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Abstract

Background: Interventions early in the course of Bipolar Disorder (BD) may have the potential to limit its functional and symptomatic impact. However, the implementation of specific early interventions for BD has been limited which may at least partly be due to the lack of guidelines focused on the early illness stages. We therefore aimed to review the current recommendations for early stage BD from clinical practice guidelines.

Methods: We searched PubMED and PsychINFO for clinical guidelines for BD published in the ten years prior to 1 November 2018. Recommendations from identified guidelines that addressed early stage BD or first episode mania were consolidated and compared. We also reviewed the guidelines relating to adolescents with BD to complement the guidelines related to ~~given the overlap between those in their early illness stages and those with BD in their early developmental stages~~those in the early illness course.

Results: We identified fourteen international and national guidelines on BD or affective psychoses. Most guidelines contained a separate section on adolescents, but only a few referred specifically to early stage BD. There were no consistent recommendations for early stage disorder, except with respect to the indications for maintenance medication treatments. For adolescents, there was a consistent recommendation for the use of second generation antipsychotics for treating acute mania.

Limitation: The main limitation is ~~the~~ that the identified guidelines did not include ~~exclusion of guidelines published prior to 2008~~ primary data that clearly separated illness and developmental stages.

Conclusions: There is a lack of emphasis on early BD among widely-respected current clinical guidelines, likely reflecting the dearth of primary data. Future evidence or consensus-based recommendations could significantly inform clinical practice for this population.

Key Words: Bipolar disorder; mania; depression; staging; adolescents; guidelines

Introduction

Bipolar disorder (BD) is the fourth most significant contributor to disability amongst adolescents and young adults (Gore et al., 2011) and has one of the highest rates of suicide amongst mental disorders (Chesney et al., 2014). Most adults with BD experience the onset of mood symptoms before their 20s (Geoffroy et al., 2013). While earlier diagnosis and rapid implementation of effective evidence-based treatment can improve outcomes for those with BD (Kessing et al., 2014), there is typically a significant delay of 5-10 years between symptom onset and diagnosis (Baldessarini et al., 2003; Post et al., 2010).

Earlier diagnosis and interventions (termed Early Intervention or EI) refer to strategies to allow prompt and timely access to care, with appropriate and comprehensive interventions that are tailored to the 'stage' of disorder (Vieta et al., 2018). Staging models have helped articulate the imperative for EI by combining characteristics such as severity and time course of symptoms and level of functioning in profiling individuals with BD (Berk et al., 2007a; Berk et al., 2017b). Although staging models are a fairly new conceptualization, they can help clinicians to focus on the needs of persons with BD at different 'disorder stages' and potentially personalise treatment approaches. Staging models conceptualise interventions in earlier stages as preventing illness progression (Berk et al., 2011) and as minimising functional and cognitive impairment, thereby limiting illness-related disability (Berk et al., 2007a; McGorry et al., 2006). Although direct evidence for prevention of illness progression is limited, there is already evidence that interventions in earlier illness stages may be more effective than those in later illness stages (Joyce et al., 2016). Those with fewer lifetime episodes show greater treatment improvement with Cognitive Behavioural Therapy (CBT) (Scott et al., 2006) and psychoeducation (Colom et al., 2010b).

Although there are several definitions on defining stages for BD, we considered early stage BD to be those in the first few episodes of BD as recommended by the International Society of Bipolar Disorders (ISBD) Staging Task Force (Kapczinski et al., 2014). This taskforce considers early stages as those "at the first or the first few episodes and are in aggregate associated with better functioning after recovery". and corresponds to Stage 2 disorder as outlined by Berk (Berk et al., 2007a) and Cosci (Cosci and Fava,

2013). Thus, we included those in the early course of BD, after their onset of clear mania or hypomania that define BD I or II. This should be contrasted with the earlier stages of BD described by Duffy (Duffy, 2014)and Post (Post, 2010)which include subthreshold states, a vulnerability for the disorders, internalising disorders and anxiety symptoms as being in the earlier illness stages. However, these syndromes would be better categorised as prodromes, precursor syndromes or states (Eaton et al., 1995) rather than the more accepted ISBD consensus definition of early stage BD.

Among those in ~~such earlier stages~~an earlier illness course, interventions have had limited and sporadic uptake, especially in comparison to services for those with early psychosis (though the latter often include a proportion of people with bipolar psychosis). Persons with early stage BD receive treatment from a variety of clinical services (e.g., EI services , community mental health teams, youth services), none of which are specialists in bipolar care, thus treatments vary greatly. Although there is promising data that specialised mood disorder services have better treatment outcomes (Kessing et al., 2013), it is highly likely that generalist clinicians are likely to provide interventions for those in earlier stages of BD in most parts of the world. These clinicians need access to high quality clinical guidance to support the care of those with early stage BD.

While there are several clinical guidelines with regards to the care for persons with BD (Goodwin et al., 2016; Grunze et al., 2009; Grunze et al., 2010, 2013b; Yatham et al., 2018), few relate to early stage disorder (or early in the course of the disorder). These guidelines typically categorise treatments based on acute (manic, depressive, mixed episodes) or maintenance phases, and interventions for children and adolescents may receive a separate mention (Goodwin et al., 2016; Grunze et al., 2009; Grunze et al., 2010, 2013b; Yatham et al., 2018). However, those in early course of the disorder (early stage) are rarely considered. The guidelines relating to adolescents may be relevant to those in early stage disorder, as the categories are overlapping, given that the peak age of onset of the disorder is in the late teens(Lin et al., 2006). However, as a substantial proportion of those with BD will have an onset in adulthood (Geoffroy

et al., 2013), there is a need for a focus on early stage or course of the disorder rather than a focus on age of the affected individuals alone.

Therefore, clinicians currently have limited guidance in providing care for clients with early stage BD despite their clinical needs and outcomes being different to those with established illness. Consequently, it is important to review and compile recommendations from current guidelines that are specific to those with early stage BD. A set of such recommendations could also identify gaps in current evidence and develop a roadmap for future research which could in-turn generate future evidence-informed guidelines. Thus, we aimed to scope the literature and summarise the recommendations from clinical guidelines pertaining to treatment for early stage with a secondary focus on adolescents with BD.

Methods

We conducted a comprehensive scoping review for clinical guidelines describing treatment for those with BD, mania or affective psychoses.

Data sources

A search of the electronic PubMED and PsychINFO databases was conducted in March 2018 and updated in November 2018. Search terms were arranged in groups and included the following: (group 1) bipolar disorder, or mania, or hypomania, or manic depression, or affective psychoses, AND (group 2) clinical or therapeutic guidelines. The search was limited to guidelines published in the English language and after 1st March 2008. This date was chosen to include all guidelines published in the prior decade and to ensure that only recent recommendations were considered for inclusion. Additional guidelines were identified by ancestry searching and those known to the authors were included.

Study Screening and Selection

All articles were screened for eligibility by title and abstract to meet the following inclusion criteria: (a) guidelines on treatment of BD I and/or II, and (b) guidelines published by international or national mental health organisations. Guidelines from local or regional guidelines were not included. All treatment modalities including pharmacological, psychological or other treatments were considered. We proposed to include treatment recommendations for those with a clear onset of BD (i.e., those with BD I or II), not those in the pre-onset stage or prodrome. Exclusion criteria were: (a) guidelines limited to special populations such as pregnant women and the elderly; (b) case-series data; (c) reviews of guidelines; and (d) guidelines related to prodromal BD. Screening was conducted by the first author (MF) and confirmed by the senior author (AR) in the event of ambiguity.

Data Extraction

An electronic search was conducted to extract statements containing the terms 'early stage' and/or 'first episode', and 'adolescents' and/or 'youth'. The terms 'adolescents' and 'youth' were used to ensure that recommendations relevant to adolescents were identified. Although age itself may not define adolescence in its entirety, w~~W~~e utilised the World Health Organisation definition for adolescents to include those aged 10-19 years. For the purposes of this review, we utilised additional definitions of 'early stage BD' which was operationalised as no more than five lifetime mood episodes (Magalhaes et al., 2012). When guidelines referred to those with 'first episode mania', these were considered to mean first treatment-seeking episode of mania.

Quality Rating

Guideline quality was assessed using the Appraisal of Guidelines Research and Evaluation Global Rating Scale (AGREE GRS) (Brouwers et al., 2012) instrument. The AGREE GRS is the international standard for evaluation of clinical guidelines and comprises four core items: (i) process of development; (ii) presentation style; (iii) completeness of reporting; and (iv) clinical validity. Each item scored on a 7-point scale ranging from 1 '*lowest quality'* to 7 '*highest quality'*, with the anchors ranging from no information or poorly presented information to exceptional presentation and quality of reporting. An additional

question evaluated the overall assessment of each guideline by rating the overall quality of the guideline. Two reviewers (MC, AR) independently rated items (i) and (ii). MC was a medical student who completed the ratings under the supervision of AR, SC or KF. AR is an experienced psychiatrist who rated items (iii) and (iv).

Results

The keywords search of the electronic databases yielded 823 potentially eligible articles, of which 30 articles met the final criteria for inclusion. This included two guidelines (the *National Institute of Health and Care Excellence* guideline for Bipolar Disorder - Guideline 185 (NICE) *(National Collaborating Centre for Mental Health (UK), 2014)* and *Australian Clinical Guidelines for Early Psychosis* (ACGEP) (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016)), which were identified from ancestry searches. After excluding previous editions and those specific to special populations, a total of thirteen international and national guidelines were identified (Table 1). The national guidelines originated from several countries across Europe, North America, Asia, Africa and Australasia.

<Insert Table 1 about here>

<Insert Figure 1 about here>

Assessment of Guideline Quality

As determined using the AGREE GRS instrument, the overall quality of the included guidelines varied considerably (see Table 2). Among the guidelines, the international guidelines (Fountoulakis et al., 2017; Grunze et al., 2009; Grunze et al., 2010, 2013b) demonstrated higher rigour of development, while several national guidelines failed to describe the guideline development method (e.g., (Bai et al., 2013; Emsley et al., 2013; Kanba et al., 2013; Mok et al., 2011; Shah et al., 2017)) . The national BD guidelines

from the United Kingdom (Goodwin et al., 2016; National Collaborating Centre for Mental Health (UK), 2014), Canada (Yatham et al., 2018) and Australia (Malhi et al., 2015) were the exceptions: they provided details on the search methods, levels of evidence and consultation with experts and consumers. These guidelines also scored highly on completeness and clinical validity. Guidelines from Singapore, Japan, Taiwan, South Africa and India scored lower on rigour of guideline development as well as completeness of reporting.

<Insert Table 2 about here>

Specific recommendations for early stage BD

Within the guidelines, recommendations were stratified based on the polarity of BD (manic, depressive or mixed) or treatment phase (acute or maintenance). In most, there was no differentiation between guidance for first episode or multi-episode BD and little in the way of stage specific recommendations. Recommendations for early stage BD from the guidelines are summarised in Table 3.

<Insert Table 3 about here>

Recommendations for treating first episode mania

The *British Association of Psychopharmacology* (BAP) guideline (Goodwin et al., 2016) recommended that individuals presenting with first episode mania be offered an assessment by a psychiatrist, as well as prompt and assertive interventions, including hospital admissions if necessary. The *Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders* (CANMAT-ISBD) guideline (Yatham et al., 2018) recommended starting comprehensive treatment such as mood stabilisers and psychosocial interventions (e.g., psychoeducation) from the first presentation.

According to the *ACGEP* guideline (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016), first-line treatment for first episode psychotic mania should be combination therapy with mood stabilisers and atypical antipsychotics. The first-line mood stabilisers recommended were lithium carbonate, and sodium valproate second-line. Other mood stabilisers such as carbamazepine, oxcarbazepine or combinations of mood stabilisers were recommended after these trials. Second generation antipsychotics suggested included risperidone, quetiapine, ziprasidone and aripiprazole. If there was inadequate response, switching to another second-generation antipsychotic and optimizing psychosocial interventions were advised. If no further improvement was seen after 6-8 weeks, switching to another atypical antipsychotic such as olanzapine was recommended. For persistent and severe manic episodes, the use of electroconvulsive therapy (ECT) was supported.

Recommendations for maintenance treatment after first episode mania

Five guidelines mentioned the role of long-term maintenance therapy after a first manic episode. The *CANMAT-ISBD* and *RANZCP* guidelines suggested that maintenance treatment should be considered from the first episode of mania (Malhi et al., 2015; Yatham et al., 2018). The *World Federation of Societies of Biological Psychiatry (WFSBP)* guidelines (Grunze et al., 2013b) recommended maintenance treatment if the first manic episode was severe and/or there was a family history of BD. The *BAP* guideline (Goodwin et al., 2016) recommended enhanced psychoeducation, motivational and family support in the maintenance treatment phase. The *Taiwanese* national guideline (Bai et al., 2013) supported long-term maintenance therapy for first episode BD if severe symptoms were present or if they had a family history of mental disorders. However, there is a lack of information on the duration and dose of maintenance treatments in the included guidelines. Additionally, while some guidelines clearly distinguish continuation phase and longer-term maintenance treatment (Grunze et al., 2013a; Malhi et al., 2015) for those with established disorder, such distintinctions were not made for those with first episode mania.

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Recommendations for assessing depression in the early stages of BD

The *WFSBP* and *Singapore Ministry of Health* guidelines emphasized that those who present with a first episode depression should be questioned for past manic and hypomanic episodes (Grunze et al., 2010; Mok et al., 2011). Similarly, BAP guidelines recommend careful assessment of persons with early episodes of depression for bipolar characteristics (Goodwin et al., 2016). For those with first episode psychotic depression as part of BD, the *ACGEP* guideline recommended a combination of mood stabilisers and atypical antipsychotics (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016).

Recommendations for maintenance treatment after first episode mania

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Specific recommendations for adolescents with BD

Seven of the included guidelines described specific strategies for adolescents with BD, and are summarised in Table 4. General principles for treatment were similar to those described for adults, often with the caveat that medications can cause more side-effects in adolescents (Goodwin et al., 2016; Yatham et al., 2018).

<Insert Table 4 about here>

Recommendations for acute treatment of mania in adolescents

The *WFSBP* guidelines (Grunze et al., 2009; Grunze et al., 2010, 2013b) recommended higher therapeutic lithium levels in acute mania for adolescents and young adults on the basis that they often need and tolerate higher lithium levels (serum levels between 0.6-1.3 mmol/L). The *BAP* guideline (Goodwin et al., 2016) recommendations were similar to those for adults, with aripiprazole proposed as first choice treatment for adolescents presenting with mania. Olanzapine, quetiapine and risperidone were also recommended to be efficacious in those with acute mania. However, the guideline warns of the increased potential for side-effects with these agents in young people. The *NICE* guideline (National Collaborating Centre for Mental Health (UK), 2014) recommended aripiprazole as a first-line agent for up to 12 weeks in adolescents presenting with moderate to severe mania. In the latest edition of the *CANMAT-ISBD* guidelines (Yatham et al., 2018), pharmacological treatments for adults were advised to be utilised with caution in adolescents, specifically due to their greater susceptibility to metabolic side-effects. For acute mania, recommended first-line pharmacological agents were lithium, risperidone, aripipirazole, asenapine and quetiapine. Ziprasidone, quetiapine and olanzapine were considered second-line due to an increased risk of side-effects (Conus et al., 2015; Findling et al., 2013). Monitoring for side-effects is further outlined in the *ISBD* guideline for the same (Ng et al., 2009). The *RANZCP* guideline (Malhi et al., 2015) recommended second generation antipsychotic (olanzapine, quetiapine, ziprasidone, risperidone, aripiprazole) monotherapy or second generation antipsychotic and quetiapine/sodium valproate

combination therapy. Lithium and valproate were considered to have lower levels of evidence due to limited data from open label studies.

Recommendations for treating acute bipolar depression in adolescents

The *NICE* guideline recommended at least three months of psychological interventions as first-line therapy, with adjunctive pharmacotherapy recommended for those with moderate to severe bipolar depression (National Collaborating Centre for Mental Health (UK), 2014). Lurasidone was nominated as the first-line pharmacological agent in the *CANMAT-ISBD* guidelines, with lithium and lamotrigine suggested as second-line treatment options (Yatham et al., 2018). The *BAP* guideline warns of the increased risk of switch from depression to mania with antidepressant agents in this population. The *RANZCP* guideline noted that lamotrigine could be an effective option based on open-label evidence (Malhi et al., 2015). This guideline also recommended ECT in bipolar depression with severe affective, psychotic or catatonic symptoms. Apart from pharmacotherapy, adjunctive psychosocial interventions such as CBT, emotional regulation skills training and psychoeducation for both the adolescent and their families were advised.

Recommendations for continuation and maintenance treatment and adolescents

The *WFSBP*, *CANMAT/ISBD* and *NICE* guidelines recommended that sodium valproate be used cautiously in women of childbearing age due to the risk of teratogenicity and polycystic ovary syndrome (Grunze et al., 2009; Grunze et al., 2010, 2013b; National Collaborating Centre for Mental Health (UK), 2014). The *NICE* guidelines (National Collaborating Centre for Mental Health (UK), 2014) recommended diagnosing BD in adolescents only after a period of intensive monitoring. The *CANMAT-ISBD* guideline (Yatham et al., 2018) recommended psychosocial interventions such as psychoeducation, CBT, family-focused therapy, interpersonal and social-rhythm therapy in adolescents. The *RANZCP* guidelines (Malhi et al., 2015) recommend a combination of psychotherapy and pharmacotherapy for those with BD I. The *Indian Psychiatric Society* (Shah et al., 2017) does not specifically mention any pharmacotherapy or

psychotherapy for adolescents except to “start at lower doses and titrate slowly”. The guidelines from Japan (Kanba et al., 2013), South Africa (Emsley et al., 2013), Taiwan (Bai et al., 2013) and Singapore (Mok et al., 2011) and the International College of Neuropsychopharmacology (Fountoulakis et al., 2017) did not contain specific maintenance treatment recommendations for adolescents with BD.

Discussion

In our review of the international and national guidelines on BD published in the last decade, we identified a relative lack of recommendations for early stage disorder. Among the fourteen guidelines, half did not have any specific recommendations for the early stages of BD. This indicates a clear evidence gap in the literature which is likely to be preventing optimal care of people with early stage BD. This stands in comparison to the focus on, and positive outcomes from 20 years of early intervention for psychosis (Malla et al., 2016) and the consequent imperative for similar interventions in BD (Post, 2018; Vieta et al., 2018). However, a promising signal from recent guidelines was the broad recommendation to initiate comprehensive assessment and treatment early in illness course. Additionally, there are emerging recommendations regarding indications for maintenance treatment although the evidence underpinning these recommendations is unclear.

A majority of the guidelines contained specific sections for adolescents. For treatment of acute mania among children and adolescents, second generation antipsychotics were most likely to be recommended as first-line therapy, with aripiprazole described as first-line in four guidelines (Goodwin et al., 2016; Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014; Yatham et al., 2018). Lithium (Grunze et al., 2009; Yatham et al., 2018) and risperidone (Malhi et al., 2015; Yatham et al., 2018) were also recommended for children and adolescents as first-line therapy in two guidelines. For treatment of acute bipolar depression, psychosocial interventions (Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014) and adjunctive pharmacotherapy (Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014; Woo et al., 2015; Yatham et al., 2018) were

recommended. For ongoing treatment, psychosocial treatments were recommended in two guidelines (Malhi et al., 2015; Yatham et al., 2018).

The overall quality of the guidelines varied considerably and may impact the validity of the recommendations. Recency of guideline was another variable, which appeared to impact on recommendations. For example, the *WFSBP* guidelines were published between 2009 and 2013, the *ACGEP* in 2010 and the Singapore guidelines in 2011. Further clinical trials may have been published and included in the later guidelines such as the *BAP* (2016) and *CANMAT* guidelines (2018). *CANMAT* was the only guideline to be updated in the included time period. The updated version of this guideline did indicate a greater focus on treatment, including maintenance treatments from the first episode of mania (Yatham et al., 2018). International guidelines such as *WFSBP* or *CINP* and national guidelines from the UK, Australia and Canada demonstrated a greater rigour of development and completeness of reporting. Hence, the recommendations from these guidelines may be more valid in comparison to the other national guidelines, especially when considering discordant recommendations. Such discordance was observed across several phases of treatment. For treatment of acute mania in adolescents, lithium was recommended as first-line therapy in *WFSBP* (Grunze et al., 2009) and *CANMAT-ISBD* (Yatham et al., 2018) guidelines, but was less strongly recommended due to a lower level of evidence in the *RANZCP* (Malhi et al., 2015) guideline. The recommendation to use psychological therapies as first line treatment for those with bipolar depression by the *NICE* guideline is not supported by *BAP*. These discrepancies within widely respected guidelines indicate that definitive evidence may be lacking.

Among adolescents, the recommended therapeutic serum level for lithium in acute mania also varied. According to *WFSBP* (Grunze et al., 2009) and *ACGEP* (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016), it was 0.6-1.3 mmol/L and 1-1.2 mmol/L, respectively. The *WFSBP* (Grunze et al., 2009) guidelines suggested that adolescents were more likely to require and tolerate lithium levels at the higher end of this range. It should be borne in mind that *WFSBP* guidelines primarily refer to age-specific recommendations (adolescents) while *ACGEP* have stage specific

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recommendations (first episode). It should be borne in mind that both these guidelines make these recommendations without primary data to support this, but from the clinical experience of the authors. *CANMAT* was cautious about higher lithium levels, not because of pharmacological reasons, but because of the possibility that "initial experiences prime expectations of tolerability and hence long term adherence".

An important distinction that should be mentioned is the lack of definitions and accepted terminology regarding staging, onset and early intervention in clinical guidelines. In our review, we identified the lack of a clear definition of 'early stage BD' in the included guidelines. The ISBD Staging Taskforce recommends a broad use of the term 'early stage' to include those in the first or first few episodes of BD with better functioning after symptomatic recovery (Kapczinski et al., 2014). However, few guidelines specifically refer to this or another accepted definition. Additionally, it is not known if the first few episodes should refer to manic/hypomanic episodes alone or whether depressive episodes that occur prior to the onset of mania also contribute to the staging definition. Thus, it is possible that patients in their first treatment seeking episode of mania could have had many prior depressive episodes (Berk et al., 2007b)which could already place them in a later stage category. The differences in staging models also contribute to difficulties for clinicians. Those that are considered early stage in the ISBD staging recommendation as well as other commonly accepted staging models (Berk et al., 2007a; Cosci and Fava, 2013) are considered later stages in other staging systems that have a greater focus on precursor syndromes or prodromes (Duffy, 2014). Future staging systems should be more uniform such that early and later stages, prodromes, and early interventions are better defined in operational terms.

Another confusion relates to the distinction between early onset BD and early stage BD. Interventions among youth with 'early onset BD' relates to the age-specific needs of these young people with BD, while interventions in 'early stage' (or EI) relate to requirements of the earlier illness stage, most commonly defined using illness course (Berk et al., 2007a), or a combination of illness course and functioning (Kapczinski et al., 2009). While those with at an earlier age may be in an earlier illness stage,

they may well not be. For example, children (under 18 years) in their third episode of acute and severe mania may be in the early onset group, but already in a later stage of the disorder. It is also possible that adolescents with an earlier onset of illness may have a neurodevelopmental expression of the disorder that progresses more often to a later stage, than those with an adult onset. Those with earlier onset of BD were noted to have poorer functional recovery (Perlis et al., 2009), a marker of later stage disorder. In our review there was a need to include the guideline statements relating to an earlier age of participants, as well as an earlier stage of the disorder due to the overlap of developmental and illness stages. However, a review of pediatric or pre-pubertal BD, prodromes of BD and precursor stages were beyond the scope of the current review.

The above mentioned discrepancies as well as difficulties in operationalisations may be confusing for clinicians who would benefit from clear guidance on managing young people with BD in their earlier stages of the disorder. Such disparities require further clinical trials to identify adequate therapeutic levels in adolescents, and will help develop evidence-based guidelines for EI for BD. One promising finding from our review compared to an earlier review (Conus et al., 2006) is that several of the BD guidelines have started to make general recommendations regarding early and comprehensive interventions for those with BD, although specific recommendations are lacking. However, these recommendations have a lower level of evidence due to the limited number of randomised controlled trials (RCTs) available in this population.

One of the major drivers of the lack of specific recommendations for early stage BD is the paucity of primary studies. There are relatively few RCTs examining pharmacotherapy in early stage BD (Berk et al., 2017a; Conus et al., 2015). One promising finding indicating a stage-specific effect was from one of these RCTs which investigated maintenance pharmacological treatment for youth in their first treatment-seeking episode of mania (Berk et al., 2017a). In this study, lithium was more effective than quetiapine on symptomatic measures and functioning over 12 months of follow up. This is in contrast to the lack of

difference between these two medications among adults with established BD, albeit in a shorter six-month trial (Nierenberg et al., 2016).

Similar to the dearth of evidence for pharmacological interventions, an 'evidence-map' of psychosocial interventions for early stage BD identified few evidence-based RCTs, especially when compared to early stage psychosis or depression (Vallarino et al., 2015). That review identified that the common psychological therapies utilised in earlier illness stages were based on cognitive-behavioral, psychoeducational, family based or interpersonal approaches. Among these, group psychoeducation has been one intervention identified to be more efficacious in those with fewer number of illness episodes (Colom et al., 2010a), or among those who were younger (Kessing et al., 2014). While both studies were randomised and controlled in design, group psychoeducation was studied as a sole intervention in the former while it was a component of a larger mood-disorder early intervention clinic in the latter study. Thus, while there is emergent evidence of illness stage or developmental stage impacting on efficacy of psychosocial interventions, clinical guidelines have had a limited focus on these populations. Two previous reviews on early detection and/or pharmacological and psychosocial therapies in the early phase of BD also highlighted the need for more research and development of therapeutic approaches specific to this population (Conus et al., 2006; Elanjithara et al., 2011).

The gaps in the evidence-base could be addressed by future clinical trials of EI for BD and by intervention trials that stratify by stage of the disorder. Future studies should also aim to identify the optimal timing for commencement of interventions for those with BD, identification of specific interventions that are effective for different phases of the disorder in early illness stages and the duration of optimal maintenance treatment in early illness stages. Such studies should also consider the interaction between age and stage of the disorder. At present, most studies are conducted in adults over the age of 18 with early emerging evidence amongst adolescents and children. However, the age of onset of the disorder peaks across this adolescent-adult divide (Diler, 2007; Perlis et al., 2009). New intervention trials should include post-pubertal adolescents as well as young adults in their early illness course. Targets such

as functioning and biomarkers that may be stage-specific should be included to understand the impact of treatments on progression, beyond symptom control or relapse prevention.

Limitations

Our findings should also be considered in the light of a number of limitations. First, none of the guidelines aimed to provide guidance on early stage BD. This could mean that the recommendations in each guideline were different in their scope and intent, making comparability limited. A related concern is that the included guidelines were not able to separate illness stages from developmental stages due to the lack of primary data. Primary intervention studies that clearly separate those in an earlier illness stage from those in a later illness stage, taking into account the developmental stages of included participants are necessary to create evidence informed clinical practice guidelines. Second, guidelines published prior to March 2008 were not included in this review, which may contain treatment recommendations for the specific population. However, this selection criterion was included in order to keep the recommendations current and to avoid including expired guidelines. ~~, none of the guidelines aimed to provide guidance on early stage BD. This could mean that the recommendations in each guideline were different in their scope and intent, making comparability limited.~~

Despite these, the current review is a critical first step in consolidating the available recommendations to further the goal of EI for BD. In all, given that there is little consensus on the treatment for either early stage BD/first-episode presentation or adolescents with BD, there is a critical need for primary research in this area. Till such time, these summative recommendations may better inform clinicians when treating young people with early stage BD. It can also form the basis of a future evidence-informed guideline developed specifically for these populations.

There should be several considerations in devising new guidelines for those with early stage BD. First, stratification of this highly heterogeneous disorder across stages of the disorder, type of disorder, and symptom dimensions are necessary. Thus, those with clear onset of BD I or II should have separate

guidelines from those with prodromal or pre-onset symptoms. Similarly, the specific needs of those with BD II should be considered separately from those with BD I or NOS. Those with prodromal BD should be clearly delineated from those in the early post-onset period in primary intervention research, as well as in future guidelines. Those with psychotic or anxious symptoms merit dimensional assessment and treatment recommendations. However, any such guideline should clearly outline the missing evidence, and be modified or revised as such evidence becomes available. Clear and operational definitions should underpin the language for such guidelines, as well as in future research and translation.

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Table 1: Overview of International and National Guidelines for Bipolar Disorder

Organisation	Author(s)	Year	Specific Recommendations ~~For~~regarding	
			Early Stage BD	Adolescents
World Federation of Societies of Biological Psychiatry (WFSBP) **(Grunze et al., 2009; Grunze et al., 2010, 2013b)**	Grunze et al.	2009 2010 2013	+++	++
Australian Clinical Guidelines for Early Psychosis (ACGEP) **(Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016)**	Early Psychosis Guidelines Writing Group and EPPIC National Support Program	2010	++	+++
Singapore Ministry of Health **(Mok et al., 2011)**	Mok et al.	2011	+	-
Japanese Society of Mood Disorders **(Kanba et al., 2013)**	Kanba et al.	2012	-	-
Taiwan Society of Biological Psychiatry and Neuropsychopharmacology **(Bai et al., 2013)**	Bai et al.	2013	+	-
South African Society of Psychiatrists **(Emsley et al., 2013)**	Emsley and Seedat	2013	++	-
National Institute of Health and Care Excellence (NICE) **(National Collaborating Centre for Mental Health (UK), 2014)**	National Collaborating Centre for Mental Health and Guideline Development Group	2014	-	+++
Royal Australian and New Zealand College of Psychiatrists (RANZCP) **(Malhi**	Mahli et al.	2015	-	+++

et al., 2015)				
British Association of Psychopharmacology **(Goodwin et al., 2016)**	Goodwin et al.	2016	++	+++
Indian Psychiatric Society **(Shah et al., 2017)**	Shah et al.	2017	-	++
International College of Neuropsychopharmacology (CINP) **(Fountoulakis et al., 2017)**	Fountoulakis et al.	2017	-	-
Canadian Network for Mood (CANMAT) and Anxiety Treatments and International Society for Bipolar Disorders (ISBD) **(Yatham et al., 2018)**	Yatham et al.	2018	+	+++

+ One to two sentences relevant to early stage BD or adolescents
++ More than two sentences relevant to early stage BD or adolescents
+++ More than one paragraph relevant to early stage BD or adolescents

Table 2. Quality Assessment of Guidelines for BD Using the AGREE GRS Instrument

Guideline	Development	Presentation	Completeness	Clinical Validity	Overall Quality
International guidelines					
WFSBP **Mania (Grunze et al., 2009)** **Depression (Grunze et al., 2010)** **Maintenance (Grunze et al., 2013b)**	6 6 6	6 6 6	6 6 6	6 7 7	6 6 6
BAP **(Goodwin et al., 2016)**	5	6	5	6	6
CINP **(Fountoulakis et al., 2017)**	6	7	6	7	6.5
CANMAT-ISBD (Yatham et al., 2018)	7*	7	6	6	6.5
National guidelines					
ACGEP **(Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016)**	4	6	5	5	5
NICE **(National Collaborating Centre for Mental Health (UK), 2014)**	7	6	7	7	7
RANZCP **(Malhi et al., 2015)**	7	7	6	6	6.5
Singapore **(Mok et al., 2011)**	2	6	3	4	3
Japan **(Kanba et al., 2013)**	2	6	3	4	3
Taiwan **(Bai et al., 2013)**	2	6	3	4	3
South Africa **(Emsley et al., 2013)**	2	6	3	4	3
India **(Shah et al., 2017)**	1	6	2	4	2.5

*based on correspondence with authors
AGREE GRS: Appraisal of Guidelines for Reseach and Evaluation; Global Rating Scale. 1 (lowest quality) – Given if there is no information that is relevant to the AGREE GRS item, if the concept is very poorly presented in the guideline, or if the authors explicitly state that the criteria were not met (Brouwers et al., 2012).
7 Highest quality - Given if the quality of reporting and presentation is exceptional and if the considerations have been fully met (Brouwers et al., 2012).

Table 3. Summary of recommendations relevant for those with early stage BD.

Episode	Recommendation
Mania	a) Comprehensive and early interventions, including hospital admissions should be considered (Goodwin et al., 2016; Yatham et al., 2018) **For those with First Episode Psychotic Mania** (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016) a) First-line treatment recommendation is a combination of a mood stabiliser and an atypical antipsychotic b) Recommended mood stabilisers i. First-line: Lithium carbonate ii. Second-line: Sodium valproate iii. Third-line: Carbamazepine, oxcarba~~ma~~zepine, mood stabiliser combinations c) Recommended atypical antipsychotics i. First-line: Risperidone, quetiapine, ziprasidone, aripiprazole ii. Second-line: Switch to another atypical antipsychotic and optimize psychosocial interventions iii. Third-line: Crossover to another atypical antipsychotic including olanzapine or ECT
Bipolar Depression	a) Ask for previous manic and hypomanic episodes (Grunze et al., 2010; Mok et al., 2011) **For those with psychotic bipolar depression** (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016) b) First-line treatment recommendation is a combination of a mood stabiliser and atypical antipsychotic i. Mood stabilisers included: Lithium carbonate, lamotrigine, quetiapine ii. Second line options included adding an antidepressant such as fluoxetine along with a mood stabiliser
Maintenance treatment	a) Commence long-term therapy if there have been: • Significant family history of affective disorders (Bai et al., 2013; Grunze et al., 2013b) , or • High level of severity of first episode (Bai et al., 2013; Grunze et al., 2013b) b) First-line treatment: Lithium, valproate, aripiprazole, lithium + risperidone, lithium + aripiprazole or~~,~~ valproate ~~or divalproex~~ (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016)

	• Lithium serum level according to *ACGEP*: 0.6-0.8 mmol/L (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016) c) Enhanced psychoeducation, motivational and family support (Goodwin et al., 2016)

Table 4: Summary of Recommendations for adolescents

Episode	Recommendation
Mania	• Aripiprazole was recommended most consistently as first-line treatment (Goodwin et al., 2016; Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014; Yatham et al., 2018) • Lithium (Grunze et al., 2009; Yatham et al., 2018) and risperidone (Malhi et al., 2015; Yatham et al., 2018) were considered first-line therapy in two guidelines each • Olanzapine (Goodwin et al., 2016; Yatham et al., 2018) and quetiapine (Goodwin et al., 2016; Yatham et al., 2018) were recommended as second-line treatment by two guidelines due to the increased risk of side effects
Bipolar Depression	• Adjunctive pharmacotherapy was recommended by three guidelines (Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014; Woo et al., 2015; Yatham et al., 2018) • Psychosocial interventions were recommended by two guidelines (Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2014) • Lamotrigine was considered first-line therapy by two guidelines (Malhi et al., 2015; Woo et al., 2015)
Specific psychosocial treatments	• Psychosocial treatments recommended included (Malhi et al., 2015; Yatham et al., 2018) o Psychoeducation o CBT o Family-focused therapy o Interpersonal therapy o Social-rhythm therapy
General Recommendations	• According to two guidelines (Goodwin et al., 2016; Yatham et al., 2018), general principles for treatment were similar to those described for adults, but with the caveat regarding monitoring for the increased risk of side effects • Sodium valproate should be used with caution in young women of childbearing age according to four guidelines (Grunze et al., 2009; Grunze et al., 2010, 2013b; National Collaborating Centre for Mental Health (UK), 2014)

Figure 1: Flow diagram of included reports