007; 164:1340-7.

85. Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder - Outcome of the first year. Archives of General Psychiatry. 2003; 60:145-52.

86. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders - Randomised controlled trial. British Journal of Psychiatry. 2006; 188:313-20.

87. Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychological Medicine. 2010; 40:9-24.

88. Ye BY, Jiang ZY, Li X, Cao B, Cao LP, Lin Y, et al. Effectiveness of cognitive behavioral therapy in treating bipolar disorder: An updated meta-analysis with randomized controlled trials. Psychiatry Clin Neurosci. 2016; 70:351-61.

89. Szentagotai A, David D. The Efficacy of Cognitive-Behavioral Therapy in Bipolar Disorder: A Quantitative Meta-Analysis. Journal of Clinical Psychiatry. 2010; 71:66-72.

90. Jones SH, Smith G, Mulligan LD, Lobban F, Law H, Dunn G, et al. Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial. Br J Psychiatry. 2015; 206:58-66.

91. Gomes BC, Abreu LN, Brietzke E, Caetano SC, Kleinman A, Nery FG, et al. A Randomized Controlled Trial of Cognitive Behavioral Group Therapy for Bipolar Disorder. Psychotherapy and Psychosomatics. 2011; 80:144-50.

92. Cuijpers P. Are all psychotherapies equally effective in the treatment of adult depression? The lack of statistical power of comparative outcome studies. Evid Based Ment Health. 2016; 19:39-42.

93. Miklowitz DJ, Goldstein MJ. Bipolar Disorder: Family-Focused Treatment Approach, A. Guilford Publications; 1997.

94. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, et al. Psychosocial treatments for bipolar depression - A 1-year randomized trial from the systematic treatment enhancement program. Archives of General Psychiatry. 2007; 64:419-27.

95. Miklowitz DJ, Chung B. Family-Focused Therapy for Bipolar Disorder: Reflections on 30 Years of Research. Fam Process. 2016; 55:483-99.

96. McMahon K, Herr NR, Zerubavel N, Hoertel N, Neacsiu AD. Psychotherapeutic Treatment of Bipolar Depression. Psychiatric Clinics of North America. 2016; 39:35-+.

97. Haynes PL, Gengler D, Kelly M. Social Rhythm Therapies for Mood Disorders: an Update. Current Psychiatry Reports. 2016; 18:75.

98. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archives of General Psychiatry. 2005; 62:996-1004.

99. Inder ML, Crowe MT, Luty SE, Carter JD, Moor S, Frampton CM, et al. Randomized, controlled trial of Interpersonal and Social Rhythm Therapy for young people with bipolar disorder. Bipolar Disorders. 2015; 17:128-38.

100. Swartz HA, Levenson JC, Frank E. Psychotherapy for Bipolar II Disorder: The Role of Interpersonal and Social Rhythm Therapy. Prof Psychol Res Pr. 2012; 43:145-53.

101. Bouwkamp CG, de Kruiff ME, van Troost TM, Snippe D, Blom MJ, de Winter RF, et al. Interpersonal and social rhythm group therapy for patients with bipolar disorder. Int J Group Psychother. 2013; 63:97-115.

102. Hoberg AA, Vickers KS, Ericksen J, Bauer G, Kung S, Stone R, et al. Feasibility evaluation of an interpersonal and social rhythm therapy group delivery model. Arch Psychiatr Nurs. 2013; 27:271-7.

103. Swartz HA, Frank E, O'Toole K, Newman N, Kiderman H, Carlson S, et al. Implementing interpersonal and social rhythm therapy for mood disorders across a continuum of care. Psychiatr Serv. 2011; 62:1377-80.

104. Parikh, V. S, Velyvis V. Psychosocial

interventions in bipolar disorder: Theories, mechanisms and key clinical trials. Cambridge University Press; 2010.

105. Proudfoot JG, Jayawant A, Whitton AE, Parker G, Manicavasagar V, Smith M, et al. Mechanisms underpinning effective peer support: a qualitative analysis of interactions between expert peers and patients newly-diagnosed with bipolar disorder. Bmc Psychiatry. 2012; 12.

106. Lloyd-Evans B, Mayo-Wilson E, Harrison B, Istead H, Brown E, Pilling S, et al. A systematic review and meta-analysis of randomised controlled trials of peer support for people with severe mental illness. Bmc Psychiatry. 2014; 14:12.

107. Chinman M, George P, Dougherty RH, Daniels AS, Ghose SS, Swift A, et al. Peer support services for individuals with serious mental illnesses: assessing the evidence. Psychiatr Serv. 2014; 65:429-41.

108. Mahlke CI, Priebe S, Heumann K, Daubmann A, Wegscheider K, Bock T. Effectiveness of one-to-one peer support for patients with severe mental illness - a randomised controlled trial. Eur Psychiatry. 2017; 42:103-10.

109. Cabassa LJ, Camacho D, Velez-Grau CM, Stefancic A. Peer-based health interventions for people with serious mental illness: A systematic literature review. J Psychiatr Res. 2017; 84:80-9.

110. Morriss R, Lobban F, Riste L, Davies L, Holland F, Long R, et al. Clinical effectiveness and acceptability of structured group psychoeducation versus optimised unstructured peer support for patients with remitted bipolar disorder (PARADES): a pragmatic, multicentre, observer-blind, randomised controlled superiority trial. Lancet Psychiatry. 2016; 3:1029-38.

111. Naslund JA, Grande SW, Aschbrenner KA, Elwyn G. Naturally occurring peer support through social media: the experiences of individuals with severe mental illness using YouTube. PLoS One. 2014; 9:e110171.

112. Naslund JA, Aschbrenner KA, Bartels SJ. How people with serious mental illness use smartphones, mobile apps, and social media. Psychiatr Rehabil J. 2016; 39:364-7.

113. Reinares M, Colom F, Sanchez-Moreno J, Torrent C, Martinez-Aran A, Comes M, et al. Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial. Bipolar Disorders. 2008; 10:511-9.

114. Berk L, Berk M, Dodd S, Kelly C, Cvetkovski S, Jorm AF. Evaluation of the acceptability and usefulness of an information website for caregivers of people with bipolar disorder. BMC Med. 2013; 11:162.

115. Perich T, Manicavasagar V, Mitchell PB, Ball JR, Hadzi-Pavlovic D. A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. Acta Psychiatrica Scandinavica. 2013; 127:333-43.

116. Ives-Deliperi VL, Howells F, Stein DJ, Meintjes EM, Horn N. The effects of mindfulness-based cognitive therapy in patients with bipolar disorder: a controlled functional MRI investigation. J Affect Disord. 2013; 150:1152-7.

117. Torrent C, Bonnin Cdel M, Martinez-Aran A, Valle J, Amann BL, Gonzalez-Pinto A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am J Psychiatry. 2013; 170:852-9.

118. Sole B, Jimenez E, Torrent C, Reinares M, Del Mar Bonnin C, Torres I, et al. Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. Int J Neuropsychopharmacol. 2017.

119. Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, et al. Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): Efficacy of a Randomized Controlled Trial of Cognitive Remediation Versus Active Control. J Clin Psychiatry. 2017.

120. Parikh SV, Huniewicz P. E-health: an overview of the uses of the Internet, social media, apps, and websites for mood disorders. Curr Opin Psychiatry. 2015; 28:13-7.

121. Leitan ND, Michalak EE, Berk L, Berk M, Murray G. Optimizing delivery of recovery-oriented online self-management strategies for bipolar disorder: a review. Bipolar Disorders. 2015; 17:115-27.

122. Hidalgo-Mazzei D, Mateu A, Reinares M, Matic A, Vieta E, Colom F. Internet-based psychological interventions for bipolar disorder: Review of the present and insights into the future. Journal of Affective Disorders. 2015; 188:1-13.

123. Young AH, Eberhard J. Evaluating depressive symptoms in mania: a naturalistic study of patients with bipolar disorder. Neuropsychiatric Disease and Treatment. 2015; 11:1137-43.

124. Dundar Y, Greenhalgh J, Richardson M, Dwan K. Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis. Human Psychopharmacology-Clinical and Experimental. 2016; 31:268-85.

125. Garriga M, Pacchiarotti I, Kasper S, Zeller SL, Allen MH, Vazquez G, et al. Assessment and management of agitation in psychiatry: Expert consensus. World Journal of Biological Psychiatry. 2016; 17:86-128.

126. Zimbroff DL, Marcus RN, Manos G, Stock E, McQuade RD, Auby P, et al. Management of acute agitation in patients with bipolar disorder - Efficacy and safety of intramuscular aripiprazole. Journal of Clinical Psychopharmacology. 2007; 27:171-6.

127. De Filippis S, Cuomo I, Lionetto L, Janiri D, Simmaco M, Caloro M, et al. Intramuscular aripiprazole in the acute management of psychomotor agitation. Pharmacotherapy. 2013; 33:603-14.

128. Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. Journal of Clinical Psychopharmacology. 2001; 21:389-97.

129. Citrome L. Inhaled loxapine for agitation revisited: focus on effect sizes from 2 Phase III randomised controlled trials in persons with schizophrenia or bipolar disorder. International journal of clinical practice. 2012; 66:318-25.

130. Kwentus J, Riesenberg RA, Marandi M, Manning RA, Allen MH, Fishman RS, et al. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. Bipolar disorders. 2012; 14:31-40.

131. Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P. Calming versus sedative effects of intramuscular olanzapine in agitated patients. American Journal of Emergency Medicine. 2003; 21:192-8.

132. Baldacara L, Sanches M, Cordeiro DC, Jackoswski AP. Rapid tranquilization for agitated patients in emergency psychiatric rooms: a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. Revista Brasileira De Psiquiatria. 2011; 33:30-9.

133. Perrin E, Anand E, Dyachkova Y, Wagner T, Frediani S, Ballerini A. A prospective, observational study of the safety and effectiveness of intramuscular psychotropic treatment in acutely agitated patients with schizophrenia and bipolar mania. European psychiatry : the journal of the Association of European Psychiatrists. 2012; 27:234-9.

134. Kishi T, Matsunaga S, Iwata N. Intramuscular olanzapine for agitated patients: A systematic review and meta-analysis of randomized controlled trials. Journal of psychiatric research. 2015; 68:198-209.

135. Pratts M, Citrome L, Grant W, Leso L, Opler LA. A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. Acta Psychiatrica Scandinavica. 2014; 130:61-8.

136. Lenox RH, Newhouse PA, Creelman WL, Whitaker TM. Adjunctive treatment of manic agitation with lorazepam versus haloperidol: a double-blind study. The Journal of clinical psychiatry. 1992; 53:47-52.

137. Lim HK, Kim JJ, Pae CU, Lee CU, Lee C, Paik IH. Comparison of risperidone orodispersible tablet and intramuscular haloperidol in the treatment of acute psychotic agitation: a randomized open, prospective study. Neuropsychobiology. 2010; 62:81-6.

138. Mantovani C, Labate CM, Sponholz A, Jr., de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, et al. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. Journal of clinical psychopharmacology. 2013; 33:306-12.

139. Raveendran NS, Tharyan P, Alexander J, Adams CE. Rapid tranquillisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine. BMJ (Clinical research ed). 2007; 335:865.

140. Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. The Journal of clinical psychiatry. 2001; 62:12-8.

141. Currier GW, Chou JC, Feifel D, Bossie CA, Turkoz I, Mahmoud RA, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. The Journal of clinical psychiatry. 2004; 65:386-94.

142. Villari V, Rocca P, Fonzo V, Montemagni C, Pandullo P, Bogetto F. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. Progress in neuro-psychopharmacology & biological psychiatry. 2008; 32:405-13.

143. Ketter TA. Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. J Clin Psychiatry. 2008; 69 Suppl 5:9-15.

144. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychological Medicine. 2015; 45:299-317.

145. Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa T. Mood Stabilizers and Antipsychotics for Acute Mania: A Systematic Review and Meta-Analysis of Combination/Augmentation Therapy Versus Monotherapy. Cns Drugs. 2014; 28:989-1003.

146. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. Cns Drugs. 2006; 20:29-42.

147. Geoffroy PA, Etain B, Henry C, Bellivier F. Combination therapy for manic phases: a critical review of a common practice. CNS Neurosci Ther. 2012; 18:957-64.

148. Bourin MS, Severus E, Schronen JP, Gass P, Szamosi J, Eriksson H, et al. Lithium as add-on to quetiapine XR in adult patients with acute mania: a 6-week, multicenter, double-blind, randomized, placebo-controlled study. Int J Bipolar Disord. 2014; 2:14.

149. Reischies FM, Hartikainen J, Berghoefer A. Initial lithium and valproate combination therapy in acute mania. Neuropsychobiology. 2002; 46:22-7.

150. Reischies FM, Hartikainen J, Berghofer AM. Initial triple therapy of acute mania, adding lithium and valproate to neuroleptics. Pharmacopsychiatry. 2002; 35:244-6.

151. Sharma V, Persad E, Mazmanian D, Karunaratne K. TREATMENT OF RAPID CYCLING BIPOLAR DISORDER WITH COMBINATION THERAPY OF VALPROATE AND LITHIUM. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 1993; 38:137-9.

152. Granneman GR, Schneck DW, Cavanaugh JH, Witt GF. Pharmacokinetic interactions and side effects resulting from concomitant administration of lithium and divalproex sodium. Journal of Clinical Psychiatry. 1996; 57:204-6.

153. Sikdar S, Kulhara P, Avasthi A, Singh H. COMBINED CHLORPROMAZINE AND ELECTROCONVULSIVE-THERAPY IN MANIA. British Journal of Psychiatry. 1994; 164:806-10.

154. Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, et al. Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry. 1988; 45:727-32.

155. Mohan TSP, Tharyan P, Alexander J, Raveendran NS. Effects of stimulus intensity on the efficacy and safety of twice-weekly, bilateral electroconvulsive therapy (ECT) combined with antipsychotics in acute mania: a randomised controlled trial. Bipolar Disorders. 2009; 11:126-34.

156. Hiremani RM, Thirthalli J, Tharayil BS, Gangadhar BN. Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. Bipolar Disorders. 2008; 10:701-7.

157. Barekatain M, Jahangard L, Haghighi M, Ranjkesh F. Bifrontal versus bitemporal electroconvulsive therapy in severe manic patients. Journal of Ect. 2008; 24:199-202.

158. Prien RF, Caffey EM, Klett CJ. COMPARISON OF LITHIUM CARBONATE AND CHLORPROMAZINE IN TREATMENT OF MANIA - REPORT OF VETERANS-ADMINISTRATION AND NATIONAL-INSTITUTE OF MENTAL HEALTH COLLABORATIVE STUDY GROUP. Archives of General Psychiatry. 1972; 26:146-&.

159. Curtin F, Schulz P. Clonazepam and lorazepam in acute mania: a Bayesian meta-analysis. Journal of Affective Disorders. 2004; 78:201-8.

160. Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, et al. Clozapine for treatment-refractory mania. American Journal of Psychiatry. 1996; 153:759-64.

161. Kimmel SE, Calabrese JR, Woyshville MJ, Meltzer HY. CLOZAPINE IN TREATMENT-REFRACTORY MOOD DISORDERS. Journal of Clinical Psychiatry. 1994; 55:91-3.

162. Barbini B, Scherillo P, Benedetti F, Crespi G, Colombo C, Smeraldi E. Response to clozapine in acute mania is more rapid than that of chlorpromazine. International Clinical Psychopharmacology. 1997; 12:109-12.

163. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. American Journal of Psychiatry. 1999; 156:1164-9.

164. Juruena MF, Ottoni GL, Machado-Vieira R, Carneiro RM, Weingarthner N, Marquardt AR, et al. Bipolar I and II disorder residual symptoms: Oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2009; 33:94-9.

165. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: A double-blind, placebo-controlled comparison of efficacy and safety. American Journal of Psychiatry. 2002; 159:1146-54.

166. Talaei A, Pourgholami M, Khatibi-Moghadam H, Faridhosseini F, Farhoudi F, Askari-Noghani A, et al. Tamoxifen: A Protein Kinase C Inhibitor to Treat Mania A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. Journal of Clinical Psychopharmacology. 2016; 36:272-5.

167. Praharaj SK, Ram D, Arora M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: A randomized sham controlled study. Journal of Affective Disorders. 2009; 117:146-50.

168. Weiser M, Burshtein S, Gershon AA, Marian G, Vlad N, Grecu IG, et al. Allopurinol for mania: a randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. Bipolar Disorders. 2014; 16:441-7.

169. Grunze H, Kotlik E, Costa R, Nunes T, Falcao A, Almeida L, et al. Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: Experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. Journal of Affective Disorders. 2015; 174:70-82.

170. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for Bipolar Disorder: Meta-Analyses of Use in Mania and Bipolar Depression. Journal of Clinical Psychiatry. 2012; 73:81-6.

171. Bersudsky Y, Applebaum J, Gaiduk Y, Sharony L, Mishory A, Podberezsky A, et al. Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial. Bipolar Disord. 2010; 12:376-82.

172. Weiser M, Levi L, Levine SZ, Bialer M, Shekh-Ahmad T, Matei V, et al. A randomized, double-blind, placebo- and risperidone-controlled study on valnoctamide for acute mania. Bipolar Disord. 2017; 19:285-94.

173. Dauphinais D, Knable M, Rosenthal J, Polanski M, Rosenthal N. Zonisamide for Bipolar Disorder, Mania or Mixed States: A Randomized, Double Blind, Placebo-Controlled Adjunctive Trial. Psychopharmacology Bulletin. 2011; 44:5-17.

174. Tohen M, Vieta E, Goodwin GM, Sun B, Amsterdam JD, Banov M, et al. Olanzapine Versus Divalproex Versus Placebo in the Treatment of Mild to Moderate Mania: A Randomized, 12-Week, Double-Blind Study. Journal of Clinical Psychiatry. 2008; 69:1776-89.

175. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania - International, double-blind, randomised controlled trial. British Journal of Psychiatry. 2003; 182:141-7.

176. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disorders. 2011; 13:454-65.

177. Behzadi AH, Omrani Z, Chalian M, Asadi S, Ghadiri M. Folic acid efficacy as an alternative drug added to sodium valproate in the treatment of acute phase of mania in bipolar disorder: a double-blind randomized controlled trial. Acta Psychiatrica Scandinavica. 2009; 120:441-5.

178. Chouinard G, Young SN, Annable L. A controlled clinical trial of l-tryptophan in acute mania. Biological Psychiatry. 20:546-57.

179. Kulkarni J, Berk M, Wang W, Mu L, Scarr E, Van Rheenen TE, et al. A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. Psychoneuroendocrinology. 2014; 43:52-61.

180. Kulkarni J, Garland KA, Scaffidi A, Headey B, Anderson R, de Castella A, et al. A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder. Psychoneuroendocrinology. 2006; 31:543-7.

181. Keck PE, Jr., Hsu H-A, Papadakis K, Russo J, Jr. Memantine Efficacy and Safety in Patients With Acute Mania Associated With Bipolar I Disorder: A Pilot Evaluation. Clinical Neuropharmacology. 2009; 32:199-204.

182. Schaffer A, Levitt AJ, Joffe RT. Mexiletine in treatment-resistant bipolar disorder. Journal of Affective Disorders. 2000; 57:249-53.

183. Bersani G. Levetiracetam in bipolar spectrum disorders: first evidence of efficacy in an open, add- on study. Human Psychopharmacology-Clinical and Experimental. 2004; 19:355-6.

184. Mishory A, Yaroslavsky Y, Bersudsky Y, Belmaker RH. Phenytoin as an antimanic anticonvulsant: A controlled study. American Journal of Psychiatry. 2000; 157:463-5.

185. Henriksen TEG, Skrede S, Fasmer OB, Schoeyen H, Leskauskaite I, Bjorke-Bertheussen J, et al. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disorders. 2016; 18:221-32.

186. Janicak PG, Sharma RP, Pandey G, Davis JM. Verapamil for the treatment of acute mania: A double-blind, placebo-controlled trial. American Journal of Psychiatry. 1998; 155:972-3.

187. Mallinger AG, Thase ME, Haskett R, Buttenfield J, Luckenbaugh DA, Frank E, et al. Verapamil augmentation of lithium treatment improves outcome in mania unresponsive to lithium alone: preliminary findings and a discussion of therapeutic mechanisms. Bipolar Disord. 2008; 10:856-66.

188. Wisner KL, Peindl KS, Perel JM, Hanusa BH, Piontek CM, Baab S. Verapamil treatment for women with bipolar disorder. Biol Psychiatry. 2002; 51:745-52.

189. Kusumakar V, Yatham LN, Haslam DRS, Parikh SV, Matte R, Silverstone PH, et al. Treatment of mania, mixed state, and rapid cycling. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 1997; 42:S79-S86.

190. Bowden CL. Key treatment studies of lithium in manic-depressive illness: Efficacy and side effects. Journal of Clinical Psychiatry. 1998; 59:13-9.

191. Bowden CL. Clinical correlates of therapeutic response in bipolar disorder. Journal of Affective Disorders. 2001; 67:257-65.

192. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, et al. Depression during mania - Treatment response to lithium or divalproex. Archives of General Psychiatry. 1997; 54:37-42.

193. Swann AC. Predicting therapeutic response in acute manic episodes: data from controlled studies with divalproex. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique. 2001; 27:277-9.

194. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. Neuropsychopharmacology. 2002; 26:530-6.

195. Keck PE, McElroy SL, Strakowski SM. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. Journal of Clinical Psychiatry. 1998; 59:74-81.

196. McIntyre RS, Yoon J. Efficacy of antimanic treatments in mixed states. Bipolar Disorders. 2012; 14:22-36.

197. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disorders. 2005; 7:5-69.

198. Gonzalez-Pinto A, Galan J, Martin-Carrasco M, Ballesteros J, Maurino J, Vieta E. Anxiety as a marker of severity in acute mania. Acta Psychiatrica Scandinavica. 2012; 126:351-5.

199. Feske U, Frank E, Mallinger AG, Houck PR, Fagiolini A, Shear MK, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. American Journal of Psychiatry. 2000; 157:956-62.

200. Rakofsky JJ, Dunlop BW. Treating Nonspecific Anxiety and Anxiety Disorders in Patients With Bipolar Disorder: A Review. Journal of Clinical Psychiatry. 2011; 72:81-90.

201. Vieta E, Morralla C. Prevalence of mixed mania using 3 definitions. Journal of Affective Disorders. 2010; 125:61-73.

202. Reinares M, Bonnin CDM, Hidalgo-Mazzei D, Undurraga J, Mur M, Nieto E, et al. Making sense of DSM-5 mania with depressive features. Australian and New Zealand Journal of Psychiatry. 2015; 49:540-9.

203. Castle DJ. Bipolar mixed states: still mixed up? Current Opinion in Psychiatry. 2014; 27:38-42.

204. Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN. Treatment of mixed bipolar states. International Journal of Neuropsychopharmacology. 2012; 15:1015-26.

205. Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: A meta-analysis of placebo-controlled trials. Journal of Affective Disorders. 2013; 150:408-14.

206. Cuomo A, Nikolova VL, Yalin N, Arnone D, Fagiolini A, Young AH. Pharmacological treatment of mixed states. CNS Spectr. 2017; 22:186-95.

207. Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. Journal of Affective Disorders. 2001; 67:79-88.

208. Swann AC, Daniel DG, Kochan LD, Wozniak PJ, Calabrese JR. Psychosis in mania: Specificity of its role in severity and treatment response. Journal of Clinical Psychiatry. 2004; 65:825-9.

209. Toni C, Perugi G, Mata B, Madaro D, Maremmani I, Akiskal HS. Is mood-incongruent manic psychosis a distinct subtype? European Archives of Psychiatry and Clinical Neuroscience. 2001; 251:12-7.

210. Tohen M, Tsuang MT, Goodwin DC. PREDICTION OF OUTCOME IN MANIA BY MOOD-CONGRUENT OR MOOD-INCONGRUENT PSYCHOTIC FEATURES. American Journal of Psychiatry. 1992; 149:1580-4.

211. Strakowski SM, Williams JR, Sax KW, Fleck DE, DelBello MP, Bourne ML. Is impaired outcome following a first manic episode due to mood-incongruent psychosis? Journal of Affective Disorders. 2000; 61:87-94.

212. Fennig S, Bromet EJ, Karant MT, Ram R, Jandorf L. Mood-congruent versus mood-incongruent psychotic symptoms in first-admission patients with affective disorder. Journal of Affective Disorders. 1996; 37:23-9.

213. Carlson GA, Kotov R, Chang SW, Ruggero C, Bromet EJ. Early determinants of four-year clinical outcomes in bipolar disorder with psychosis. Bipolar Disorders. 2012; 14:19-30.

214. Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. European Neuropsychopharmacology. 2005; 15:75-84.

215. Hirschfeld RMA, Keck PE, Kramer M, Karcher K, Canuso C, Eerdekens M, et al. Rapid Antimanic effect of risperidone monotherapy: A 3-week multicenter, double-blind, placebo-controlled trial. American Journal of Psychiatry. 2004; 161:1057-65.

216. Valenti M, Pacchiarotti I, Undurraga J, Bonnin CM, Popovic D, Goikolea JM, et al. Risk factors for rapid cycling in bipolar disorder. Bipolar Disorders. 2015; 17:549-59.

217. Nierenberg AA, Akiskal HS, Angst J, Hirschfeld RM, Merikangas KR, Petukhova M, et al. Bipolar disorder with frequent mood episodes in the national comorbidity survey replication (NCS-R). Molecular Psychiatry. 2010; 15:1075-87.

218. Lee S, Tsang A, Kessler RC, Jin R, Sampson N, Andrade L, et al. Rapid-cycling bipolar disorder: cross-national community study. British Journal of Psychiatry. 2010; 196:217-25.

219. Carvalho AF, Dimellis D, Gonda X, Vieta E, McIntyre RS, Fountoulakis KN. Rapid Cycling in Bipolar Disorder: A Systematic Review. Journal of Clinical Psychiatry. 2014; 75:E578-E86.

220. Fountoulakis KN, Kontis D, Gonda X, Yatham LN. A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. Bipolar Disorders. 2013; 15:115-37.

221. Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. American Journal of Psychiatry. 2005; 162:2152-61.

222. Kemp DE, Gao KM, Fein EB, Chan PK, Conroy C, Obral S, et al. Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. Bipolar Disorders. 2012; 14:780-9.

223. Murray G, Lam RW, Beaulieu S, Sharma V, Cervantes P, Parikh SV, et al. Do symptoms of bipolar disorder exhibit seasonal variation? A multisite prospective investigation. Bipolar Disorders. 2011; 13:687-95.

224. Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH Life Chart Method. Journal of Clinical Psychiatry. 2003; 64:680-90.

225. Forte A, Baldessarini RJ, Tondo L, Vazquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. J Affect Disord. 2015; 178:71-8.

226. Yatham LN, Lecrubier Y, Fieve RR, Davis KH, Harris SD, Krishnan AA. Quality of life in patients with bipolar I depression: data from 920 patients. Bipolar Disorders. 2004; 6:379-85.

227. Vojta C, Kinosian B, Glick H, Altshuler L, Bauer MS. Self-reported quality of life across mood states in bipolar disorder. Comprehensive Psychiatry. 2001; 42:190-5.

228. Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. Journal of Clinical Psychiatry. 2002; 63:807-11.

229. Marangell LB, Dennehy EB, Miyahara S, Wisniewski SR, Bauer MS, Rapaport MH, et al. The functional impact of subsyndromal depressive symptoms in bipolar disorder: data from STEP-BD. J Affect Disord. 2009; 114:58-67.

230. Gitlin MJ, Miklowitz DJ. The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment. J Affect Disord. 2017; 209:147-54.

231. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: Update and new findings. Journal of Clinical Psychiatry. 2003; 64:44-52.

232. Tondo L, Pompili M, Forte A, Baldessarini RJ. Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand. 2016; 133:174-86.

233. Holma KM, Haukka J, Suominen K, Valtonen HM, Mantere O, Melartin TK, et al. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. Bipolar Disord. 2014; 16:652-61.

234. Bonnin CD, Gonzalez-Pinto A, Sole B, Reinares M, Gonzalez-Ortega I, Alberich S, et al. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. Journal of Affective Disorders. 2014; 160:50-4.

235. Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. Psychological Medicine. 2013; 43:1187-96.

236. Demant KM, Vinberg M, Messing LV, Miskowiak KW. Assessment of subjective and objective cognitive function in bipolar disorder: Correlations, predictors and the relation to psychosocial function. Psychiatry Research. 2015; 229:565-71.

237. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychological Medicine. 2014; 44:2029-40.

238. Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. Bipolar Disord. 2012; 14:217-26.

239. Kozicky J-M, Torres IJ, Bond DJ, Lam RW, Yatham LN. Comparison of neuropsychological effects of adjunctive risperidone or quetiapine in euthymic patients with bipolar I disorder. International Clinical Psychopharmacology. 2012; 27:91-9.

240. Miskowiak KW, Carvalho AF, Vieta E, Kessing LV. Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations. European Neuropsychopharmacology. 2016; 26:1541-61.

241. Yatham LN, Mackala S, Basivireddy J, Ahn S, Walji N, Hu C, et al. Lurasidone versus treatment as usual for cognitive impairment in euthymic patients with bipolar I disorder: a randomised, open-label, pilot study. Lancet Psychiatry. 2017; 4:208-17.

242. Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Quetiapine monotherapy in acute phase for major depressive disorder: a meta-analysis of randomized, placebo-controlled trials. BMC Psychiatry. 2012; 12:160.

243. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for Acute Bipolar Depression: Meta-analyses of Placebo-controlled, Monotherapy Trials of Anticonvulsants, Lithium and Antipsychotics. Pharmacopsychiatry. 2014; 47:43-52.

244. Datto C, Pottorf WJ, Feeley L, LaPorte S, Liss C. Bipolar II compared with bipolar I disorder: baseline characteristics and treatment response to quetiapine in a pooled analysis of five placebo-controlled clinical trials of acute bipolar depression. Annals of General Psychiatry. 2016; 15.

245. Srisurapanont M, Yatham LN, Zis AP. Treatment of acute bipolar depression: a review of the literature. Can J Psychiatry. 1995; 40:533-44.

246. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. New England Journal of Medicine. 2007; 356:1711-22.

247. Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. American Journal of Psychiatry. 2001; 158:906-12.

248. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. British Journal of Psychiatry. 2009; 194:4-9.

249. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Journal of Clinical Psychiatry. 1999; 60:79-+.

250. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study. American Journal of Psychiatry. 2014; 171:169-77.

251. Pikalov A, Tohen M, Tsai J, Loebel A. Efficacy of lurasidone in bipolar depression: pooled results of two adjunctive studies with lithium or valproate. Bipolar Disorders. 2016; 18:178-.

252. Geddes JR, Gardiner A, Rendell J, Voysey M, Tunbridge E, Hinds C, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 x 2 factorial randomised trial. Lancet Psychiatry. 2016; 3:31-9.

253. van der Loos MLM, Mulder PGH, Hartong EGTM, Blom MBJ, Vergouwen AC, de Keyzer HJUEM, et al. Efficacy and Safety of Lamotrigine as Add-On Treatment to Lithium in Bipolar Depression: A Multicenter, Double-Blind, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2009; 70:223-31.

254. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A Double-Blind, Placebo-Controlled Study of Quetiapine and Lithium Monotherapy in Adults in the Acute Phase of Bipolar Depression (EMBOLDEN I). Journal of Clinical Psychiatry. 2010; 71:150-62.

255. Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disorders. 2008; 10:323-33.

256. Unholzer S, Haen E. Retrospective Analysis of Therapeutic Drug Monitoring Data for Treatment of Bipolar Disorder with Lamotrigine. Pharmacopsychiatry. 2015; 48:211-4.

257. Kemp DE, Ganocy SJ, Brecher M, Carlson BX, Edwards S, Eudicone JM, et al. Clinical value of early partial symptomatic improvement in the prediction of response and remission during short-term treatment trials in 3369 subjects with bipolar I or II depression. Journal of Affective Disorders. 2011; 130:171-9.

258. Grande I, Bernardo M, Bobes J, Saiz-Ruiz J, Alamo C, Vieta E. Antipsychotic switching in bipolar disorders: a systematic review. International Journal of Neuropsychopharmacology. 2014; 17:497-507.

259. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: A systematic review and meta-analysis. Journal of Affective Disorders. 2010; 124:228-34.

260. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016; 3:1138-46.

261. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. American Journal of Psychiatry. 2013; 170:1249-62.

262. Schoeyen HK, Kessler U, Andreassen OA, Auestad BH, Bergsholm P, Malt UF, et al. Treatment-Resistant Bipolar Depression: A Randomized Controlled Trial of Electroconvulsive Therapy Versus Algorithm-Based Pharmacological Treatment. American Journal of Psychiatry. 2015; 172:41-51.

263. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Nemeth G, et al. An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. American Journal of Psychiatry. 2016; 173:271-81.

264. Yatham, LN, E V, S D, W E, K L, et al. Efficacy of Cariprazine in Bipolar Depression: Post Hoc Band-Pass Analyses of 2

Randomized, Double-Blind, Placebo-Controlled Trials. American

Psychiatric Association Annual meeting. Atlanta, Georga, 2016.

265. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Archives of General Psychiatry. 2003; 60:1079-88.

266. Brown EB, McElroy SL, Keck PE, Jr., Deldar A, Adams DH, Tohen M, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. Journal of Clinical Psychiatry. 2006; 67:1025-33.

267. Dunn RT, Stan VA, Chriki LS, Filkowski MM, Ghaemi SN. A prospective, open-label study of Aripiprazole mono- and adjunctive treatment in acute bipolar depression. Journal of Affective Disorders. 2008; 110:70-4.

268. McElroy SL, Suppes T, Frye MA, Altshuler LL, Stanford K, Martens B, et al. Open-label aripiprazole in the treatment of acute bipolar depression: A prospective pilot trial. Journal of Affective Disorders. 2007; 101:275-81.

269. Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Walden J, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. American Journal of Psychiatry. 2007; 164:1242-9.

270. Calabrese JR, Frye MA, Yang R, Ketter TA. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. J Clin Psychiatry. 2014; 75:1054-61.

271. Berk M, Tiller JWG, Zhao J, Yatham LN, Malhi GS, Weiller E. Effects of Asenapine in Bipolar I Patients Meeting Proxy Criteria for Moderate-to-Severe Mixed Major Depressive Episodes: A Post Hoc Analysis. Journal of Clinical Psychiatry. 2015; 76:728-+.

272. Bauer M, Berman S, Stamm T, Plotkin M, Adli M, Pilhatsch M, et al. Levothyroxine effects on depressive symptoms and limbic glucose metabolism in bipolar disorder: a randomized, placebo-controlled positron emission tomography study. Molecular Psychiatry. 2016; 21:229-36.

273. Stamm TJ, Lewitzka U, Sauer C, Pilhatsch M, Smolka MN, Koeberle U, et al. Supraphysiologic Doses of Levothyroxine as Adjunctive Therapy in Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Study. Journal of Clinical Psychiatry. 2014; 75:162-8.

274. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. American Journal of Psychiatry. 2004; 161:564-6.

275. Zarate CA, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: A placebo-controlled proof of concept study. Biological Psychiatry. 2004; 56:54-60.

276. McGirr A, Karmani S, Arsappa R, Berlim MT, Thirthalli J, Muralidharan K, et al. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. World Psychiatry. 2016; 15:85-6.

277. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry. 2006; 189:124-31.

278. Himmelhoch JM, Fuchs CZ, Symons BJ. A DOUBLE-BLIND-STUDY OF TRANYLCYPROMINE TREATMENT OF MAJOR ANERGIC DEPRESSION. Journal of Nervous and Mental Disease. 1982; 170:628-34.

279. Himmelhoch JM, Thase ME, Mallinger AG, Houck P. TRANYLCYPROMINE VERSUS IMIPRAMINE IN ANERGIC BIPOLAR DEPRESSION. American Journal of Psychiatry. 1991; 148:910-6.

280. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One. 2014; 9:e96905.

281. Rosenblat JD, Kakar R, Berk M, Kessing LV, Vinberg M, Baune BT, et al. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disorders. 2016; 18:89-101.

282. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder - A double-blind randomized placebo-controlled trial. Biological Psychiatry. 2008; 64:468-75.

283. Tseng PT, Chen YW, Tu KY, Chung WL, Wang HY, Wu CK, et al. Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. European Neuropsychopharmacology. 2016; 26:1037-47.

284. Sit DK, McGowan J, Wiltrout C, Diler RS, Dills JJ, Luther J, et al. Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial. Am J Psychiatry. 2017:appiajp201716101200.

285. Romeo B, Choucha W, Fossati P, Rotge JY. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Research. 2015; 230:682-8.

286. Andrade C. Ketamine for Depression, 5: Potential Pharmacokinetic and Pharmacodynamic Drug Interactions. J Clin Psychiatry. 2017; 78:e858-e61.

287. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. J Affect Disord. 2015; 181:87-91.

288. Frye MA, Amchin J, Bauer M, Adler C, Yang R, Ketter TA. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. Int J Bipolar Disord. 2015; 3:34.

289. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive Armodafinil for Major Depressive Episodes Associated With Bipolar I Disorder: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Proof-of-Concept Study. Journal of Clinical Psychiatry. 2010; 71:1363-70.

290. Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PKE, et al. The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer. American Journal of Psychiatry. 2014; 171:1067-73.

291. McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, et al. A Double-Blind, Placebo-Controlled Study of Quetiapine and Paroxetine as Monotherapy in Adults With Bipolar Depression (EMBOLDEN II). Journal of Clinical Psychiatry. 2010; 71:163-74.

292. Peet M. INDUCTION OF MANIA WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS. British Journal of Psychiatry. 1994; 164:549-50.

293. Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, et al. Aripiprazole monotherapy in non-psychotic bipolar I depression. Journal of Clinical Psychopharmacology. 2008; 28:13-20.

294. Fountoulakis KN, Vieta E, Schmidt F. Aripiprazole monotherapy in the treatment of bipolar disorder: A meta-analysis. Journal of Affective Disorders. 2011; 133:361-70.

295. Sachs GS, Ice KS, Chappell PB, Schwartz JH, Gurtovaya O, Vanderburg DG, et al. Efficacy and Safety of Adjunctive Oral Ziprasidone for Acute Treatment of Depression in Patients With Bipolar I Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2011; 72:1413-22.

296. Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer S, et al. A Randomized Trial to Examine the Effect of Mifepristone on Neuropsychological Performance and Mood in Patients with Bipolar Depression. Biological Psychiatry. 2012; 72:943-9.

297. Saroukhani S, Emami-Parsa M, Modabbernia A, Ashrafi M, Farokhnia M, Hajiaghaee R, et al. Aspirin for treatment of lithium-associated sexual dysfunction in men: randomized double-blind placebo-controlled study. Bipolar Disorders. 2013; 15:650-6.

298. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Human Psychopharmacology-Clinical and Experimental. 2008; 23:87-94.

299. Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. Journal of Clinical Psychopharmacology. 2000; 20:607-14.

300. Saricicek A, Maloney K, Muralidharan A, Ruf B, Blumberg HP, Sanacora G, et al. Levetiracetam in the Management of Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2011; 72:744-50.

301. McElroy SL, Martens BE, Mori N, Blom TJ, Casuto LS, Hawkins JM, et al. Adjunctive lisdexamfetamine in bipolar depression: a preliminary randomized, placebo-controlled trial. International Clinical Psychopharmacology. 2015; 30:6-13.

302. Anand A, Gunn AD, Barkay G, Karne HS, Nurnberger JI, Mathew SJ, et al. Early antidepressant effect of memantine during augmentation of lamotrigine inadequate response in bipolar depression: a double-blind, randomized, placebo-controlled trial. Bipolar Disorders. 2012; 14:64-70.

303. Kemp DE, Schinagle M, Gao KM, Conroy C, Ganocy SJ, Ismail-Beigi F, et al. PPAR-gamma Agonism as a Modulator of Mood: Proof-of-Concept for Pioglitazone in Bipolar Depression. Cns Drugs. 2014; 28:571-81.

304. Zeinoddini A, Sorayani M, Hassanzadeh E, Arbabi M, Farokhnia M, Salimi S, et al. PIOGLITAZONE ADJUNCTIVE THERAPY FOR DEPRESSIVE EPISODE OF BIPOLAR DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. Depression and Anxiety. 2015; 32:167-73.

305. Zarate CA, Quiroz JA, Singh JB, Denicoff KD, De Jesus G, Luckenbaugh DA, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biological Psychiatry. 2005; 57:430-2.

306. Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. Journal of Clinical Psychiatry. 2004; 65:1715-9.

307. Brown ES, Park J, Marx CE, Hynan LS, Gardner C, Davila D, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Pregnenolone for Bipolar Depression. Neuropsychopharmacology. 2014; 39:2867-73.

308. Loebel A, Siu C, Rajagopalan K, Pikalov A, Cucchiaro J, Ketter TA. Recovery in bipolar depression: Post-hoc analysis of a placebo-controlled lurasidone trial followed by a long-term continuation study. Journal of Affective Disorders. 2015; 186:376-82.

309. Chiesa A, Chierzi F, De Ronchi D, Serretti A. Quetiapine for bipolar depression: a systematic review and meta-analysis. International Clinical Psychopharmacology. 2012; 27:76-90.

310. Mitchell PB, Hadzi-Pavlovic D, Evoniuk G, Calabrese JR, Bowden CL. A factor analytic study in bipolar depression, and response to lamotrigine. Cns Spectrums. 2013; 18:214-24.

311. Pacchiarotti I, Valenti M, Bonnin CM, Rosa AR, Murru A, Kotzalidis GD, et al. Factors associated with initial treatment response with antidepressants in bipolar disorder. European Neuropsychopharmacology. 2011; 21:362-9.

312. Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB. Effects of anxiety on the long-term course of depressive disorders. British Journal of Psychiatry. 2012; 200:210-5.

313. Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. ANXIOUS AND NONANXIOUS BIPOLAR DISORDER. Journal of Affective Disorders. 1993; 29:49-52.

314. Lydiard RB, Culpepper L, Schioler H, Gustafsson U, Paulsson B. Quetiapine monotherapy as treatment for anxiety symptoms in patients with bipolar depression: a pooled analysis of results from 2 double-blind, randomized, placebo-controlled studies. Primary care companion to the Journal of clinical psychiatry. 2009; 11:215-25.

315. Tohen M, Calabrese J, Vieta E, Bowden C, Gonzalez-Pinto A, Lin D, et al. Effect of comorbid anxiety on treatment response in bipolar depression. Journal of Affective Disorders. 2007; 104:137-46.

316. Tsai J, Thase ME, Mao Y, Ng-Mak D, Pikalov A, Loebel A. Lurasidone for major depressive disorder with mixed features and anxiety: a post-hoc analysis of a randomized, placebo-controlled study. CNS Spectr. 2017; 22:236-45.

317. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: A placebo-controlled study. Journal of Affective Disorders. 2005; 85:259-66.

318. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, et al. Manic Symptoms During Depressive Episodes in 1,380 Patients With Bipolar Disorder: Findings From the STEP-BD. American Journal of Psychiatry. 2009; 166:173-81.

319. Montgomery SA, Schatzberg AF, Guelfi JD, Kasper S, Nemeroff C, Swann A, et al. Pharmacotherapy of depression and mixed states in bipolar disorder. Journal of Affective Disorders. 2000; 59:S39-S56.

320. Fornaro M, Stubbs B, De Berardis D, Perna G, Valchera A, Veronese N, et al. Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials. International Journal of Molecular Sciences. 2016; 17.

321. Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. Am J Psychiatry. 2016; 173:400-7.

322. Thase ME, Mallinger AG, McKnight D, Himmelhoch JM. TREATMENT OF IMIPRAMINE-RESISTANT RECURRENT DEPRESSION .4. A DOUBLE-BLIND

CROSSOVER STUDY OF TRANYLCYPROMINE FOR ANERGIC BIPOLAR DEPRESSION. American Journal of Psychiatry. 1992; 149:195-8.

323. Black DW, Nasrallah A. HALLUCINATIONS AND DELUSIONS IN 1,715 PATIENTS WITH UNIPOLAR AND BIPOLAR AFFECTIVE-DISORDERS. Psychopathology. 1989; 22:28-34.

324. Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Journal of Clinical Psychiatry. 2000; 61:841-50.

325. El-Mallakh RS, Vohringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. Journal of Affective Disorders. 2015; 184:318-21.

326. Vieta E, Reinares M, Rosa AR. Staging Bipolar Disorder. Neurotoxicity Research. 2011; 19:279-85.

327. Kozicky JM, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN. Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. J Clin Psychiatry. 2014; 75:e587-93.

328. Kozicky JM, McGirr A, Bond DJ, Gonzalez M, Silveira LE, Keramatian K, et al. Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disord. 2016; 18:511-9.

329. Berk M, Berk L, Dodd S, Cotton S, Macneil C, Daglas R, et al. Stage managing bipolar disorder. Bipolar Disorders. 2014; 16:471-7.

330. Daglas R, Cotton SM, Allott K, Yucel M, Macneil CA, Hasty MK, et al. A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study. Eur Psychiatry. 2016; 31:20-8.

331. Berk M, Dandash O, Daglas R, Cotton SM, Allott K, Fornito A, et al. Neuroprotection after a first episode of mania: a randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. Transl Psychiatry. 2017; 7:e1041.

332. Vazquez GH, Holtzman JN, Lolich M, Ketter TA, Baldessarini RJ. Recurrence rates in bipolar disorder: Systematic comparison of long-term prospective, naturalistic studies versus randomized controlled trials. European Neuropsychopharmacology. 2015; 25:1501-12.

333. Gignac A, McGirr A, Lam RW, Yatham LN. Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. J Clin Psychiatry. 2015; 76:1241-8.

334. Kessing LV, Hansen MG, Andersen PK, Angst J. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. Acta Psychiatrica Scandinavica. 2004; 109:339-44.

335. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang HW, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: Primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). American Journal of Psychiatry. 2006; 163:217-24.

336. Yen S, Stout R, Hower H, Killam MA, Weinstock LM, Topor DR, et al. The influence of comorbid disorders on the episodicity of bipolar disorder in youth. Acta Psychiatr Scand. 2016; 133:324-34.

337. Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Archives of General Psychiatry. 2008; 65:386-94.

338. De Dios C, Ezquiaga E, Agud JL, Vieta E, Soler B, Garcia-Lopez A. Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. Journal of Affective Disorders. 2012; 143:160-5.

339. Cohen AN, Hammen C, Henry RM, Daley SE. Effects of stress and social support on recurrence in bipolar disorder. Journal of Affective Disorders. 2004; 82:143-7.

340. Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, et al. Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol. 2010; 25:1-16.

341. Berk M, Berk L, Castle D. A collaborative approach to the treatment alliance in bipolar disorder. Bipolar Disord. 2004; 6:504-18.

342. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. Assessment of Adherence Problems in Patients with Serious and Persistent Mental Illness: Recommendations from the Expert Consensus Guidelines. Journal of Psychiatric Practice. 2010; 16:34-45.

343. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatrica Scandinavica. 2002; 105:164-72.

344. Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatric Services. 2007; 58:855-63.

345. Moon E, Chang JS, Kim MY, Seo MH, Cha B, Ha TH, et al. Dropout rate and associated factors in patients with bipolar disorders. Journal of Affective Disorders. 2012; 141:47-54.

346. Baker JP. OUTCOMES OF LITHIUM DISCONTINUATION - A METAANALYSIS. Lithium. 1994; 5:187-92.

347. Suppes T, Baldessarini RJ, Faedda GL, Tohen M. RISK OF RECURRENCE FOLLOWING DISCONTINUATION OF LITHIUM TREATMENT IN BIPOLAR DISORDER. Archives of General Psychiatry. 1991; 48:1082-8.

348. Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. OUTCOME AFTER RAPID VS GRADUAL DISCONTINUATION OF LITHIUM TREATMENT IN BIPOLAR DISORDERS. Archives of General Psychiatry. 1993; 50:448-55.

349. Sharma P, Kongasseri S, Praharaj SK. Outcome of Mood Stabilizer Discontinuation in Bipolar Disorder After 5 Years of Euthymia. Journal of Clinical Psychopharmacology. 2014; 34:504-7.

350. Franks MA, Macritchie KAN, Mahmood T, Young AH. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study. Journal of Psychopharmacology. 2008; 22:452-6.

351. Scott J, Pope M. Nonadherence with mood stabilizers: Prevalence and predictors. Journal of Clinical Psychiatry. 2002; 63:384-90.

352. Hong J, Reed C, Novick D, Maria Haro J, Windmeijer F, Knapp M. The Cost of Relapse for Patients with a Manic/Mixed Episode of Bipolar Disorder in the EMBLEM Study. Pharmacoeconomics. 2010; 28:555-66.

353. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disorders. 2006; 8:625-39.

354. Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: A comprehensive review. Journal of Affective Disorders. 2013; 149:247-52.

355. MacDonald L, Chapman S, Syrett M, Bowskill R, Horne R. Improving medication adherence in bipolar disorder: A systematic review and meta-analysis of 30 years of intervention trials. Journal of Affective Disorders. 2016; 194:202-21.

356. Crowe M, Wilson L, Inder M. Patients' reports of the factors influencing medication adherence in bipolar disorder - An integrative review of the literature. International Journal of Nursing Studies. 2011; 48:894-903.

357. Sajatovic M, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disorder. Psychiatric Services. 2004; 55:264-9.

358. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. Strategies for Addressing Adherence Problems in Patients with Serious and Persistent Mental Illness: Recommendations from the Expert Consensus Guidelines. Journal of Psychiatric Practice. 2010; 16:306-24.

359. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DPJ. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World Psychiatry. 2016; 15:53-8.

360. Kessing LV, Hellmund G, Andersen PK. Predictors of excellent response to lithium: results from a nationwide register-based study. International Clinical Psychopharmacology. 2011; 26:323-8.

361. Kessing LV, Hellmund G, Geddes JR, Goodwin GM, Andersen PK. Valproate V. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. British Journal of Psychiatry. 2011; 199:57-63.

362. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. Jama-Journal of the American Medical Association. 2003; 290:1467-73.

363. Hayes JF, Pitman A, Marston L, Walters K, Geddes JR, King M, et al. Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment A UK Population-Based Electronic Health Records Study. Jama Psychiatry. 2016; 73:630-7.

364. Baldessarini RJ, Tondo L. Does lithium treatment still work? Evidence of stable responses over three decades. Archives of General Psychiatry. 2000; 57:187-90.

365. Rybakowski JK, Chlopocka-Wozniak M, Suwalska A. The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. Bipolar Disorders. 2001; 3:63-7.

366. Peselow ED, Clevenger S, IsHak WW. Prophylactic efficacy of lithium, valproic acid, and carbamazepine in the maintenance phase of bipolar disorder: a naturalistic study. Int Clin Psychopharmacol. 2016; 31:218-23.

367. Altshuler L, Suppes T, Black D, Nolen WA, Keck PE, Frye MA, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. American Journal of Psychiatry. 2003; 160:1252-62.

368. Yatham LN, Beaulieu S, Schaffer A, Kauer-Sant'Anna M, Kapczinski F, Lafer B, et al. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: A CANMAT randomized double-blind trial. Mol Psychiatry. 2016; 21:1050-6.

369. Severus E, Taylor M, Sauer C, Pfennig A, Bauer M, Geddes J. Efficacy of lithium in the long-term treatment of bipolar disorders: a new meta-analysis. Bipolar Disorders. 2014; 16:96-.

370. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014; 1:351-9.

371. Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B, Trial 144 Study I. Continuation of Quetiapine Versus Switching to Placebo or Lithium for Maintenance Treatment of Bipolar I Disorder (Trial 144: A Randomized Controlled Study). Journal of Clinical Psychiatry. 2011; 72:1452-64.

372. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database of Systematic Reviews. 2013.

373. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Archives of General Psychiatry. 2000; 57:481-9.

374. Calabrese JR, Goldberg JF, Ketter TA, Suppes T, Frye M, White R, et al. Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. Biol Psychiatry. 2006; 59:1061-4.

375. Szegedi A, Durgam S, Mackle M, Yu SY, Wu X, Mathews M, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Asenapine Maintenance Therapy in Adults With an Acute Manic or Mixed Episode Associated With Bipolar I Disorder. American Journal of Psychiatry. 2017:appi.ajp.2017.16040419.

376. Keck PE, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. Journal of Clinical Psychiatry. 2006; 67:626-37.

377. Keck PE, Jr., Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JA, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: A 100-week, double-blind study versus placebo. Journal of Clinical Psychiatry. 2007; 68:1480-91.

378. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, et al. Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study. J Clin Psychiatry. 2017; 78:324-31.

379. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B, Trial I. Maintenance Treatment for Patients With Bipolar I Disorder: Results From a North American Study of Quetiapine in Combination With Lithium or Divalproex (Trial 127). American Journal of Psychiatry. 2009; 166:476-88.

380. Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). Journal of Affective Disorders. 2008; 109:251-63.

381. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disorders. 2011; 13:133-44.

382. Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder

responding to acute treatment with olanzapine. American Journal of Psychiatry. 2006; 163:247-56.

383. Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, Martinez L, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. European Neuropsychopharmacology. 2012; 22:825-35.

384. Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V. Risperidone Long-Acting Injectable Monotherapy in the Maintenance Treatment of Bipolar I Disorder. Biological Psychiatry. 2010; 68:156-62.

385. Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, Bossie C, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disorders. 2009; 11:827-39.

386. Post RM, Speer AM, Obrocea GV, Leverich GS. Acute and prophylactic effects of anticonvulsants in bipolar depression. Clinical Neuroscience Research. 2002; 2:228-51.

387. Berwaerts J, Melkote R, Nuamah I, Lim P. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. Journal of Affective Disorders. 2012; 138:247-58.

388. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone Plus a Mood Stabilizer in Subjects With Bipolar I Disorder: A 6-Month, Randomized, Placebo-Controlled, Double-Blind Trial. Journal of Clinical Psychiatry. 2010; 71:130-7.

389. Calabrese JR, Pikalov A, Streicher C, Cucchiaro J, Mao Y, Loebel A. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. Eur Neuropsychopharmacol. 2017.

390. Carlson BX, Ketter TA, Sun W, Timko K, McQuade RD, Sanchez R, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disorders. 2012; 14:41-53.

391. Vieta E, Goikolea JM, Martinez-Aran A, Comes M, Verger K, Masramon X, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. Journal of Clinical Psychiatry. 2006; 67:473-7.

392. Brown E, Dunner DL, McElroy SL, Keck PE, Jr., Adams DH, Degenhardt E, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. International Journal of Neuropsychopharmacology. 2009; 12:773-82.

393. Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord. 2015; 174:296-302.

394. Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, et al. Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatr Scand. 1981; 64:226-37.

395. Vasudev A, Macritchie K, Watson S, Geddes JR, Young AH. Oxcarbazepine in the maintenance treatment of bipolar disorder. Cochrane Database of Systematic Reviews. 2008.

396. Mazza M, Di Nicola M, Martinotti G, Taranto C, Pozzi G, Conte G, et al. Oxcarbazepine in bipolar disorder: a critical review of the literature. Expert Opin Pharmacother. 2007; 8:649-56.

397. Vieta E, Cruz N, Garcia-Campayo J, de Arce R, Manuel Crespo J, Valles V, et al. A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. International Journal of Neuropsychopharmacology. 2008; 11:445-52.

398. Zarate CA, Tohen M. Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. American Journal of Psychiatry. 2004; 161:169-71.

399. Prien RF, Klett CJ, Caffey EM. LITHIUM-CARBONATE AND IMIPRAMINE IN PREVENTION OF AFFECTIVE EPISODES - COMPARISON IN RECURRENT AFFECTIVE ILLNESS. Archives of General Psychiatry. 1973; 29:420-5.

400. Kane JM, Quitkin FM, Rifkin A, Ramoslorenzi JR, Nayak DD, Howard A. LITHIUM-CARBONATE AND IMIPRAMINE IN THE PROPHYLAXIS OF UNIPOLAR AND BIPOLAR-II ILLNESS - A PROSPECTIVE, PLACEBO-CONTROLLED COMPARISON. Archives of General Psychiatry. 1982; 39:1065-9.

401. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry. 1984; 41:1096-104.

402. Solomon DA, Keitner GI, Miller IW, Shea MT, Keller MB. COURSE OF ILLNESS AND MAINTENANCE TREATMENTS FOR PATIENTS WITH BIPOLAR DISORDER. Journal of Clinical Psychiatry. 1995; 56:5-13.

403. MacQueen GM, Young LT, Robb JC, Marriott M, Cooke RG, Joffe RT. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. Acta Psychiatrica Scandinavica. 2000; 101:374-81.

404. Baldessarini RJ, Tondo L, Baethge CJ, Lepri B, Bratti IM. Effects of treatment latency on response to maintenance treatment in manic-depressive disorders. Bipolar Disorders. 2007; 9:386-93.

405. Berghofer A, Alda M, Adli M, Baethge C, Bauer M, Bschor T, et al. Long-Term Effectiveness of Lithium in Bipolar Disorder: A Multicenter Investigation of Patients With Typical and Atypical Features. Journal of Clinical Psychiatry. 2008; 69:1860-8.

406. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: Results of the MAP study. Neuropsychobiology. 2000; 42:2-10.

407. Nolen WA, Weisler RH. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disorders. 2013; 15:100-9.

408. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. A history of substance abuse complicates remission from acute mania in bipolar disorder. Journal of Clinical Psychiatry. 1999; 60:733-40.

409. Riemann G, Weisscher N, Post RM, Altshuler L, McElroy S, Frye MA, et al. The relationship between self-reported borderline personality features and prospective illness course in bipolar disorder. Int J Bipolar Disord. 2017; 5:31.

410. Coppen A, Standishbarry H, Bailey J, Houston G, Silcocks P, Hermon C. DOES LITHIUM REDUCE THE MORTALITY OF RECURRENT MOOD DISORDERS. Journal of Affective Disorders. 1991; 23:1-7.

411. Coppen A, Farmer R. Suicide mortality in patients on lithium maintenance therapy. Journal of Affective Disorders. 1998; 50:261-7.

412. Ahrens B, Grof P, Moller HJ, Mulleroerlinghausen B, Wolf T. EXTENDED SURVIVAL OF PATIENTS ON LONG-TERM LITHIUM TREATMENT. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 1995; 40:241-6.

413. Ahrens B, Muller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect? Pharmacopsychiatry. 2001; 34:132-6.

414. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. Bmj-British Medical Journal. 2013; 346.

415. Grof P, Alda M, Grof E, Fox D, Cameron P. THE CHALLENGE OF PREDICTING RESPONSE TO STABILIZING LITHIUM TREATMENT - THE IMPORTANCE OF PATIENT SELECTION. British Journal of Psychiatry. 1993; 163:16-9.

416. Calabrese JR, Fatemi H, Kujawa M, Woyshville MJ. Predictors of response to mood stabilizers. Journal of Clinical Psychopharmacology. 1996; 16:S24-S31.

417. Rohayem J, Bayle JF, Richa S. Predictors of prophylactic response to lithium. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique. 2008; 34:394-9.

418. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry. 2002; 63:942-7.

419. Ikeda A, Kato T. Biological predictors of lithium response in bipolar disorder. Psychiatry and Clinical Neurosciences. 2003; 57:243-50.

420. Mertens J, Wang QW, Kim Y, Yu DX, Pham S, Yang B, et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature. 2015; 527:95-9.

421. Passmore MJ, Garnham J, Duffy A, MacDougall M, Munro A, Slaney C, et al. Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. Bipolar Disorders. 2003; 5:110-4.

422. Ketter TA, Calabrese JR. Stabilization of mood from below versus above baseline in bipolar disorder: A new nomenclature. Journal of Clinical Psychiatry. 2002; 63:146-51.

423. Vieta E, Suppes T, Ekholm B, Udd M, Gustafsson U. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. J Affect Disord. 2012; 142:36-44.

424. Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. Bipolar Disorders. 2008; 10:163-78.

425. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders - A prospective, comparative, longitudinal study. Archives of General Psychiatry. 2005; 62:1322-30.

426. Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. Journal of Affective Disorders. 2011; 129:79-83.

427. Altshuler LL, Sugar CA, McElroy SL, Calimlim B, Gitlin M, Keck PE, Jr., et al. Switch Rates During Acute Treatment for Bipolar II Depression With Lithium, Sertraline, or the Two Combined: A Randomized Double-Blind Comparison. Am J Psychiatry. 2017:appiajp201615040558.

428. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Archives of General Psychiatry. 2003; 60:261-9.

429. Kupka RW, Altshuler LL, Nolen WA, Suppes T, Luckenbaugh DA, Leverich GS, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disorders. 2007; 9:531-5.

430. Schaffer A, Isometsa ET, Tondo L, Moreno DH, Turecki G, Reis C, et al. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disorders. 2015; 17:1-16.

431. Sani G, Tondo L, Koukopoulos A, Reginaldi D, Kotzalidis GD, Koukopoulos AE, et al. Suicide in a large population of former psychiatric inpatients. Psychiatry and Clinical Neurosciences. 2011; 65:286-95.

432. Greil W, Kleindienst N, Erazo N, Muller-Oerlinghausen B. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. Journal of Clinical Psychopharmacology. 1998; 18:455-60.

433. McElroy SL, Martens BE, Creech RS, Welge JA, Jefferson L, Guerdjikova AI, et al. Randomized, Double-Blind, Placebo-Controlled Study of Divalproex Extended Release Loading Monotherapy in Ambulatory Bipolar Spectrum Disorder Patients With Moderate-to-Severe Hypomania or Mild Mania. Journal of Clinical Psychiatry. 2010; 71:557-65.

434. Magalhaes P, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, et al. A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. Australian and New Zealand Journal of Psychiatry. 2013; 47:564-8.

435. McElroy SLy, Martens BE, Winstanley EL, Creech R, Malhotra S, Keck PE, Jr. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. Journal of Affective Disorders. 2010; 124:157-63.

436. Suppes T, Ketter TA, Gwizdowski IS, Dennehy EB, Hill SJ, Fischer EG, et al. First controlled treatment trial of bipolar II hypomania with mixed symptoms: Quetiapine versus placebo. Journal of Affective Disorders. 2013; 150:37-43.

437. Vieta E, Gasto C, Colom F, Reinares M, Martinez-Aran A, Banabarre A, et al. Role of risperidone in bipolar II: an open 6-month study. Journal of Affective Disorders. 2001; 67:213-9.

438. Young AH, Calabrese JR, Gustafsson U, Berk M, McElroy SL, Thase ME, et al. Quetiapine monotherapy in bipolar II depression: combined data from four large, randomized studies. International Journal of Bipolar Disorders. 2013; 1:10.

439. Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. American Journal of Psychiatry. 2005; 162:1351-60.

440. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression - A double-blind, placebo-controlled study (The BOLDER II study). Journal of Clinical Psychopharmacology. 2006; 26:600-9.

441. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. Journal of Affective Disorders. 2010; 121:106-15.

442. Jeong JH, Bahk WM, Woo YS, Seo HJ, Hong SC, Jon DI, et al. Efficacy of quetiapine in patients with bipolar I and II depression: a multicenter, prospective, open-label, observational study. Neuropsychiatric Disease and Treatment. 2013; 9:197-204.

443. Ahn YM, Nam JY, Culver JL, Marsh WK, Bonner JC, Ketter TA. Lamotrigine plus quetiapine combination therapy in treatment-resistant bipolar depression. Annals of Clinical Psychiatry. 2011; 23:17-24.

444. Amsterdam J. Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. Journal of Clinical Psychopharmacology. 1998; 18:414-7.

445. Amsterdam JD, Garcia-Espana F. Venlafaxine monotherapy in women with bipolar II and unipolar major depression. Journal of Affective Disorders. 2000; 59:225-9.

446. Suppes T, Marangell LB, Bernstein IH, Kelly DI, Fischer EG, Zboyan HA, et al. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. Journal of Affective Disorders. 2008; 111:334-43.

447. Donnelly EF, Goodwin FK, Waldman IN, Murphy DL. PREDICTION OF ANTIDEPRESSANT RESPONSES TO LITHIUM. American Journal of Psychiatry. 1978; 135:552-6.

448. Goodwin FK, Murphy DL, Bunney WE. LITHIUM-CARBONATE TREATMENT IN DEPRESSION AND MANIA - A LONGITUDINAL DOUBLE-BLIND STUDY. Archives of General Psychiatry. 1969; 21:486-&.

449. Goodwin FK, Bunney WE, Dunner DL, Murphy DL. LITHIUM RESPONSE IN UNIPOLAR VERSUS BIPOLAR DEPRESSION. American Journal of Psychiatry. 1972; 129:44-&.

450. Baron M, Gershon ES, Rudy V, Jonas WZ, Buchsbaum M. LITHIUM-CARBONATE RESPONSE IN DEPRESSION - PREDICTION BY UNIPOLAR BIPOLAR ILLNESS, AVERAGE-EVOKED RESPONSE, CATECHOL-O-METHYL TRANSFERASE, AND FAMILY HISTORY. Archives of General Psychiatry. 1975; 32:1107-11.

451. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: effectiveness and mood conversion rate. British Journal of Psychiatry. 2016; 208:359-65.

452. Fieve RR, Kumbaraci T, Dunner DL. LITHIUM PROPHYLAXIS OF DEPRESSION IN BIPOLAR-1, BIPOLAR-2, AND UNIPOLAR PATIENTS. American Journal of Psychiatry. 1976; 133:925-9.

453. Dunner DL, Fieve RR. CLINICAL FACTORS IN LITHIUM-CARBONATE PROPHYLAXIS FAILURE. Archives of General Psychiatry. 1974; 30:229-33.

454. Nierenberg AA, McElroy SL, Friedman ES, Ketter TA, Shelton RC, Deckersbach T, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): A Pragmatic 6-Month Trial of Lithium Versus Quetiapine for Bipolar Disorder. Journal of Clinical Psychiatry. 2016; 77:90-9.

455. Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-Associated Mood Elevations in Bipolar II Disorder Compared With Bipolar I Disorder and Major Depressive Disorder: A Systematic Review and Meta-Analysis. Journal of Clinical Psychiatry. 2008; 69:1589-601.

456. Vohringer PA, Ostacher MJ, El-Mallakh RS, Holtzman NS, Thommi SB, Whitham EA, et al. Antidepressants in Type II Versus Type I Bipolar Depression A Randomized Discontinuation Trial. Journal of Clinical Psychopharmacology. 2015; 35:605-8.

457. Amsterdam JD, Wang C-H, Shwarz M, Shults J. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: A randomized, parallel group, open-label trial. Journal of Affective Disorders. 2009; 112:219-30.

458. Amsterdam JD, Luo LL, Shults J. Effectiveness and Mood Conversion Rate of Short-Term Fluoxetine Monotherapy in Patients With Rapid Cycling Bipolar II Depression Versus Patients With Nonrapid Cycling Bipolar II Depression. Journal of Clinical Psychopharmacology. 2013; 33:420-4.

459. Amsterdam JD, Luo LL, Shults J. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. British Journal of Psychiatry. 2013; 202:301-6.

460. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. Journal of Clinical Psychiatry. 2003; 64:1013-24.

461. Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, et al. Valproate for the treatment of acute bipolar depression: Systematic review and meta-analysis. Journal of Affective Disorders. 2010; 122:1-9.

462. Sachs GS. A 25-year-old woman with bipolar disorder. Jama. 2001; 285:454-62.

463. Muzina DJ, Gao K, Kemp DE, Khalife S, Ganocy SJ, Chan PK, et al. Acute Efficacy of Divalproex Sodium Versus Placebo in Mood Stabilizer-Naive Bipolar I or II Depression: A Double-Blind, Randomized, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2011; 72:813-9.

464. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. American Journal of Psychiatry. 2000; 157:124-6.

465. Winsberg ME, DeGolia SG, Strong CM, Ketter TA. Divalproex therapy in medication-naive and mood-stabilizer-naive bipolar II depression. Journal of Affective Disorders. 2001; 67:207-12.

466. Wang PW, Nowakowska C, Chandler RA, Hill SJ, Nam JY, Culver JL, et al. Divalproex extended-release in acute bipolar II depression. Journal of Affective Disorders. 2010; 124:170-3.

467. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: A double-blind placebo-controlled pilot study. Journal of Clinical Psychiatry. 2002; 63:442-6.

468. Amsterdam JD, Shults J, Brunswick DJ, Hundert M. Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate. Bipolar Disorders. 2004; 6:75-81.

469. Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. Journal of Clinical Psychopharmacology. 1998; 18:435-40.

470. Amsterdam JD, Shults J. Efficacy and Safety of Long-Term Fluoxetine Versus Lithium Monotherapy of Bipolar II Disorder: A Randomized, Double-Blind, Placebo-Substitution Study. American Journal of Psychiatry. 2010; 167:792-800.

471. Patkar A, Gilmer W, Pae CU, Vohringer PA, Ziffra M, Pirok E, et al. A 6 Week Randomized Double-Blind Placebo-Controlled Trial of Ziprasidone for the Acute Depressive Mixed State. Plos One. 2012; 7.

472. Liebowitz MR, Salman E, Mech A, Dunner D, Johnson AE, Akhtar J, et al. Ziprasidone monotherapy in bipolar II depression: An open trial. Journal of Affective Disorders. 2009; 118:205-8.

473. Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M, et al. Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatric Disease and Treatment. 2013; 9:243-51.

474. Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega 3 fatty acids in bipolar disorder - A preliminary double-blind, placebo-controlled trial. Archives of General Psychiatry. 1999; 56:407-12.

475. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. British Journal of Psychiatry. 2006; 188:46-50.

476. Keck PE, Mintz J, McElroy SL, Freeman MP, Frye T, Altshuler LL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biological Psychiatry. 2006; 60:1020-2.

477. Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. Journal of Affective Disorders. 2011; 129:317-20.

478. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A Randomized Add-on Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Bipolar Depression. Archives of General Psychiatry. 2010; 67:793-802.

479. Zarate CA, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-On Trial. Biological Psychiatry. 2012; 71:939-46.

480. McClure D, Greenman SC, Koppolu SS, Varvara M, Yaseen ZS, Galynker, II. A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression. Journal of Nervous and Mental Disease. 2015; 203:827-35.

481. Kelly TF, Lieberman DZ. The utility of the combination of dextromethorphan and quinidine in the treatment of bipolar II and bipolar NOS. Journal of Affective Disorders. 2014; 167:333-5.

482. Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. Psychiatry Research. 2012; 196:57-61.

483. Sit D, Wisner KL, Hanusa BH, Stull S, Terman M. Light therapy for bipolar disorder: a case series in women. Bipolar Disorders. 2007; 9:918-27.

484. Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, et al. Rapid and Sustained Antidepressant Response with Sleep Deprivation and Chronotherapy in Bipolar Disorder. Biological Psychiatry. 2009; 66:298-301.

485. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry Research. 2000; 95:43-53.

486. Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E. Morning light treatment hastens the antidepressant effect of citalopram: A placebo-controlled trial. Journal of Clinical Psychiatry. 2003; 64:648-53.

487. Kirino E. Efficacy of Olanzapine for Treating Depressive Episodes in Bipolar Disorder. Clinical Neuropsychopharmacology and Therapeutics. 2014; 5:11-7.

488. Daryani, K K, Bokade NK, Raichandani OP. A

comparative study of efficacy of lamotrigine and levetiracetam in the

continuous maintenance phase of patients with bipolar depressive disorder. International Journal of Bioassays. 2014; 3.

489. Lipinski JF, Cohen BM, Frankenburg F, Tohen M, Waternaux C, Altesman R, et al. OPEN TRIAL OF S-ADENOSYLMETHIONINE FOR TREATMENT OF DEPRESSION. American Journal of Psychiatry. 1984; 141:448-50.

490. Carney MWP, Chary TKN, Bottiglieri T, Reynolds EH. THE SWITCH MECHANISM AND THE BIPOLAR UNIPOLAR DICHOTOMY. British Journal of Psychiatry. 1989; 154:48-51.

491. Murphy BL, Babb SM, Ravichandran C, Cohen BM. Oral SAMe in Persistent Treatment-Refractory Bipolar Depression A Double-Blind, Randomized Clinical Trial. Journal of Clinical Psychopharmacology. 2014; 34:413-6.

492. Brennan BP, Jensen JE, Hudson JI, Coit CE, Beaulieu A, Pope HG, et al. A Placebo-Controlled Trial of Acetyl-L-Carnitine and alpha-Lipoic Acid in the Treatment of Bipolar Depression. Journal of Clinical Psychopharmacology. 2013; 33:627-35.

493. Hu SH, Lai JB, Xu DR, Qi HL, Peterson BS, Bao AM, et al. Efficacy of repetitive transcranial magnetic stimulation with quetiapine in treating bipolar II depression: a randomized, double-blinded, control study. Scientific Reports. 2016; 6.

494. Gilmer WS, Lorenzen KM, Zarnicki J. Transcranial magnetic stimulation (TMS) for treatment resistant bipolar depression: a naturalistic case series with clinical outcomes and observations. Bipolar Disorders. 2013; 15:80-1.

495. Lee SY, Chen SL, Chang YH, Chen PS, Huang SY, Tzeng NS, et al. The Effects of Add-On Low-Dose Memantine on Cytokine Levels in Bipolar II Depression A 12-Week Double-Blind, Randomized Controlled Trial. Journal of Clinical Psychopharmacology. 2014; 34:337-43.

496. Young AH, McElroy SL, Olausson B, Paulsson BR, Embolden IDCI, Embolden IIDCI. A randomised, placebo-controlled 52-week trial of continued quetiapine treatment in recently depressed patients with bipolar I and bipolar II disorder. World Journal of Biological Psychiatry. 2014; 15:96-112.

497. Calabrese JR, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Findling RL. New data on the use of lithium, divalproate, and lamotrigine in rapid cycling bipolar disorder. European Psychiatry. 2005; 20:92-5.

498. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. J Affect Disord. 2015; 185:31-7.

499. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. British Journal of Psychiatry. 2001; 178:S184-S90.

500. Suppes T, Brown ES, McElroy SL, Keck PE, Nolen W, Kupka R, et al. Lamotrigine for the treatment of bipolar disorder: a clinical case series. Journal of Affective Disorders. 1999; 53:95-8.

501. Chang JS, Moon E, Cha B, Ha K. Adjunctive lamotrigine therapy for patients with bipolar II depression partially responsive to mood stabilizers. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2010; 34:1322-6.

502. Sharma V, Khan M, Corpse C. Role of lamotrigine in the management of treatment-resistant bipolar II depression: A chart review. Journal of Affective Disorders. 2008; 111:100-5.

503. Jung IK, Lee MS, Kang BJ, Kim MJ, Lee JH. Lamotrigine treatment for patients with bipolar ii disorder: Retrospective report of 30 cases. Bipolar Disorders. 2008; 10:45-6.

504. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar ll depression: A randomized, double-blind, parallel-group, prospective study. Journal of Affective Disorders. 2015; 185:31-7.

505. Amsterdam JD, Shults J. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. International Clinical Psychopharmacology. 2005; 20:257-64.

506. Bowden CL, Singh V, Weisler R, Thompson P, Chang X, Quinones M, et al. Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. Acta Psychiatrica Scandinavica. 2012; 126:342-50.

507. Parker G, Tully L, Olley A, Hadzi-Pavlovic D. SSRIs as mood stabilizers for Bipolar II Disorder? A proof of concept study. Journal of Affective Disorders. 2006; 92:205-14.

508. Pan PY, Lee MS, Lo MC, Yang EL, Yeh CB. Olanzapine is superior to lamotrigine in the prevention of bipolar depression: a naturalistic observational study. Bmc Psychiatry. 2014; 14.

509. Viguera AC, Cohen LS, Bouffard S, Whitfield TH, Baldessarini RJ. Reproductive decisions by women with bipolar disorder after prepregnancy psychiatric consultation. Am J Psychiatry. 2002; 159:2102-4.

510. Rusner M, Berg M, Begley C. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. Bmc Pregnancy and Childbirth. 2016; 16.

511. Boden R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. Bmj. 2012; 345:e7085.

512. Joffe H. Reproductive biology and psychotropic treatments in premenopausal women with bipolar disorder. Journal of Clinical Psychiatry. 2007; 68:10-5.

513. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: Prospective study of mood stabilizer discontinuation. American Journal of Psychiatry. 2007; 164:1817-24.

514. Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GF, Wright R, et al. The impact of reproductive events on the course of bipolar disorder in women. Journal of Clinical Psychiatry. 2002; 63:284-7.

515. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. American Journal of Psychiatry. 2000; 157:179-84.

516. Iqbal MM, Gundlapalli SP, Ryan WG, Ryals T, Passman TE. Effects of antimanic mood-stabilizing drugs on fetuses, neonates, and nursing infants. Southern Medical Journal. 2001; 94:304-22.

517. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, et al. Management of bipolar disorder during pregnancy and the postpartum period. American Journal of Psychiatry. 2004; 161:608-20.

518. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Research. 2001; 47:151-4.

519. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. Cns Drugs. 2002; 16:263-72.

520. N P, A V, RJ B. Mood-Stabilising Anticonvulsants, Spina Bifida, and Folate Supplementation: Commentary. Journal of Clinical Psychopharmacology. In press.

521. Health Product InfoWatch. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/health-product-infowatch-april-2017-page-2.html.

522. Kuehn BM. No easy answers for physicians caring for pregnant women with depression. Jama. United States, 2009: 2413-4, 20.

523. Frey BN, Simpson W, Wright L, Steiner M. Sensitivity and Specificity of the Mood Disorder Questionnaire as a Screening Tool for Bipolar Disorder During Pregnancy and the Postpartum Period. Journal of Clinical Psychiatry. 2012; 73:1456-61.

524. Sharma V, Xie B. Screening for postpartum bipolar disorder: Validation of the Mood Disorder Questionnaire. Journal of Affective Disorders. 2011; 131:408-11.

525. Clark CT, Sit DK, Driscoll K, Eng HF, Confer AL, Luther JF, et al. DOES SCREENING WITH THE MDQ AND EPDS IMPROVE IDENTIFICATION OF BIPOLAR DISORDER IN AN OBSTETRICAL SAMPLE? Depression and Anxiety. 2015; 32:518-26.

526. Merrill L, Mittal L, Nicoloro J, Caiozzo C, Maciejewski PK, Miller LJ. Screening for bipolar disorder during pregnancy. Archives of Womens Mental Health. 2015; 18:579-83.

527. Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry. 2013; 70:490-8.

528. Sharma V, Pope CJ. Pregnancy and bipolar disorder: a systematic review. J Clin Psychiatry. 2012; 73:1447-55.

529. Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. N Engl J Med. 2017; 376:2245-54.

530. Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. Journal of Clinical Psychiatry. 2002; 63:42-55.

531. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med. 2010; 362:2185-93.

532. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009; 360:1597-605.

533. Information for Healthcare Professionals: Risk of Neural Tube Birth Defects following prenatal exposure to Valproate. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm192649.htm.

534. Freedman R, Ross RG. Prenatal choline and the development of schizophrenia. Shanghai Arch Psychiatry. 2015; 27:90-102.

535. Raghavan R, Riley AW, Volk H, Caruso D, Hironaka L, Sices L, et al. Maternal Multivitamin Intake, Plasma Folate and Vitamin B12 Levels and Autism Spectrum Disorder Risk in Offspring. Paediatr Perinat Epidemiol. 2017.

536. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJM, Kushner SA, Bergink V. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. American Journal of Psychiatry. 2016; 173:117-27.

537. Bergink V, Burgerhout KM, Koorengevel KM, Kamperman AM, Hoogendijk WJ, Lambregtse-van den Berg MP, et al. Treatment of Psychosis and Mania in the Postpartum Period. American Journal of Psychiatry. 2015; 172:115-23.

538. Sharma V, Khan M, Sommerdyk C. Quetiapine in the Acute Treatment of Bipolar Postpartum Depression A Chart Review. Journal of Clinical Psychopharmacology. 2015; 35:733-5.

539. Sharma V, Doobay M, Baczynski C. Bipolar postpartum depression: An update and recommendations. J Affect Disord. 2017; 219:105-11.

540. Heron J, McGuinness M, Blackmore ER, Craddock N, Jones I. Early postpartum symptoms in puerperal psychosis. Bjog. 2008; 115:348-53.

541. Menon SJ. Psychotropic medication during pregnancy and lactation. Archives of Gynecology and Obstetrics. 2008; 277:1-13.

542. Pacchiarotti I, Leon-Caballero J, Murru A, Verdolini N, Furio MA, Pancheri C, et al. Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. Eur Neuropsychopharmacol. 2016; 26:1562-78.

543. Ward RM, Bates BA, Benitz WE, Burchfield DJ, Ring JC, Walls RP, et al. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108:776-89.

544. M T, V S. Between a rock-a-bye and a hard place: mood disorders during the perinatal period. CNS Spectrums. In press.

545. Sharma V, Xie B, Campbell MK, Penava D, Hampson E, Mazmanian D, et al. A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. Bipolar Disord. 2014; 16:16-21.

546. Dias RS, Lafer B, Russo C, Del Debbio A, Nierenberg AA, Sachs GS, et al. Longitudinal Follow-Up of Bipolar Disorder in Women With Premenstrual Exacerbation: Findings From STEP-BD. American Journal of Psychiatry. 2011; 168:386-94.

547. Frey BN, Minuzzi L. Comorbid bipolar disorder and premenstrual dysphoric disorder: real patients, unanswered questions. Arch Womens Ment Health. 2013; 16:79-81.

548. Slyepchenko A, Frey BN, Lafer B, Nierenberg AA, Sachs GS, Dias RS. Increased illness burden in women with comorbid bipolar and premenstrual dysphoric disorder: data from 1 099 women from STEP-BD study. Acta Psychiatr Scand. 2017; 136:473-82.

549. Teatero ML, Mazmanian D, Sharma V. Effects of the menstrual cycle on bipolar disorder. Bipolar Disorders. 2014; 16:22-36.

550. Wittchen HU, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. Psychol Med. 2002; 32:119-32.

551. Smith M, Frey BN. Treating comorbid premenstrual dysphoric disorder in women with bipolar disorder. J Psychiatry Neurosci. 2016; 41:E22-3.

552. Sajatovic M, Friedman SH, Schuermeyer IN, Safavi R, Ignacio RV, Hays RW, et al. Menopause knowledge and subjective experience among peri- and postmenopausal women with bipolar disorder, schizophrenia and major depression. Journal of Nervous and Mental Disease. 2006; 194:173-8.

553. Blackmore ER, Craddock N, Walters J, Jones I. Is the perimenopause a time of increased risk of recurrence in women with a history of bipolar affective postpartum psychosis? A case series. Archives of Womens Mental Health. 2008; 11:75-8.

554. Marsh WK, Ketter TA, Crawford SL, Johnson JV, Kroll-Desrosiers AR, Rothschild AJ. Progression of female reproductive stages associated with bipolar illness exacerbation. Bipolar Disorders. 2012; 14:515-26.

555. Marsh WK, Templeton A, Ketter TA, Rasgon NL. Increased frequency of depressive episodes during the menopausal transition in women with bipolar disorder: preliminary report. J Psychiatr Res. 2008; 42:247-51.

556. Soares CN, Taylor V. Effects and management of the menopausal transition in women with depression and bipolar disorder. Journal of Clinical Psychiatry. 2007; 68:16-21.

557. Goldstein BI, Birmaher B. Prevalence, Clinical Presentation and Differential Diagnosis of Pediatric Bipolar Disorder. Israel Journal of Psychiatry and Related Sciences. 2012; 49:3-14.

558. Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. J Clin Psychiatry. 2011; 72:1250-6.

559. Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar Disorders. 2016; 18:19-32.

560. Leibenluft E, Rich BA. Pediatric bipolar disorder. Annu Rev Clin Psychol. 2008; 4:163-87.

561. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry. 2003; 160:430-7.

562. Goldstein BI, Birmaher B, Carlson GA, DelBello MP, Findling RL, Fristad M, et al. The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. Bipolar Disord. 2017.

563. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biological Psychiatry. 2004; 55:875-81.

564. Goldstein BI, Levitt AJ. Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the national epidemiologic survey on alcohol and related conditions. Am J Psychiatry. 2006; 163:1633-6.

565. Axelson DA, Birmaher B, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, et al. Concerns Regarding the Inclusion of Temper Dysregulation Disorder With Dysphoria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Journal of Clinical Psychiatry. 2011; 72:1257-62.

566. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-Year Longitudinal Course of Children and Adolescents With Bipolar Spectrum Disorders: The Course and Outcome of Bipolar Youth (COBY) Study. American Journal of Psychiatry. 2009; 166:795-804.

567. Parens E, Johnston J. Controversies concerning the diagnosis and treatment of bipolar disorder in children. Child Adolesc Psychiatry Ment Health. 2010; 4:9.

568. Kozloff N, Cheung AH, Schaffer A, Cairney J, Dewa CS, Veldhuizen S, et al. Bipolar disorder among adolescents and young adults: results from an epidemiological sample. J Affect Disord. 2010; 125:350-4.

569. Khazanov GK, Cui L, Merikangas KR, Angst J. Treatment patterns of youth with bipolar disorder: results from the National Comorbidity Survey-Adolescent Supplement (NCS-A). J Abnorm Child Psychol. 2015; 43:391-400.

570. Goldstein BI. Recent Progress in Understanding Pediatric Bipolar Disorder. Archives of Pediatrics & Adolescent Medicine. 2012; 166:362-71.

571. Post RM, Leverich GS, Kupka RW, Keck PE, Jr., McElroy SL, Altshuler LL, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry. 2010; 71:864-72.

572. Miller S, Chang KD, Ketter TA. Bipolar disorder and attention-deficit/hyperactivity disorder comorbidity in children and adolescents: evidence-based approach to diagnosis and treatment. J Clin Psychiatry. 2013; 74:628-9.

573. Fonseka TM, Swampillai B, Timmins V, Scavone A, Mitchell R, Collinger KA, et al. Significance of borderline personality-spectrum symptoms among adolescents with bipolar disorder. J Affect Disord. 2015; 170:39-45.

574. Uchida M, Serra G, Zayas L, Kenworthy T, Faraone SV, Biederman J. Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression. Journal of Affective Disorders. 2015; 176:1-7.

575. Uchida M, Serra G, Zayas L, Kenworthy T, Hughes B, Koster A, et al. Can manic switches be predicted in pediatric major depression? A systematic literature review. Journal of Affective Disorders. 2015; 172:300-6.

576. Ratheesh A, Davey C, Hetrick S, Alvarez-Jimenez M, Voutier C, Bechdolf A, et al. A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. Acta Psychiatr Scand. 2017; 135:273-84.

577. Chang K, Steiner H, Dienes K, Adleman N, Ketter T. Bipolar offspring: a window into bipolar disorder evolution. Biol Psychiatry. 2003; 53:945-51.

578. Birmaher B, Axelson D, Monk K, Kalas C, Goldstein B, Hickey MB, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. Arch Gen Psychiatry. 2009; 66:287-96.

579. Goldstein BI, Shamseddeen W, Axelson DA, Kalas C, Monk K, Brent DA, et al. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2010; 49:388-96.

580. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? Paediatr Drugs. 2011; 13:225-43.

581. Youngstrom EA, Frazier TW, Demeter C, Calabrese JR, Findling RL. Developing a Ten Item Mania Scale from the Parent General Behavior Inventory for Children and Adolescents. The Journal of clinical psychiatry. 2008; 69:831-9.

582. Diler RS, Birmaher B, Axelson D, Goldstein B, Gill M, Strober M, et al. The Child Behavior Checklist (CBCL) and the CBCL-Bipolar Phenotype Are Not Useful in Diagnosing Pediatric Bipolar Disorder. Journal of Child and Adolescent Psychopharmacology. 2009; 19:23-30.

583. Post RM, Rowe M, Kaplan D, Findling R. The Child Network for Parents to Track Their Child's Mood and Behavior. J Child Adolesc Psychopharmacol. 2017.

584. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, et al. Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease A Scientific Statement From the American Heart Association. Circulation. 2015; 132:965-86.

585. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disorders. 2010; 12:116-41.

586. Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, et al. A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents. Archives of General Psychiatry. 2012; 69:515-28.

587. Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, et al. Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study. Pediatrics. 2015; 136:885-94.

588. Haas M, DelBello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disorders. 2009; 11:687-700.

589. Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute Treatment of Pediatric Bipolar I Disorder, Manic or Mixed Episode, With Aripiprazole: A Randomized, Double-Blind, Placebo-Controlled Study. Journal of Clinical Psychiatry. 2009; 70:1441-51.

590. Findling RL, Landbloom RL, Szegedi A, Koppenhaver J, Braat S, Zhu Q, et al. Asena pine for the Acute Treatment of Pediatric Manic or Mixed Episode of Bipolar I Disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2015; 54:1032-41.

591. Pathak S, Findling RL, Earley WR, Acevedo LD, Stankowski J, DelBello MP. Efficacy and Safety of Quetiapine in Children and Adolescents With Mania Associated With Bipolar I Disorder: A 3-Week, Double-Blind, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2013; 74:E100-U47.

592. Tohen M, Kryzhanovskaya L, Carlson G, DelBello M, Wozniak J, Kowatch R, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. American Journal of Psychiatry. 2007; 164:1547-56.

593. Findling RL, Cavus I, Pappadopulos E, Vanderburg DG, Schwartz JH, Gundapaneni BK, et al. Efficacy, Long-Term Safety, and Tolerability of Ziprasidone in Children and Adolescents with Bipolar Disorder. Journal of Child and Adolescent Psychopharmacology. 2013; 23:545-57.

594. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. Journal of the American Academy of Child and Adolescent Psychiatry. 2002; 41:1216-23.

595. R K, R F, R S. Pediatric Bipolar Collaborative Mood Stabilizer Trial. Annual Meeting of the American Academy of Child and

Adolescent Psychiatry. Boston MA, 2007.

596. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. American Journal of Psychiatry. 2006; 163:1179-86.

597. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double-Blind, Placebo-Controlled Study. Journal of the American Academy of Child & Adolescent Psychiatry.

598. Patel NC, Delbello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, et al. Open-label lithium for the treatment of adolescents with bipolar depression. Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45:289-97.

599. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45:298-304.

600. Detke HC, DelBello MP, Landry J, Usher RW. Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2015; 54:217-24.

601. DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disorders. 2009; 11:483-93.

602. Findling RL, Pathak S, Earley WR, Liu S, DelBello MP. Efficacy and Safety of Extended-Release Quetiapine Fumarate in Youth with Bipolar Depression: An 8 Week, Double-Blind, Placebo-Controlled Trial. Journal of Child and Adolescent Psychopharmacology. 2014; 24:325-35.

603. Bhowmik D, Aparasu RR, Rajan SS, Sherer JT, Ochoa-Perez M, Chen H. Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. J Child Adolesc Psychopharmacol. 2014; 24:551-61.

604. Findling RL, Correll CU, Nyilas M, Forbes RA, McQuade RD, Jin N, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disorders. 2013; 15:138-49.

605. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, et al. Double-Blind, Randomized, Placebo-Controlled Long-Term Maintenance Study of Aripiprazole in Children With Bipolar Disorder. Journal of Clinical Psychiatry. 2012; 73:57-63.

606. Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2005; 44:409-17.

607. Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG. Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. Bipolar Disorders. 2005; 7:266-73.

608. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2000; 39:713-20.

609. Findling RL, Chang K, Robb A, Foster VJ, Horrigan J, Krishen A, et al. Adjunctive Maintenance Lamotrigine for Pediatric Bipolar I Disorder: A Placebo-Controlled, Randomized Withdrawal Study. Journal of the American Academy of Child and Adolescent Psychiatry. 2015; 54:1020-31.

610. Findling RL, Landbloom RL, Mackle M, Wu X, Snow-Adami L, Chang K, et al. Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. Paediatr Drugs. 2016; 18:367-78.

611. Duffy A, Milin R, Grof P. Maintenance treatment of adolescent bipolar disorder: open study of the effectiveness and tolerability of quetiapine. Bmc Psychiatry. 2009; 9.

612. Findling RL, Pathak S, Earley WR, Liu S, DelBello M. Safety, Tolerability, and Efficacy of Quetiapine in Youth with Schizophrenia or Bipolar I Disorder: A 26-Week, Open-Label, Continuation Study. Journal of Child and Adolescent Psychopharmacology. 2013; 23:490-501.

613. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. American Journal of Psychiatry. 2005; 162:58-64.

614. Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and Attention-Deficit/Hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; 46:1445-53.

615. Viktorin A, Ryden E, Thase ME, Chang Z, Lundholm C, D'Onofrio BM, et al. The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder. Am J Psychiatry. 2017; 174:341-8.

616. Hah M, Chang KK. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents with bipolar disorders. Journal of Child and Adolescent Psychopharmacology. 2005; 15:996-1004.

617. Chang KK, Nayar D, Howe M, Rana M. Atomoxetine as an Adjunct Therapy in the Treatment of Co-Morbid Attention-Deficit/Hyperactivity Disorder in Children and Adolescents with Bipolar I or II Disorder. Journal of Child and Adolescent Psychopharmacology. 2009; 19:547-51.

618. Peruzzolo TL, Tramontina S, Rodrigues RB, Rohde LA, Zeni CP. Avoiding stimulants may not prevent manic switch: a case report with atomoxetine. J Neuropsychiatry Clin Neurosci. 2014; 26:E30-1.

619. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. Journal of the American Academy of Child and Adolescent Psychiatry. 1998; 37:171-8.

620. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry. 2012; 169:805-12.

621. Prado E, Maes M, Piccoli LG, Baracat M, Barbosa DS, Franco O, et al. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. Redox Rep. 2015; 20:215-22.

622. Depp CA, Jeste DV. Bipolar disorder in older adults: a critical review. Bipolar Disorders. 2004; 6:343-67.

623. Yu C, Sylvestre JD, Segal M, Looper KJ, Rej S. Predictors of psychiatric re-hospitalization in older adults with severe mental illness. International Journal of Geriatric Psychiatry. 2015; 30:1114-9.

624. Sajatovic M, Bingham CR, Campbell EA, Fletcher DF. Bipolar disorder in older adult inpatients. Journal of Nervous and Mental Disease. 2005; 193:417-9.

625. Jeste DV, Alexopoulos GS, Bartels SJ, Cummings JL, Gallo JJ, Gottlieb GL, et al. Consensus statement on the upcoming crisis in geriatric mental health - Research agenda for the next 2 decades. Archives of General Psychiatry. 1999; 56:848-53.

626. Hirschfeld RMA, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. Journal of Clinical Psychiatry. 2003; 64:53-9.

627. Yassa R, Nair NPV, Iskandar H. LATE-ONSET BIPOLAR DISORDER. Psychiatric Clinics of North America. 1988; 11:117-31.

628. Subramaniam H, Dennis MS, Byrne EJ. The role of vascular risk factors in late onset bipolar disorder. International Journal of Geriatric Psychiatry. 2007; 22:733-7.

629. Sajatovic M, Blow FC, Ignacio RV, Kales HC. New-onset bipolar disorder in later life. American Journal of Geriatric Psychiatry. 2005; 13:282-9.

630. Depp CA, Jin H, Mohamed S, Kaskow J, Moore DJ, Jeste DV. Bipolar disorder in middle-aged and elderly adults: Is age of onset important? Journal of Nervous and Mental Disease. 2004; 192:796-9.

631. Young RC, Kiosses D, Heo M, Schulberg HC, Murphy C, Klimstra S, et al. Age and ratings of manic psychopathology. Bipolar Disorders. 2007; 9:301-4.

632. Oostervink F, Boomsma MM, Nolen WA, Board EA. Bipolar disorder in the elderly; different effects of age and of age of onset. Journal of Affective Disorders. 2009; 116:176-83.

633. Lala SV, Sajatovic M. Medical and Psychiatric Comorbidities Among Elderly Individuals With Bipolar Disorder: A Literature Review. Journal of Geriatric Psychiatry and Neurology. 2012; 25:20-5.

634. Depp CA, Lindamer LA, Folsom DP, Gilmer T, Hough RL, Garcia P, et al. Differences in clinical features and mental health service use in bipolar disorder across the lifespan. American Journal of Geriatric Psychiatry. 2005; 13:290-8.

635. Tsai S-Y, Lee H-C, Chen C-C, Huang Y-L. Cognitive impairment in later life in patients with early-onset bipolar disorder. Bipolar Disorders. 2007; 9:868-75.

636. Gildengers AG, Chisholm D, Butters MA, Anderson SJ, Begley A, Holm M, et al. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychological Medicine. 2013; 43:801-11.

637. Schouws S, Comijs HC, Dols A, Beekman ATF, Stek ML. Five-year follow-up of cognitive impairment in older adults with bipolar disorder. Bipolar Disorders. 2016; 18:148-54.

638. Santos JL, Aparicio A, Bagney A, Sanchez-Morla EM, Rodriguez-Jimenez R, Mateo J, et al. A five-year follow-up study of neurocognitive functioning in bipolar disorder. Bipolar Disorders. 2014; 16:722-31.

639. Kessing LV, Sondergard L, Forman JL, Andersen PK. Lithium Treatment and Risk of Dementia. Archives of General Psychiatry. 2008; 65:1331-5.

640. Kessing LV, Gerds TA, Knudsen NN, Jorgensen LF, Kristiansen SM, Voutchkova D, et al. Association of Lithium in Drinking Water With the Incidence of Dementia. JAMA Psychiatry. 2017; 74:1005-10.

641. Morris G, Berk M. The Putative Use of Lithium in Alzheimer's Disease. Curr Alzheimer Res. 2016; 13:853-61.

642. Andreou C, Bozikas VP. The predictive significance of neurocognitive factors for functional outcome in bipolar disorder. Current Opinion in Psychiatry. 2013; 26:54-9.

643. Tsai S-Y, Kuo C-J, Chung K-H, Huang Y-L, Lee H-C, Chen C-C. Cognitive Dysfunction and Medical Morbidity in Elderly Outpatients With Bipolar Disorder. American Journal of Geriatric Psychiatry. 2009; 17:1004-11.

644. Westman J, Hallgren J, Wahlbeck K, Erlinge D, Alfredsson L, Osby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. Bmj Open. 2013; 3.

645. Kilbourne AM, Goodrich DE, Lai ZS, Post EP, Schumacher K, Nord KM, et al. Randomized Controlled Trial to Assess Reduction of Cardiovascular Disease Risk in Patients With Bipolar Disorder: The Self-Management Addressing Heart Risk Trial (SMAHRT). Journal of Clinical Psychiatry. 2013; 74:E655-E62.

646. Young RC, Mulsant BH, Sajatovic M, Gildengers AG, Gyulai L, Al Jurdi RK, et al. GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder. American Journal of Psychiatry. 2017:appi.ajp.2017.15050657.

647. Marras C, Herrmann N, Fischer HD, Fung KW, Gruneir A, Rochon PA, et al. Lithium Use in Older Adults is Associated with Increased Prescribing of Parkinson Medications. American Journal of Geriatric Psychiatry. 2016; 24:301-9.

648. Rej S, Elie D, Mucsi I, Looper KJ, Segal M. Chronic kidney disease in lithium-treated older adults: a review of epidemiology, mechanisms, and implications for the treatment of late-life mood disorders. Drugs Aging. 2015; 32:31-42.

649. Svendal G, Fasmer OB, Engeland A, Berk M, Lund A. Co-prescription of medication for bipolar disorder and diabetes mellitus: a nationwide population-based study with focus on gender differences. BMC Med. 2012; 10:148.

650. Dols A, Sienaert P, van Gerven H, Schouws S, Stevens A, Kupka R, et al. The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. Int Clin Psychopharmacol. 2013; 28:287-96.

651. Graff-Guerrero A, Rajji TK, Mulsant BH, Nakajima S, Caravaggio F, Suzuki T, et al. Evaluation of Antipsychotic Dose Reduction in Late-Life Schizophrenia: A Prospective Dopamine D2/3 Receptor Occupancy Study. JAMA Psychiatry. 2015; 72:927-34.

652. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015; 72:438-45.

653. Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. Ann Intern Med. 2014; 161:242-8.

654. Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord. 2009; 11:559-95.

655. Al Jurdi RK, Marangell LB, Petersen NJ, Martinez M, Gyulai L, Sajatovic M. Prescription patterns of psychotropic medications in elderly compared with younger participants who achieved a "recovered" status in the systematic treatment enhancement program for bipolar disorder. Am J Geriatr Psychiatry. 2008; 16:922-33.

656. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disorders. 2015; 17:689-704.

657. Sajatovic M, Calabrese JR, Mullen J. Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disorders. 2008; 10:662-71.

658. Baruch Y, Tadger S, Plopski I, Barak Y. Asenapine for elderly bipolar manic patients. Journal of Affective Disorders. 2013; 145:130-2.

659. Sajatovic M, Dines P, Fuentes-Casiano E, Athey M, Cassidy KA, Sams J, et al. Asenapine in the treatment of older adults with bipolar disorder. International Journal of Geriatric Psychiatry. 2015; 30:710-9.

660. Sajatovic M, Coconcea N, Ignacio RV, Blow FC, Hays RW, Cassidy KA, et al. Aripiprazole therapy in 20 older adults with bipolar disorder: A 12-week, open-label trial. Journal of Clinical Psychiatry. 2008; 69:41-6.

661. Madhusoodanan S, Brenner R, Araujo L, Abaza A. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry. 1995; 56:514-8.

662. Shulman RW, Singh A, Shulman KI. Treatment of elderly institutionalized bipolar patients with clozapine. Psychopharmacology Bulletin. 1997; 33:113-8.

663. M S, B. P. Quetiapine for the treatment of depressive episodes in adults aged 55 to 65 years with bipolar disorder. AAGP Annual Meeting. New Orleans Louisiana, 2007.

664. Sajatovic M, Forester BP, Tsai J, Kroger H, Pikalov A, Cucchiaro J, et al. Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression: Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies. J Clin Psychiatry. 2016; 77:e1324-e31.

665. Robillard M, Conn DK. Lamotrigine use in geriatric patients with bipolar depression. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 2002; 47:767-70.

666. Sajatovic M, Gildengers A, Al Jurdi RK, Gyulai L, Cassidy KA, Greenberg RL, et al. Multisite, open-label, prospective trial of lamotrigine for geriatric bipolar depression: a preliminary report. Bipolar Disorders. 2011; 13:294-302.

667. Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, et al. Carbamazepine for treatment-resistant melancholia. J Clin Psychiatry. 1991; 52:472-6.

668. Rej S, Herrmann N, Shulman K, Fischer HD, Fung K, Gruneir A. Current psychotropic medication prescribing patterns in late-life bipolar disorder. Int J Geriatr Psychiatry. 2016.

669. Geddes JR, Goodwin GM, Rendell J, Azorin J-M, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010; 375:385-95.

670. Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, et al. Maintenance treatment outcomes in older patients with bipolar I disorder. Am J Geriatr Psychiatry. 2005; 13:305-11.

671. Lish JD, Dimemeenan S, Whybrow PC, Price RA, Hirschfeld RMA. THE NATIONAL DEPRESSIVE AND MANIC-DEPRESSIVE ASSOCIATION (DMDA) SURVEY OF BIPOLAR MEMBERS. Journal of Affective Disorders. 1994; 31:281-94.

672. McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. Human Psychopharmacology-Clinical and Experimental. 2004; 19:369-86.

673. Stratford HJ, Cooper MJ, Di Simplicio M, Blackwell SE, Holmes EA. Psychological therapy for anxiety in bipolar spectrum disorders: A systematic review. Clinical Psychology Review. 2015; 35:19-34.

674. Provencher MD, Hawke LD, Thienot E. Psychotherapies for comorbid anxiety in bipolar spectrum disorders. Journal of Affective Disorders. 2011; 133:371-80.

675. Secades-Alvarez A, Fernandez-Rodriguez C. Review of the efficacy of treatments for bipolar disorder and substance abuse. Rev Psiquiatr Salud Ment. 2017; 10:113-24.

676. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: Systematic review and meta-analysis. J Affect Disord. 2016; 206:321-30.

677. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: Systematic review and meta-analysis. J Affect Disord. 2016; 206:331-49.

678. Sonne SC, Brady KT, Morton WA. SUBSTANCE-ABUSE AND BIPOLAR AFFECTIVE-DISORDER. Journal of Nervous and Mental Disease. 1994; 182:349-52.

679. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disorders. 2001; 3:181-8.

680. Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. Bipolar Disorders. 2003; 5:58-61.

681. Beaulieu S, Saury S, Sareen J, Tremblay J, Schutz CG, McIntyre RS, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. Annals of Clinical Psychiatry. 2012; 24:38-55.

682. Messer T, Lammers G, Muller-Siecheneder F, Schmidt RF, Latifi S. Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry Res. 2017; 253:338-50.

683. Soyka M, Kranzler HR, Hesselbrock V, Kasper S, Mutschler J, Moller HJ. Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision. World J Biol Psychiatry. 2017; 18:86-119.

684. Kemp DE, Gao K, Ganocy SJ, Elhaj O, Bilali SR, Conroy C, et al. A 6-Month, Double-Blind, Maintenance Trial of Lithium Monotherapy Versus the Combination of Lithium and Divalproex for Rapid-Cycling Bipolar Disorder and Co-Occurring Substance Abuse or Dependence. Journal of Clinical Psychiatry. 2009; 70:113-21.

685. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism - A double-blind placebo-controlled study. Archives of General Psychiatry. 2005; 62:37-45.

686. Rubio G, Lopez-Munoz F, Alamo C. Effects of lamotrigine in patients with bipolar disorder and alcohol dependence. Bipolar disorders. 2006; 8:289-93.

687. Brady KT, Sonne SC, Anton R, Ballenger JC. Valproate in the treatment of acute bipolar affective episodes complicated by substance abuse: a pilot study. The Journal of clinical psychiatry. 1995; 56:118-21.

688. Albanese MJ, Clodfelter RC, Jr., Khantzian EJ. Divalproex sodium in substance abusers with mood disorder. The Journal of clinical psychiatry. 2000; 61:916-21.

689. Hertzman M. Divalproex sodium to treat concomitant substance abuse and mood disorders. Journal of substance abuse treatment. 2000; 18:371-2.

690. Mueser KT, Noordsy DL, Fox L, Wolfe R. Disulfiram treatment for alcoholism in severe mental illness. The American journal on addictions. 2003; 12:242-52.

691. Larson EW, Olincy A, Rummans TA, Morse RM. Disulfiram treatment of patients with both alcohol dependence and other psychiatric disorders: a review. Alcoholism, clinical and experimental research. 1992; 16:125-30.

692. Kofoed L, Kania J, Walsh T, Atkinson RM. Outpatient treatment of patients with substance abuse and coexisting psychiatric disorders. The American journal of psychiatry. 1986; 143:867-72.

693. Petrakis IL, Nich C, Ralevski E. Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. Schizophrenia bulletin. 2006; 32:644-54.

694. Petrakis I, Ralevski E, Nich C, Levinson C, Carroll K, Poling J, et al. Naltrexone and disulfiram in patients with alcohol dependence and current depression. Journal of clinical psychopharmacology. 2007; 27:160-5.

695. Sonne S, Brady K. Naltrexone for individuals with comorbid bipolar disorder and alcohol dependence. Journal of clinical psychopharmacology. 2000; 20:114-5.

696. Brown ES, Beard L, Dobbs L, Rush AJ. Naltrexone in patients with bipolar disorder and alcohol dependence. Depress Anxiety. 2006; 23:492-5.

697. Brown ES, Carmody TJ, Schmitz JM, Caetano R, Adinoff B, Swann AC, et al. A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence. Alcoholism, clinical and experimental research. 2009; 33:1863-9.

698. Perugi G, Toni C, Frare F, Ruffolo G, Moretti L, Torti C, et al. Effectiveness of adjunctive gabapentin in resistant bipolar disorder: Is it due to anxious-alcohol abuse comorbidity? Journal of Clinical Psychopharmacology. 2002; 22:584-91.

699. Azorin JM, Bowden CL, Garay RP, Perugi G, Vieta E, Young AH. Possible new ways in the pharmacological treatment of bipolar disorder and comorbid alcoholism. Neuropsychiatr Dis Treat. 2010; 6:37-46.

700. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. Jama. 2014; 311:1889-900.

701. Stedman M, Pettinati HM, Brown ES, Kotz M, Calabrese JR, Raines S. A Double-Blind, Placebo-Controlled Study With Quetiapine as Adjunct Therapy With Lithium or Divalproex in

Bipolar I Patients With Coexisting Alcohol Dependence. Alcoholism-Clinical and Experimental Research. 2010; 34:1822-31.

702. Brown ES, Davila D, Nakamura A, Carmody TJ, Rush AJ, Lo A, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Quetiapine in Patients with Bipolar Disorder, Mixed or Depressed Phase, and Alcohol Dependence. Alcoholism-Clinical and Experimental Research. 2014; 38:2113-8.

703. Gao KM, Wu RR, Kemp DE, Chen J, Karberg E, Conroy C, et al. Efficacy and Safety of Quetiapine-XR as Monotherapy or Adjunctive Therapy to a Mood Stabilizer in Acute Bipolar Depression With Generalized Anxiety Disorder and Other Comorbidities: A Randomized, Placebo-Controlled Trial. Journal of Clinical Psychiatry. 2014; 75:1062-8.

704. Tolliver BK, DeSantis SM, Brown DG, Prisciandaro JJ, Brady KT. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. Bipolar Disorders. 2012; 14:54-63.

705. Weinstock LM, Gaudiano BA, Wenze SJ, Epstein-Lubow G, Miller IW. Demographic and clinical characteristics associated with comorbid cannabis use disorders (CUDs) in hospitalized patients with bipolar I disorder. Compr Psychiatry. 2016; 65:57-62.

706. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE, Jr., et al. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. Arch Gen Psychiatry. 2007; 64:57-64.

707. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. Journal of Clinical Psychopharmacology. 2007; 27:498-502.

708. Brown ES, Todd JP, Hu LT, Schmitz JM, Carmody TJ, Nakamura A, et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Citicoline for Cocaine Dependence in Bipolar I Disorder. The American journal of psychiatry. 2015; 172:1014-21.

709. Kemp DE, Gao K, Ganocy SJ, Elhaj O, Bilali SR, Conroy C, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. The Journal of clinical psychiatry. 2009; 70:113-21.

710. Salloum IM, Douaihy A, Cornelius JR, Kirisci L, Kelly TM, Hayes J. Divalproex utility in bipolar disorder with co-occurring cocaine dependence: a pilot study. Addictive behaviors. 2007; 32:410-5.

711. Nunes EV, McGrath PJ, Wager S, Quitkin FM. Lithium treatment for cocaine abusers with bipolar spectrum disorders. The American journal of psychiatry. 1990; 147:655-7.

712. Brown ES, Nejtek VA, Perantie DC, Bobadilla L. Quetiapine in bipolar disorder and cocaine dependence. Bipolar disorders. 2002; 4:406-11.

713. Brown ES, Nejtek VA, Perantie DC, Rajan Thomas N, Rush AJ. Cocaine and amphetamine use in patients with psychiatric illness: a randomized trial of typical antipsychotic continuation or discontinuation. Journal of clinical psychopharmacology. 2003; 23:384-8.

714. Nejtek VA, Avila M, Chen L-A, Zielinski T, Djokovic M, Podawiltz A, et al. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. Journal of Clinical Psychiatry. 2008; 69:1257-66.

715. Albanese MJ, Suh JJ. Risperidone in cocaine-dependent patients with comorbid psychiatric disorders. Journal of psychiatric practice. 2006; 12:306-11.

716. Sepede G, Di Lorio G, Lupi M, Sarchione F, Acciavatti T, Fiori F, et al. Bupropion as an Add-on Therapy in Depressed Bipolar Disorder Type I Patients With Comorbid Cocaine Dependence. Clinical Neuropharmacology. 2014; 37:17-21.

717. Brown ES, Gabrielson B. A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. Journal of Affective Disorders. 2012; 143:257-60.

718. Brown ES, Sunderajan P, Hu LT, Sowell SM, Carmody TJ. A randomized, double-blind, placebo-controlled, trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012; 37:2347-54.

719. Maremmani I, Zolesi O, Aglietti M, Marini G, Tagliamonte A, Shinderman M, et al. Methadone dose and retention during treatment of heroin addicts with Axis I psychiatric comorbidity. Journal of addictive diseases. 2000; 19:29-41.

720. Maremmani AG, Rovai L, Bacciardi S, Rugani F, Pacini M, Pani PP, et al. The long-term outcomes of heroin dependent-treatment-resistant patients with bipolar 1 comorbidity after admission to enhanced methadone maintenance. Journal of affective disorders. 2013; 151:582-9.

721. Sani G, Kotzalidis GD, Vohringer P, Pucci D, Simonetti A, Manfredi G, et al. Effectiveness of Short-Term Olanzapine in Patients With Bipolar I Disorder, With or Without Comorbidity With Substance Use Disorder. Journal of Clinical Psychopharmacology. 2013; 33:231-5.

722. Brown ES, Jeffress J, Liggin JD, Garza M, Beard L. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. The Journal of clinical psychiatry. 2005; 66:756-60.

723. Schaffer A, McIntosh D, Goldstein BI, Rector NA, McIntyre RS, Beaulieu S, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. Annals of Clinical Psychiatry. 2012; 24:6-22.

724. Hawke LD, Provencher MD, Parikh SV, Zagorski B. Comorbid Anxiety Disorders in Canadians With Bipolar Disorder: Clinical Characteristics and Service Use. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 2013; 58:393-401.

725. Schaffer A, Cairney J, Veldhuizen S, Cheung A, Levitt A. Comparison of antidepressant use between subjects with bipolar disorder and major depressive disorder with or without comorbid anxiety. The Journal of clinical psychiatry. 2007; 68:1785-92.

726. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011; 342.

727. Sheehan DV, Harnett-Sheehan K, Hidalgo RB, Janavs J, McElroy SL, Amado D, et al. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. Journal of Affective Disorders. 2013; 145:83-94.

728. Hirschfeld RMA, Weisler RH, Raines SR, Macfadden W, Grp BS. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: A secondary analysis from a randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 2006; 67:355-62.

729. Sheehan DV, McElroy SL, Harnett-Sheehan K, Keck PE, Jr., Janavs J, Rogers J, et al. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. Journal of Affective Disorders. 2009; 115:376-85.

730. Suppes T, McElroy SL, Sheehan DV, Hidalgo RB, Cosgrove VE, Gwizdowski IS, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Ziprasidone Monotherapy in Bipolar Disorder With Co-Occurring Lifetime Panic or Generalized Anxiety Disorder. Journal of Clinical Psychiatry. 2014; 75:77-84.

731. Maina G, Albert U, Rosso G, Bogetto F. Olanzapine or lamotrigine addition to lithium in remitted bipolar disorder patients with anxiety disorder comorbidity: A randomized, single-blind, pilot study. Journal of Clinical Psychiatry. 2008; 69:609-16.

732. Vieta E, Martinez-Aran A, Nieto E, Colom F, Reinares M, Benabarre A, et al. Adjunctive gabapentin treatment of bipolar disorder. European Psychiatry. 2000; 15:433-7.

733. Amerio A, Odone A, Marchesi C, Ghaemi SN. Treatment of comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review. Journal of Affective Disorders. 2014; 166:258-63.

734. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Ghaemi SN. The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review and meta-analysis. J Affect Disord. 2015; 186:99-109.

735. Jeon S, Baek JH, Yang SY, Choi Y, Ahn SW, Ha K, et al. Exploration of comorbid obsessive-compulsive disorder in patients with bipolar disorder: The clinic-based prevalence rate, symptoms nature and clinical correlates. J Affect Disord. 2018; 225:227-33.

736. Nabavi B, Mitchell AJ, Nutt D. A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population. EBioMedicine. 2015; 2:1405-19.

737. Sadock, B.J, Sadock VA, Ruiz P. Kaplan

and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry. New York: Wolters

Kluwer; 2014.

738. Baek JH, Cha B, Moon E, Ha TH, Chang JS, Kim JH, et al. The effects of ethnic, social and cultural factors on axis I comorbidity of bipolar disorder: Results from the clinical setting in Korea. Journal of Affective Disorders. 166:264-9.

739. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Nassir Ghaemi S. Bipolar I and II Disorders; A Systematic Review and Meta-Analysis on Differences in Comorbid Obsessive-Compulsive Disorder. Iran J Psychiatry Behav Sci. 2016; 10:e3604.

740. Kruger S, Braunig P, Cooke RG. Comorbidity of obsessive-compulsive disorder in recovered inpatients with bipolar disorder. Bipolar Disorders. 2000; 2:71-4.

741. Goes FS, McCusker MG, Bienvenu OJ, Mackinnon DF, Mondimore FM, Schweizer B, et al. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. Psychol Med. 2012; 42:1449-59.

742. Issler CK, Monkul ES, Amaral JA, Tamada RS, Shavitt RG, Miguel EC, et al. Bipolar disorder and comorbid obsessive-compulsive disorder is associated with higher rates of anxiety and impulse control disorders. Acta Neuropsychiatr. 2010; 22:81-6.

743. Magalhaes PV, Kapczinski NS, Kapczinski F. Correlates and impact of obsessive-compulsive comorbidity in bipolar disorder. Compr Psychiatry. 2010; 51:353-6.

744. Ozdemiroglu F, Sevincok L, Sen G, Mersin S, Kocabas O, Karakus K, et al. Comorbid obsessive-compulsive disorder with bipolar disorder: A distinct form? Psychiatry Res. 2015; 230:800-5.

745. Shashidhara M, Sushma BR, Viswanath B, Math SB, Janardhan Reddy YC. Comorbid obsessive compulsive disorder in patients with bipolar-I disorder. J Affect Disord. 2015; 174:367-71.

746. Raja M, Azzoni A. Clinical management of obsessive-compulsive-bipolar comorbidity: a case series. Bipolar Disorders. 2004; 6:264-70.

747. Tonna M, Amerio A, Odone A, Stubbs B, Ghaemi SN. Comorbid bipolar disorder and obsessive-compulsive disorder: Which came first? Aust N Z J Psychiatry. 2016; 50:695-8.

748. Vazquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. Depress Anxiety. 2014; 31:196-206.

749. Bisol LW, Lara DR. Improvement of Obsessive-compulsive Disorder with Divalproex and Lamotrigine in Two Patients with Bipolar II Disorder. Pharmacopsychiatry. 2009; 42:37-9.

750. Marazziti D, Pfanner C, Dell'Osso B, Ciappareli A, Presta S, Corretti G, et al. Augmentation strategy with olanzapine in resistant obsessive compulsive disorder: an Italian long-term open-label study. Journal of Psychopharmacology. 2005; 19:392-4.

751. Petrikis P, Andreou C, Bozikas VP, Karavatos A. Effective Use of Olanzapine for Obsessive-Compulsive Symptoms in a Patient With Bipolar Disorder. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie. 2004; 49:572-3.

752. Jacobsen FM. RISPERIDONE IN THE TREATMENT OF AFFECTIVE-ILLNESS AND OBSESSIVE-COMPULSIVE DISORDER. Journal of Clinical Psychiatry. 1995; 56:423-9.

753. Pfanner C, Marazziti D, Dell'Osso L, Presta S, Gemignani A, Milanfranchi A, et al. Risperidone augmentation in refractory obsessive-compulsive disorder: an open-label study. International Clinical Psychopharmacology. 2000; 15:297-301.

754. Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: A review. Journal of Clinical Psychiatry. 2006; 67:1327-40.

755. Uguz F. Successful treatment of comorbid obsessive-compulsive disorder with aripiprazole in three patients with bipolar disorder. General Hospital Psychiatry. 2010; 32:556-8.

756. Lai J, Lu Q, Zhang P, Xu T, Xu Y, Hu S. Aripiprazole augmentation in managing comorbid obsessive-compulsive disorder and bipolar disorder: a case with suicidal attempts. Neuropsychiatr Dis Treat. 2017; 13:87-90.

757. Patra S. Treat the disease not the symptoms: Successful management of obsessive compulsive disorder in bipolar disorder with aripiprazole augmentation. Australian & New Zealand Journal of Psychiatry. 2016; 50:809-10.

758. Bulbul F, Copoglu US, Alpak G, Unal A, Tastan MF, Savas HA. Maintenance therapy with electroconvulsive therapy in a patient with a codiagnosis of bipolar disorder and obsessive-compulsive disorder. J ect. 2013; 29:e21-2.

759. Sahraian A, Bigdeli M, Ghanizadeh A, Akhondzadeh S. Topiramate as an adjuvant treatment for obsessive compulsive symptoms in patients with bipolar disorder: A randomized double blind placebo controlled clinical trial. Journal of Affective Disorders. 2014; 166:201-5.

760. Friborg O, Martinsen EW, Martinussen M, Kaiser S, Overgard KT, Rosenvinge JH. Comorbidity of personality disorders in mood disorders: a meta-analytic review of 122 studies from 1988 to 2010. J Affect Disord. 2014; 152-154:1-11.

761. Rosenbluth M, MacQueen G, McIntyre RS, Beaulieu S, Schaffer A. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid personality disorders. Annals of Clinical Psychiatry. 2012; 24:56-68.

762. Preston GA, Marchant BK, Reimherr FW, Strong RE, Hedges DW. Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. Journal of Affective Disorders. 2004; 79:297-303.

763. Colom F, Vieta E, Sanchez-Moreno J, Martinez-Aran A, Torrent C, Reinares M, et al. Psychoeducation in bipolar patients with comorbid personality disorders. Bipolar Disorders. 2004; 6:294-8.

764. Alesiani R, Boccalon S, Giarolli L, Blum N, Fossati A. Systems Training for Emotional Predictability and Problem Solving (STEPPS): Program efficacy and personality features as predictors of drop-out - An Italian study. Comprehensive Psychiatry. 2014; 55:920-7.

765. Goldstein TR, Axelson DA, Birmaher B, Brent DA. Dialectical behavior therapy for adolescents with bipolar disorder: A 1-year open trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; 46:820-30.

766. Van Dijk S, Jeffrey J, Katz MR. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. J Affect Disord. 2013; 145:386-93.

767. Brus MJ, Solanto MV, Goldberg JF. Adult ADHD vs. Bipolar Disorder in the DSM-5 Era: A Challenging Differentiation for Clinicians. Journal of Psychiatric Practice. 2014; 20:428-37.

768. Bond DJ, Hadjipavlou G, Lam RW, McIntyre RS, Beaulieu S, Schaffer A, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Annals of Clinical Psychiatry. 2012; 24:23-37.

769. Wilens TE, Prince JB, Spencer T, Van Patten SL, Doyle R, Girard K, et al. An open trial of bupropion for the treatment of adults with attention-deficit/hyperactivity disorder and bipolar disorder. Biol Psychiatry. 2003; 54:9-16.

770. McIntyre RS, Alsuwaidan M, Soczynska JK, Szpindel I, Bilkey TS, Almagor D, et al. The effect of lisdexamfetamine dimesylate on body weight, metabolic parameters, and attention deficit hyperactivity disorder symptomatology in adults with bipolar I/II disorder. Human Psychopharmacology-Clinical and Experimental. 2013; 28:421-7.

771. Wu HC, Chou FHC, Tsai KY, Su CY, Shen SP, Chung TC. The Incidence and Relative Risk of Stroke among Patients with Bipolar Disorder: A Seven-Year Follow-Up Study. Plos One. 2013; 8.

772. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. Bmc Medicine. 2013; 11.

773. Forty L, Ulanova A, Jones L, Jones I, Gordon-Smith K, Fraser C, et al. Comorbid medical illness in bipolar disorder. British Journal of Psychiatry. 2014; 205:465-72.

774. Weber NS, Fisher JA, Cowan DN, Niebuhr DW. Psychiatric and General Medical Conditions Comorbid With Bipolar Disorder in the National Hospital Discharge Survey. Psychiatric Services. 2011; 62:1152-8.

775. Gomes FA, Almeida KM, Magalhaes PV, Caetano SC, Kauer-Sant'Anna M, Lafer B, et al. Cardiovascular risk factors in outpatients with bipolar disorder: a report from the Brazilian Research Network in Bipolar Disorder. Revista Brasileira De Psiquiatria. 2013; 35:126-30.

776. Sylvia LG, Shelton RC, Kemp DE, Bernstein EE, Friedman ES, Brody BD, et al. Medical burden in bipolar disorder: findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). Bipolar Disorders. 2015; 17:212-23.

777. Kemp DE, Sylvia LG, Calabrese JR, Nierenberg AA, Thase ME, Reilly-Harrington NA, et al. General medical burden in bipolar disorder: findings from the LiTMUS comparative effectiveness trial. Acta Psychiatrica Scandinavica. 2014; 129:24-34.

778. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014; 13:153-60.

779. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and Mortality in Bipolar Disorder A Swedish National Cohort Study. Jama Psychiatry. 2013; 70:931-9.

780. de Almeida KM, Moreira CL, Lafer B. Metabolic syndrome and bipolar disorder: what should psychiatrists know? CNS Neurosci Ther. 2012; 18:160-6.

781. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143-421.

782. Gans RO. The metabolic syndrome, depression, and cardiovascular disease: interrelated conditions that share pathophysiologic mechanisms. Med Clin North Am. 2006; 90:573-91.

783. Taylor V, MacQueen G. Associations between bipolar disorder and metabolic syndrome: A review. J Clin Psychiatry. 2006; 67:1034-41.

784. Krishnan KR. Psychiatric and medical comorbidities of bipolar disorder. Psychosom Med. 2005; 67:1-8.

785. McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CW, Miranda A, et al. Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"? Ann Clin Psychiatry. 2007; 19:257-64.

786. Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008; 32:675-92.

787. McIntyre RS, Kenna HA, Nguyen HT, Law CW, Sultan F, Woldeyohannes HO, et al. Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: points of pathophysiological commonality with mood disorders? Adv Ther. 2010; 27:63-80.

788. McIntyre RS, Alsuwaidan M, Goldstein BI, Taylor VH, Schaffer A, Beaulieu S, et al. The Canadian Network for Mood and Anxiety Treatments (CANWAT) task force recommendations for the management of patients with mood disorders and comorbid metabolic disorders. Annals of Clinical Psychiatry. 2012; 24:69-81.

789. Domino ME, Wells R, Morrissey JP. Serving Persons With Severe Mental Illness in Primary Care-Based Medical Homes. Psychiatric Services. 2015; 66:477-83.

790. Steele LS, Durbin A, Sibley LM, Glazier R. Inclusion of persons with mental illness in patient-centred medical homes: cross-sectional findings from Ontario, Canada. Open Med. 2013; 7:e9-20.

791. Kohler-Forsberg O, Gasse C, Berk M, Ostergaard SD. Do Statins Have Antidepressant Effects? CNS Drugs. 2017; 31:335-43.

792. Salagre E, Fernandes BS, Dodd S, Brownstein DJ, Berk M. Statins for the treatment of depression: A meta-analysis of randomized, double-blind, placebo-controlled trials. J Affect Disord. 2016; 200:235-42.

793. Williams LJ, Pasco JA, Mohebbi M, Jacka FN, Stuart AL, Venugopal K, et al. Statin and Aspirin Use and the Risk of Mood Disorders among Men. Int J Neuropsychopharmacol. 2016.

794. Brownstein DJ, Salagre E, Kohler C, Stubbs B, Vian J, Pereira C, et al. Blockade of the angiotensin system improves mental health domain of quality of life: A meta-analysis of randomized clinical trials. Aust N Z J Psychiatry. 2017:4867417721654.

795. Vian J, Pereira C, Chavarria V, Kohler C, Stubbs B, Quevedo J, et al. The renin-angiotensin system: a possible new target for depression. BMC Med. 2017; 15:144.

796. Williams LJ, Pasco JA, Kessing LV, Quirk SE, Fernandes BS, Berk M. Angiotensin Converting Enzyme Inhibitors and Risk of Mood Disorders. Psychother Psychosom. Switzerland, 2016: 250-2.

797. Lan CC, Liu CC, Lin CH, Lan TY, McInnis MG, Chan CH, et al. A reduced risk of stroke with lithium exposure in bipolar disorder: a population-based retrospective cohort study. Bipolar Disorders. 2015; 17:705-14.

798. Huang RY, Hsieh KP, Huang WW, Yang YH. Use of lithium and cancer risk in patients with bipolar disorder: population-based cohort study. British Journal of Psychiatry. 2016; 209:395-401.

799. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Lithium and renal and upper urinary tract tumors - results from a nationwide population-based study. Bipolar Disorders. 2015; 17:805-13.

800. Diniz BS, Teixeira AL, Cao F, Gildengers A, Soares JC, Butters MA, et al. History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis. Am J Geriatr Psychiatry. 2017; 25:357-62.

801. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study. British Journal of Psychiatry. 2015; 207:46-51.

802. Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disorders. 2009; 11:559-95.

803. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012; 379:721-8.

804. Locharernkul C, Shotelersuk V, Hirankarn N. Pharmacogenetic screening of carbamazepine-induced severe cutaneous allergic reactions. J Clin Neurosci. 2011; 18:1289-94.

805. Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. Journal of Affective Disorders. 2017; 217:266-80.

806. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med. 1989; 321:1489-93.

807. Malhi GS, Gershon S, Outhred T. Lithiumeter: Version 2.0. Bipolar Disord. 2016; 18:631-41.

808. Gitlin MJ, Cochran SD, Jamison KR. MAINTENANCE LITHIUM TREATMENT - SIDE-EFFECTS AND COMPLIANCE. Journal of Clinical Psychiatry. 1989; 50:127-31.

809. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. American Journal of Psychiatry. 2006; 163:272-5.

810. Hu C, Torres IJ, Qian H, Wong H, Halli P, Dhanoa T, et al. Trajectories of body mass index change in first episode of mania: 3-year data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). J Affect Disord. 2017; 208:291-7.

811. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. Human Psychopharmacology-Clinical and Experimental. 2008; 23:95-105.

812. Nemeroff CB. Safety of available agents used to treat bipolar disorder: Focus on weight gain. Journal of Clinical Psychiatry. 2003; 64:532-9.

813. Fang F, Wang Z, Wu R, Calabrese JR, Gao K. Is there a 'weight neutral' second-generation antipsychotic for bipolar disorder? Expert Rev Neurother. 2017; 17:407-18.

814. Orsolini L, Tomasetti C, Valchera A, Vecchiotti R, Matarazzo I, Vellante F, et al. An update of safety of clinically used atypical antipsychotics. Expert Opinion on Drug Safety. 2016; 15:1329-47.

815. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. EFFICACY OF DIVALPROEX VS LITHIUM AND PLACEBO IN THE TREATMENT OF MANIA. Jama-Journal of the American Medical Association. 1994; 271:918-24.

816. Persson G. LITHIUM SIDE-EFFECTS IN RELATION TO DOSE AND TO LEVELS AND GRADIENTS OF LITHIUM IN PLASMA. Acta Psychiatrica Scandinavica. 1977; 55:208-13.

817. Persson G. PLASMA LITHIUM LEVELS AND SIDE-EFFECTS DURING ADMINISTRATION OF A SLOW RELEASE LITHIUM SULFATE PREPARATION (LITHIUM-LIPETT-C) AND LITHIUM-CARBONATE TABLETS. Acta Psychiatrica Scandinavica. 1974; 50:174-82.

818. Stone KA. Lithium-induced nephrogenic diabetes insipidus. J Am Board Fam Pract. 1999; 12:43-7.

819. Bosquet S, Descombes E, Gauthier T, Fellay G, Regamey C. Nephrotic syndrome during lithium therapy. Nephrol Dial Transplant. 1997; 12:2728-31.

820. Tandon P, Wong N, Zaltzman JS. Lithium-Induced Minimal Change Disease and Acute Kidney Injury. N Am J Med Sci. 2015; 7:328-31.

821. Pradhan BK, Chakrabarti S, Irpati AS, Bhardwaj R. Distress due to lithium-induced polyuria: exploratory study. Psychiatry Clin Neurosci. 2011; 65:386-8.

822. Presne C, Fakhouri F, Noel LH, Stengel B, Even C, Kreis H, et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int. 2003; 64:585-92.

823. Johnson G. Lithium - Early development, toxicity, and renal function. Neuropsychopharmacology. 1998; 19:200-5.

824. Castro VM, Roberson AM, McCoy TH, Wiste A, Cagan A, Smoller JW, et al. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. Neuropsychopharmacology. 2016; 41:1138-43.

825. Bocchetta A, Ardau R, Fanni T, Sardu C, Piras D, Pani A, et al. Renal function during long-term lithium treatment: a cross-sectional and longitudinal study. BMC Medicine. 2015; 13:12.

826. Rej S, Herrmann N, Shulman K, Fischer HD, Fung K, Harel Z, et al. Lithium Use, but Not Valproate Use, Is Associated With a Higher Risk of Chronic Kidney Disease in Older Adults With Mental Illness. J Clin Psychiatry. 2017.

827. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. Jama. 2007; 298:2038-47.

828. Crowe E, Halpin D, Stevens P. Early identification and management of chronic kidney disease: summary of NICE guidance. Bmj. 2008; 337:a1530.

829. Okusa MD, Crystal LJT. CLINICAL MANIFESTATIONS AND MANAGEMENT OF ACUTE LITHIUM INTOXICATION. American Journal of Medicine. 1994; 97:383-9.

830. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, et al. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. Int J Bipolar Disord. 2017; 5:27.

831. Haussmann R, Bauer M, von Bonin S, Grof P, Lewitzka U. Treatment of lithium intoxication: facing the need for evidence. Int J Bipolar Disord. 2015; 3:23.

832. Stubner S, Grohmann R, Engel R, Bandelow B, Ludwig WD, Wagner G, et al. Blood dyscrasias induced by psychotropic drugs. Pharmacopsychiatry. 2004; 37:S70-S8.

833. Swann AC. Major system toxicities and side effects of anticonvulsants. Journal of Clinical Psychiatry. 2001; 62:16-21.

834. Tohen M, Castillo J, Baldessarini RJ, Zarate C, Kando JC. BLOOD DYSCRASIAS WITH CARBAMAZEPINE AND VALPROATE - A PHARMACOEPIDEMIOLOGIC STUDY OF 2,228 PATIENTS AT RISK. American Journal of Psychiatry. 1995; 152:413-8.

835. Blackburn SCF, Oliart AD, Rodriguez LAG, Gutthann SP. Antiepileptics and blood dyscrasias: A cohort study. Pharmacotherapy. 1998; 18:1277-83.

836. Trannel TJ, Ahmed I, Goebert D. Occurrence of thrombocytopenia in psychiatric patients taking valproate. American Journal of Psychiatry. 2001; 158:128-30.

837. King DJ, Wager E. Haematological safety of antipsychotic drugs. Journal of Psychopharmacology. 1998; 12:283-8.

838. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet. 2000; 355:1048-52.

839. Roose SP, Bone S, Haidorfer C, Dunner DL, Fieve RR. LITHIUM TREATMENT IN OLDER PATIENTS. American Journal of Psychiatry. 1979; 136:843-4.

840. Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D, et al. Association between lower serum free T-4 and greater mood instability and depression in lithium-maintained bipolar patients. American Journal of Psychiatry. 1999; 156:1909-14.

841. Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA. Rapid and non-rapid cycling bipolar disorder: A meta-analysis of clinical studies. Journal of Clinical Psychiatry. 2003; 64:1483-94.

842. Bendz H, Sjodin I, Toss G, Berglund K. Hyperparathyroidism and long-term lithium therapy--a cross-sectional study and the effect of lithium withdrawal. J Intern Med. 1996; 240:357-65.

843. Joffe H, Cohen LS, Suppes T, McLaughlin WL, Lavori P, Adams JM, et al. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. Biological Psychiatry. 2006; 59:1078-86.

844. Zhang L, Li H, Li S, Zou X. Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2016; 202:26-31.

845. Joffe H, Cohen LS, Suppes T, Hwang CH, Molay F, Adams JM, et al. Longitudinal follow-up of reproductive and metabolic features of valproate-associated polycystic ovarian syndrome features: A preliminary report. Biol Psychiatry. 2006; 60:1378-81.

846. Montejo AL, Arango C, Bernardo M, Carrasco JL, Crespo-Facorro B, Cruz JJ, et al. Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics. Front Neuroendocrinol. 2017; 45:25-34.

847. Montejo AL, Arango C, Bernardo M, Carrasco JL, Crespo-Facorro B, Cruz JJ, et al. Spanish consensus on the risks and detection of antipsychotic drug-related hyperprolactinaemia. Rev Psiquiatr Salud Ment. 2016; 9:158-73.

848. Pacchiarotti I, Murru A, Kotzalidis GD, Bonnin CM, Mazzarini L, Colom F, et al. Hyperprolactinemia and medications for bipolar disorder: Systematic review of a neglected issue in clinical practice. European Neuropsychopharmacology. 2015; 25:1045-59.

849. Cullen B, Ward J, Graham NA, Deary IJ, Pell JP, Smith DJ, et al. Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: A systematic review. Journal of Affective Disorders. 2016; 205:165-81.

850. Goswami U, Sharma A, Varma A, Gulrajani C, Ferrier IN, Young AH, et al. The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. Acta Psychiatr Scand. 2009; 120:456-63.

851. Dias VV, Balanza-Martinez V, Soeiro-de-Souza MG, Moreno RA, Figueira ML, Machado-Vieira R, et al. Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. Acta Psychiatrica Scandinavica. 2012; 126:315-31.

852. Malhi GS, McAulay C, Gershon S, Gessler D, Fritz K, Das P, et al. The Lithium Battery: assessing the neurocognitive profile of lithium in bipolar disorder. Bipolar Disord. 2016; 18:102-15.

853. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa R, Daniel DG, et al. Olanzapine versus placebo in the treatment of acute mania. American Journal of Psychiatry. 1999; 156:702-9.

854. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, et al. Efficacy of olanzapine in acute bipolar mania - A double-blind, placebo-controlled study. Archives of General Psychiatry. 2000; 57:841-9.

855. Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K, et al. Ziprasidone in the treatment of acute bipolar mania: A three-week, placebo-controlled, double-blind, randomized trial. American Journal of Psychiatry. 2003; 160:741-8.

856. Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, et al. Olanzapine versus divalproex in the treatment of acute mania. American Journal of Psychiatry. 2002; 159:1011-7.

857. Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. Journal of Clinical Psychiatry. 2002; 63:1148-55.

858. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. Neurology. 1999; 53:S53-67.

859. Macritchie KA, Geddes JR, Scott J, Haslam DR, Goodwin GM. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev. 2001:Cd003196.

860. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. Journal of Clinical Psychiatry. 2004; 65:432-41.

861. Karas BJ, Wilder BJ, Hammond EJ, Bauman AW. TREATMENT OF VALPROATE TREMORS. Neurology. 1983; 33:1380-2.

862. Cheng M, Tang X, Wen S, Yue J, Wang H. Valproate (VPA)-associated hyperammonemic encephalopathy independent of elevated serum VPA levels: 21 cases in China from May 2000 to May 2012. Compr Psychiatry. 2013; 54:562-7.

863. Maj M, Starace F, Nolfe G, Kemali D. MINIMUM PLASMA LITHIUM LEVELS REQUIRED FOR EFFECTIVE PROPHYLAXIS IN DSM-III BIPOLAR DISORDER - A PROSPECTIVE-STUDY. Pharmacopsychiatry. 1986; 19:420-3.

864. Vestergaard P. HOW DOES THE PATIENT PREFER HIS LITHIUM TREATMENT. Pharmacopsychiatry. 1985; 18:223-4.

865. Wirshing WC. Movement disorders associated with neuroleptic treatment. Journal of Clinical Psychiatry. 2001; 62:15-8.

866. Chue P, Kovacs CS. Safety and tolerability of atypical antipsychotics in patients with bipolar disorder: prevalence, monitoring and management. Bipolar Disorders. 2003; 5:62-79.

867. Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. Journal of Clinical Psychiatry. 2001; 62:975-80.

868. Rudolph JL, Gardner KF, Gramigna GD, McGlinchey RE. Antipsychotics and oropharyngeal dysphagia in hospitalized older patients. J Clin Psychopharmacol. 2008; 28:532-5.

869. Lee JC, Takeshita J. Antipsychotic-Induced Dysphagia: A Case Report. Prim Care Companion CNS Disord. 2015; 17.

870. Sarkar S, Gupta N. Drug information update. Atypical antipsychotics and neuroleptic malignant syndrome: nuances and pragmatics of the association. BJPsych Bull. 2017; 41:211-6.

871. Tse L, Barr AM, Scarapicchia V, Vila-Rodriguez F. Neuroleptic Malignant Syndrome: A Review from a Clinically Oriented Perspective. Current Neuropharmacology. 2015; 13:395-406.

872. Kwok JS, Chan TY. Recurrent heat-related illnesses during antipsychotic treatment. Ann Pharmacother. 2005; 39:1940-2.

873. Kreuzer P, Landgrebe M, Wittmann M, Schecklmann M, Poeppl TB, Hajak G, et al. Hypothermia associated with antipsychotic drug use: a clinical case series and review of current literature. J Clin Pharmacol. 2012; 52:1090-7.

874. Guberman AH, Besag FMC, Brodie MJ, Dooley JM, Duchowny MS, Pellock JM, et al. Lamotrigine-associated rash: Risk benefit considerations in adults and children. Epilepsia. 1999; 40:985-91.

875. Messenheimer J, Mullens EL, Giorgi L, Young F. Safety review of adult clinical trial experience with lamotrigine. Drug Safety. 1998; 18:281-96.

876. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Lancet. 1999; 353:2190-4.

877. Yeung CK, Chan HH. Cutaneous adverse effects of lithium: epidemiology and management. Am J Clin Dermatol. 2004; 5:3-8.

878. Mezuk B, Morden NE, Ganoczy D, Post EP, Kilbourne AM. Anticonvulsant Use, Bipolar Disorder, and Risk of Fracture Among Older Adults in the Veterans Health Administration. American Journal of Geriatric Psychiatry. 2010; 18:245-55.

879. Williams LJ, Henry MJ, Berk M, Dodd S, Jacka FN, Kotowicz MA, et al. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. International Clinical Psychopharmacology. 2008; 23:84-7.

880. Williams LJ, Pasco JA, Jackson H, Kiropoulos L, Stuart AL, Jacka FN, et al. Depression as a risk factor for fracture in women: A 10 year longitudinal study. J Affect Disord. 2016; 192:34-40.

881. Williams LJ, Bjerkeset O, Langhammer A, Berk M, Pasco JA, Henry MJ, et al. The association between depressive and anxiety symptoms and bone mineral density in the general population: The HUNT Study. Journal of Affective Disorders. 2011; 131:164-71.

Level	Evidence
1	Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison (n≥30 in each active treatment arm)
2	Meta-analysis with wide confidence interval or one DB-RCT with placebo or active control comparison condition (n≥30 in each active treatment arm)
3	At least one DB-RCT with placebo or active control comparison condition (n=10-29 in each active treatment arm) or health system administrative data.
4	Uncontrolled trial, anecdotal reports, or expert opinion

Table 1.1: Definitions for Level of Evidence Ratings

Table 1.2: Definitions for Line of Treatment Ratings

Line	Evidence Level
First	Level 1 or Level 2 evidence for efficacy plus clinical support for safety /tolerability and no treatment emergent switch*
Second	Level 3 or higher evidence for efficacy plus clinical support for safety /tolerability and no treatment emergent switch*
Third	Level 4 evidence or higher for efficacy plus clinical support for safety /tolerability and no treatment emergent switch*
Not Recommended	Level 1 evidence for lack of efficacy, or Level 2 evidence for lack of efficacy plus expert opinion

***** Instances where inconsistent evidence or lack of clinical support has impacted recommendations have been highlighted in the text and table

Table 1.3: Sections

Section 1: Introduction
Section 2: Foundations of Management
Section 3: Acute Management of Bipolar Mania
Section 4: Acute Management of Bipolar I Depression

Section 5: Maintenance Therapy for Bipolar I Disorder
Section 6: Acute Management and Maintenance Therapy for Bipolar II Disorder
Section 7: Specific Populations
Section 8: Safety and Monitoring

Table 1.4: Clarifying Overlapping Terminology

Term	**Use**
Mood stabilizer	Use in the literature is inconsistent, as such will not be used in these guidelines.
Divalproex	Encompass valproate, valpromide, valproic acid, divalproex sodium.
Conventional Antipsychotics	Include first generation antipsychotics with high affinity for dopamine D2 receptors. Note these are refereed to as Dopamine Receptor antagonists (D2) in the new Neuroscience based Nomenclature.
Atypical Antipsychotics	Comprise second generation antipsychotics with affinity for dopamine D2 and serotonin 5-HT2 receptors as well as those that have partial agonist effects at D2/D3 receptors. Note these are refereed to as Dopamine and Serotonin Receptor antagonists (D2, 5-HT2A), Dopamine 2 Partial agonists and Serotonin Receptor Antagonists, and Dopamine 2/3 Partial agonists in the new Neuroscience Based Nomenclature
Recurrence	Re-emerging episode(s) of mania or depression whether it be within the previous episode or a new episode. Note while the literature may use "relapse" and "recurrence", respectively inconsistencies in how they are applied and their irrelevance to treatment decisions means we will use recurrence to refer to both.
Maintenance	Prophylactic therapy after stabilization of acute manic or depressive episodes

Table 2.1: Bipolar and Related Disorders- DSM-5 Diagnostic Features

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. Persistence of three or more of the following (four if the mood is only irritable) to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).

7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the symptoms (1-7) listed above for a manic episode have persisted (four if the mood is only irritable), represent a noticeable change from usual behavior, and have been present to a significant degee

The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

C. The disturbance in mood and the change in functioning are observable by others.

D. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

E. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition \The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note diagnosis of Bipolar II Disorder also requires a current or past major depressive episode

Cyclothymic Disorder

A. For at least 2 years (at least 1 year in children and adolescents) there have been numerous periods with hypomanic symptoms that do not meet criteria for a hypomanic episode and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode.

B. During the above 2-year period (1 year in children and adolescents), the hypomanic and depressive periods have been present for at least half the time and the individual has not been without the symptoms for more than 2 months at a time.

C. Criteria for a major depressive, manic, or hypomanic episode have never been met.

D. The symptoms in Criterion A are not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

E. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or

another medical condition (e.g., hyperthyroidism).

F. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Substance/ Medication induced Bipolar and Related Disorder

A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by elevated, expansive, or irritable mood, with or without depressed mood, or markedly diminished interest or pleasure in all, or almost all, activities.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a bipolar or related disorder that is not substance/medication-induced. Such evidence of an independent bipolar or related disorder could include the following:

The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced bipolar and related disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Bipolar and Related Disorder due to another Medical Condition

A. A prominent and persistent period of abnormally elevated, expansive, or irritable mood and abnormally increased activity or energy that predominates in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.

C. The disturbance is not better explained by another mental disorder.

E. The disturbance does not occur exclusively during the course of a delirium.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning, or necessitates hospitalization to prevent harm to self or others, or there are psychotic features.

Other Specified Bipolar and Related Disorders

Presentations in which symptoms characteristic of a bipolar and related disorder that cause clinically significant distress or functional impairment but do not meet the full criteria for any of the disorders in the diagnostic class.

Used in situations in which the clinician chooses to communicate the reason the presentation does not meet criteria

Examples that can be specified using these criteria include:

1. Short-duration hypomanic episodes (2–3 days) and major depressive episodes
2. Hypomanic episodes with insufficient symptoms and major depressive episodes
3. Hypomanic episode without prior major depressive episode
4. Short-duration cyclothymia (less than 24 months)

Unspecified Bipolar and Related Disorder

Presentations in which symptoms characteristic of a bipolar and related disorder that cause clinically significant distress or functional impairment but do not meet the full criteria for any of the disorders in the diagnostic class Used in situations in which the clinician chooses not to communicate the specific reason the presentation does not meet criteria, and includes presentations in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).

Adapted from Ref 5: Diagnostic and statistical manual of mental disorders : DSM-5. Fifth edition. Arlington, VA : American Psychiatric Publishing, [2013] ©2013; 2013.

Table 2.2: DSM-5 Specifiers for Bipolar and Related Disorders

Anxious Distress	X	X	
Mixed Features	X	X	
Rapid Cycling			X
Melancholic Features		X	
Atypical Features		X	
Psychotic Features	X	X	
Catatonia	X	X	
Peripartum Onset	X	X	
Seasonal Pattern			X
Remission	X	X	
Current Episode Severity	X	X	

Table 2.3: Features of Depression that may increase suspicion of a Bipolar vs Unipolar Illness

Symptomatology and Mental State Signs	Hypersomnia and/or increased daytime napping Hyperphagia and/or increased weight Other 'atypical' depressive symptoms such as leaden paralysis Psychomotor retardation Psychotic features and/or pathological guilt Lability of mood; irritability; psychomotor agitation; racing thoughts	Initial insomnia/ reduced sleep Appetite and/or weight loss Normal or increased activity levels Somatic complaints
Course of Illness	Early onset of first depression (<25 years) Multiple prior episodes (≥ 5 episodes)	Late onset of first depression (> 25 yrs) Long duration of current episode (> 6 mo)
Family History	Positive family history of bipolar disorder	Negative family history of bipolar disorder

Adapted from (Mitchell et al. 2008 (Ref 38), Schaffer et al. 2010 (Ref 39))

Table 2.4: Differential Diagnosis of Bipolar Disorder

Major depressive disorder or persistent depressive disorder	Manic or hypomanic episodes probed for and not present
Bipolar and related disorder due to another medical condition	Episodes are judged to be a consequence of a medical condition such as traumatic brain injury, brain tumours such as frontal lobe meningiomas, multiple sclerosis, stroke, Cushings disease or hyperthyroidism. Onset or exacerbation of mood coincides with that of medical condition
Substance or medication induced mood disorder	Episodes are judged to be a consequence of a substance such as an illicit drug, or a medication (stimulants, steroids, L-dopa, antidepressants) or toxin exposure. Episodes may be related to intoxication or withdrawal.
Cyclothymic disorder	Hypomanic symptoms do not meet the full criteria for a hypomanic episode, and depressive symptoms do not meet the criteria for a major depressive episode
Psychotic disorders (schizoaffective disorder, schizophrenia, delusional disorder)	Periods of psychotic symptoms in absence of prominent mood symptoms. Consider onset, accompanying symptoms, pervious course and family history
Borderline personality disorder [a]	Instability of interpersonal relationships, self-image and mood, with marked impulsivity and a central theme of intense abandonment fears. Early onset and long-standing course. Ture euphoria and prolonged well-functioning intervals are extremely rare
Narcissistic personality disorder [a]	Grandiosity, need for admiration and lack of empathy of early onset. Grandiosity not associated with mood changes or functional impairments.
Antisocial personality disorder [a]	Early onset of disregard for, and violation of, the rights of others, which does not occur only in the context of a manic episode

a: Can occur comorbidly with bipolar disorder

Adapted from (Yatham et al. 2005 (Ref 2))

Table 2.5: Summary of Main Factors associated with Suicide Attempt and Suicide Deaths in Bipolar Disorder

Sociodemographics		
Sex	Female	Male
Age	Younger	Older- higher ratio of deaths/ attempts
	Older- higher lethality	
Race	Minorities- youth only	
Marital status	Single, divorced, single parents	
Characteristics of BD		
Age of onset	Younger	

First episode polarity	Depression	
	Mixed symptoms	
	Mania- more violent attempts	
Predominant polarity	Depressive	
Current episode polarity	Depressive	Depressive
	Mixed	Mixed
		Manic with psychotic features
Other episode characteristics	Mixed features	Hopelessness
	Greater number/ severity of episodes	Psychomotor agitation
	Rapid cycling	
	Anxiety	
	Atypical features	
	Suicidal ideation	
Comorbidity		
Psychiatric comorbidity	Substance use disorder	Anxiety disorder
	Cigarette smoking	
	Coffee intake	
	Anxiety disorder	
	Eating disorder	
Personality disorders	Present- particularly borderline or cluster B	
Physical comorbidity	Obesity or high BMI	
Other Clinical Variables		
First degree family history	Mood disorders	Mood Disorders
	BD	BD
	Suicide	Suicide
Prior suicide attempts	Present	Present
Early life trauma	Childhood abuse	
	Early life stress	
Psychosocial precipitants	Interpersonal problems	Present within a week of death
	Occupational problems	
	Bereavement	
	Social isolation	
Sexual dysfunction	Present	

(Modified from Schaffer et al. 2015 (Ref 50))

Table 2.6: The Chronic Disease Management Model

Self-Management Support
Empower and prepare patients to manage their health and health care
Use effective self-management support strategies that include assessment, goal setting, action planning, problem solving, and follow-up
Decision Support
Promote clinical care that is consistent with scientific evidence and patient preferences

Embed evidence-based guidelines into daily clinical practice and share this and other information with patients to encourage their participation
Use proven provider education materials
Community
Encourage patients to participate in effective community programs
Form partnerships with community organizations
Delivery System Design
Provide clinical care and self-management support that patients understand and that fits with their cultural background
Ensure regular follow-up by the care team, with defined tasks for different team members
Provide clinical case management services for complex patients
Clinical Information Systems
Provide timely reminders for providers and patients
Facilitate individual patient care planning
Share information with patients and providers to coordinate care
Health System
Measure outcomes and use information to promote effective improvement strategies aimed at comprehensive system change
Develop agreements that facilitate care coordination within and across organizations

From (Wagner 1998 (Ref 56))

Table 2.7. Strength of Evidence and Recommendations for Adjunctive Psychological Treatments for Bipolar Disorder*

Treatment	**Maintenance : Recommendation (Level of Evidence)**	**Acute Depression: Recommendation (Level of Evidence)**
Psychoeducation (PE)	First Line (Level 2)	Insufficient evidence
Cognitive behavioral therapy (CBT)	Second Line (Level 2)	Second Line (Level 2)
Family-focused therapy (FFT)	Second Line (Level 2)	Second Line (Level 2)
Interpersonal and social rhythm therapy (IPSRT)	Third Line (Level 2)	Third Line (Level 2)
Peer Support	Third Line (Level 2)	Insufficient evidence
Cognitive and Functional Remediation	Insufficient evidence	Insufficient evidence
Dialectical behavioural therapy (DBT)	Insufficient evidence	Insufficient evidence
Family/ caregiver interventions	Insufficient evidence	Insufficient evidence
Mindfulness based cognitive therapy (MBCT)	Insufficient evidence	Insufficient evidence
Online interventions	Insufficient evidence	Insufficient evidence

*See text for specific definitions of type of therapy and number of sessions needed ("dose of psychosocial intervention") corresponding to this recommendation and evidence

Table 3.1: Level of Evidence and Recommendations for Short-term Pharmacological Management of Agitation*

Level of Recommendation	Agent/ Formulation		Level of Evidence	Studies dose range*	
				Single dose	Max / 24h
First Line	Aripiprazole	IM	2	9.75 mg	15 mg
	Lorazepam	IM	2	2 mg IM	
	Loxapine	Inhaled	1	5 mg	10 mg
	Olanzapine	IM	2	2.5 mg	10 mg[2]
Second Line	Asenapine	Sublingual	3	10 mg	
	Haloperidol	IM	3	5 mg	15 mg
	Haloperidol+ midazolam	IM	3	haloperidol IM. 2.5 mg + midazolam IM 7.5 mg	haloperidol IM. 5 mg + midazolam IM 15 mg
	Haloperidol + promethazine	IM[4]	3	haloperidol IM 2.5 mg + promethazine IM 25 mg	haloperidol IM 5 mg + promethazine IM 50 mg
	Risperidone	ODT[4]	3	2 mg	4 mg
	Ziprasidone	IM[4]	3	2 mg	20 mg
Third Line	Haloperidol	PO[3]	4	5 mg	15 mg
	Loxapine	IM	4	N/A	
	Quetiapine	PO[3]	4	Mean (SD)= 486.7 (317.2) mg/day	
	Risperidone	PO[4]	4	2 mg	

*See text for recommendations about use of oral antipsychotics and divalproex. IM: Intramuscular; ODT: orally disintegrating tablet; PO: oral. 1: Doses are reported as per studies; 2: 26.3% received 2 or 3 10 mg injections 3: Assessed 2 hours after the dose;4 Doses are not specifically for bipolar disorder but included schizophrenia or other diagnoses.

Table 3.2: Hierarchical Rankings of First and Second Line Treatments Recommended for Management of Acute Mania

Separate file

Table 3.3 Additional agents evaluated for use in acute mania

	Agent	Level of Evidence
Third Line	Carbamazepine/ oxcarbazepine + Li/DVP	Level 3
	Chlorpromazine	Level 2
	Clonazepam	Level 2
	Clozapine	Level 4
	Haloperidol + Li/DVP	Level 2
	Repetitive transcranial magnetic stimulation (rTMS)	Level 3
	Tamoxifen	Level 2
	Tamoxifen + Li/DVP	Level 2
Not Recommended	Allopurinol	Level 1 negative
	Eslicarbazepine/ licarbazepine	Level 2 negative
	Gabapentin	Level 2 negative
	Lamotrigine(Yildiz et al. 2015)(Yildiz et al. 2015)(6)	Level 1 negative
	Omega-3 fatty acids	Level 1 negative
	Topiramate	Level 1 negative
	Valnoctamide	Level 2 negative
	Zonisamide	Level 2 negative

Table 4.1: Hierarchical Rankings of Frist and Second Line Treatments Recommended for Management of Acute Bipolar I Depression

Separate file

Table 4.2: Additional agents evaluated for use in acute bipolar I depression

	Agent	Level of Evidence
Third line	Aripiprazole (adj)	Level 4
	Armodafanil (adj)	Level 4
	Asenapine (adj)	Level 4
	Carbamazepine	Level 2
	Eicosapentaenoic acid **(**EPA) (adj)	Level 2
	Ketamine (IV) (adj)	Level 3
	Light therapy +/- total sleep deprivation (adj)	Level 3
	Levothyroxine (adj)	Level 3
	Modafanil (adj)	Level 2
	N-acetylcysteine (adj)	Level 3
	Olanzapine	Level 1
	Pramiprexole (adj)	Level 3
	Repetitive transmagnetic stimulation (rTMS) (adj)	Level 2
	SNRI/ MAOI (adj)	Level 2
Not Recommended	Antidepressant monotherapy	Level 2 negative
	Aripiprazole	Level 1 negative
	Lamotrigine + folic acid	Level 2 negative
	Mifepristone (adj)	Level 2 negative
	Ziprasidone	Level 1 negative
	Leviteracetam (adj)	Level 3 negative
	Memantine (adj)	Level 3
	Pioglitazone (adj)	Level 3
	Pregnenolone (adj)	Level 2
	Riluzole	Level 4 negative
	Risperidone (adj)	Level 3

Adj: adjunctive; MAOI: monoamine oxidase inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor

Table 5.1 Risk Factors for Partial or Non-Adherence of Medication

Sociodemographics	Male, younger age, low level of education, single
Psychology	Poor insight, lack of awareness of disease, negative attitude to treatment, fear of side effects, negative attitude to medication, low overall life satisfaction, low cognitive functioning
Comorbidity	Alcohol or cannabis use, obsessive compulsive disorder
Social	No social activities, work impairment
Chronology	Younger age of onset, current inpatient status, hospitalization or suicide attempt in past 12 months
Disease Characteristics	Mixed episode, rapid cycling, delusions and hallucinations, severity of illness, BDI diagnosis, higher number of episodes
Treatment Related Factors	Side effects of medications, inadequate efficacy of medication, use of antidepressant, low treatment doses

Adapted from (Leclerc, Mansur and Brietzke 2013)(Ref 354)

Table 5.2: Hierarchical Rankings of First and Second Line Treatments Recommended for Maintenance Treatment in Bipolar Disorder

In separate file

Table 5.3: Additional agents evaluated for use in maintenance treatment of bipolar I disorder

	Agent	Level of Evidence
Third Line	Aripiprazole + lamotrigine	Level 2
	Clozapine (adj)	Level 4
	Gabapentin (adj)	Level 4
	Olanzapine + fluoxetine	Level 2
Not Recommended	Perphenazine	Level 2 negative
	Tricyclic antidepressants	Level 2 negative

Adj: adjunctive

Table 6.1: Strength of Evidence and Treatment Recommendations for acute management of bipolar II depression

Recommendation	Agent	Level of Evidence
First Line	Quetiapine	1
Second Line	Lithium	2
	Lamotrigine	2
	Bupropion (adj)	2
	Sertraline*	2
	Venlafaxine*	2
Third Line	Divalproex	4
	Fluoxetine*	3
	Tranylcypromine	3
	Ziprasidone #	3
	Agomelatine (adj)	4
	ECT^ (adj)	4
	EPA (adj)	4
	Ketamine (IV or sublingual) (adj)^	3
	N-acetyl cysteine (adj)	4
	Pramiprexole (adj)	3
	T3/T4 thyroid hormones (adj)	4
Not Recommended	Paroxetine	2 negative

***:** for patients with pure depression (non-mixed); # for patients with depression and mixed hypomania: ^: for severely ill/ treatment refractory patients; adj: adjunctive ECT: electroconvulsive therapy; EPA: eicosapentaenoic acid

Table 6.2: Strength of Evidence and Treatment Recommendations for Maintenance Treatment of Bipolar II Disorder

Recommendation	Agent	Evidence Level
First Line	Quetiapine	1
	Lithium	2
	Lamotrigine	2
Second Line	Venlafaxine	2
Third Line	Divalproex	3
	Carbamazepine	3
	Fluoxetine	3
	Escitalopram	3
	Other antidepressants	3
	Risperidone*	4

* Primarily for prevention of hypomania

Table 7.1: FDA Classification of Teratogenicity for Medications commonly used in Bipolar Disorder*

Lithium	**D**	**L4**
Anticonvulsants		
Carbamazepine	**D_m**	**L2**
Divalproex	**D_m**	**L4**
Lamotrigine	**C_m**	**L2**
Atypical Antipsychotics		
Aripiprazole	**C_m**	**L3**
Clozapine	**B_m**	**L3**
Olanzapine	**C_m**	**L2**
Quetiapine	**C_m**	**L2**
Risperidone	**C_m**	**L2**

Ziprasidone	**C_m**	**L2**
SSRI Antidepressants		
Citalopram	**C_m**	**L2**
Escitalopram	**C_m**	**L2**
Fluoxetine	**C_m**	**L2**
Fluvoxamine	**C_m**	**L2**
Paroxetine	**D_m**	**L2**
Sertraline	**C_m**	**L2**
Other Antidepressants		
Bupropion	**B_m**	**L3**

* FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final Rule (PLLR). SEE TEXT FOR DETAILS

** Adapted from: ACOG Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician- Gynecologists. Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol. 2008;111(4):1001-20. US Food and Drug Administration Rating. A= controlled studies show no risk; B= no evidence of risk in humans; C= risk cannot be ruled out (human data lacking, animal studies positive or not done); D= positive evidence of risk (benefit may outweigh risk). The "m" subscript is for data taken from the manufacturer's package insert

*** Hale TW. Rowe *HE. Medications & Mother's Milk. Ney York (NY): Springer Publishing Company, LLC, 2017*. Lactation risk categories are listed as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated.

Table 7.2 Differential Diagnosis of Manic Symptoms in Children and Adolescents

Symptom	Bipolar Mania/Hypomania	ADHD	ODD
Elation	Episodic, prolonged, pathological (inappropriate to context or uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
Irritability	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (eg, ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
Sleep	Reduced need for sleep (ie, significantly less sleep than usual without increased daytime fatigue or somnolence); change must be mood-related	Insomnia, (ie, difficulty falling asleep), can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic, may defy bedtime rules or routine
Grandiosity	Distinct uncharacteristic increase in confidence or self-importance; change must be mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common but not necessarily mood-related
Hyperactivity and distractibility	Episodic; if comorbid ADHD is diagnosed, then distinctly "worse than usual"; change must be mood-related	Diagnostic criteria, nonepisodic	Not prominent or episodic

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder.

(Goldstein and Birmaher 2012) (Ref 557)

Table 8.1: Baseline Laboratory Investigations in patients with Bipolar Disorder

CBC
Fasting glucose
Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
Platelets
Electrolytes and calcium
Liver enzymes
Serum bilirubin
Prothrombin time and partial thromboplastin time
Urinalysis
Urine toxicology for substance use
Serum creatinine
eGFR
24h creatinine clearance (if history of renal disease)
Thyroid stimulating hormone
Electrocardiogram (>40 years or if indicated)
Pregnancy test (if relevant)
Prolactin

CBC= complete blood count; HDL= high density lipoprotein; LDL= low density lipoprotein; TC= total cholesterol; TG= triglyceride; vLDL= very low density lipoprotein

(Yatham et al. 2006)(Ref 2)

Table 8.2: Safety/ Tolerability Concerns and Risks of Treatment Emergent Switch with pharmacological agents indicated for use in Bipolar Disorder

	Acute	**Maintenance**	**Acute**	**Maintenance**	**Mania/ Hypomania**	**Depression**
Lithium	+	++	+	++	-	-
Anticonvulsants						
Carbamazepine	++	++[1]	+	++	-	-
Divalproex	-	++[1]	+	+	-	-
Gabapentin	-	-	+	+	-	-
Oxcarbazepine	+	+	+	+	-	-
Lamotrigine	++	-	-	-	-	-
Atypical Antipsychotics						
Aripiprazole	-	-	+	+	-	-
Asenapine	-	-	+	+	-	-
Cariprazine	-	-	+	-	-	-
Clozapine	++	+++	++	+++	-	-
Lurasidone	-	-	+	+	-	-
Olanzapine	+	+++	++	++	-	-
Paliperidone	-	+	+	++	-	-
Quetiapine	+	++	++	++	-	-
Risperidone	-	+	+	++	-	+
Ziprasidone	++	++	++	+	-	-
Conventional Antipsychotics						
Haloperidol	+	+++	++	++	-	+++
Loxapine	+	+	+	+	-	nk

Antidepressants (adjunctive*)						
Agomelatine	+	-	-	-	+	-
Bupropion	+	-	+	-	+	-
Ketamine i.v.	++	nk	++	nk	nk	nk
MAOIs	++	++	+	++	++	-
SNRIs	-	+	+	-	++	-
SSRIs	-	-	+	+	+	-
TCAs	++	++	++	++	+++	-
Stimulants						
Amphetamines	-	++	+	-	+++	-
Modafinil	-	-	-	-	++	nk
Dopamine Agonists						
Pramipexole	-	+	-	-	++	nk

-: Limited impact on treatment selection; + Minor impact on treatment selection; ++ Moderate impact on treatment selection; +++ Significant impact on treatment selection; nk not known; [1] Valproate and carbamazepine should be used cautiously in women of child bearing age (Section 7); *: Antidepressant monotherapy is not recommended in BDI, for more information on BDII see Section 6

MAOI: monoamine oxidase inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants