Guidelines For the Management of Bipolar Disorder
University of Louisville Depression Center

Statement of Purpose

The purpose of this document is to provide a general framework for the management of bipolar illness. This framework takes into account the quality of evidence supporting different treatment approaches. These guidelines are provided with full realization that there is no single approach that is appropriate for all patients with this illness. Additionally, it is recognized that physicians will utilize insights and experience that cannot be quantified nor categorized which can improve outcome. These guidelines are to be implemented as a resource for evidence-based approaches to treatment of bipolar illness. Previous clinical guidelines are used heavily to draw up the current guidelines.

Utilization of Guidelines

The guidelines are divided into diagnosis- and state-based treatment approaches. Both the patient's diagnosis and current disease state need to be taken into account to provide optimal treatment. The data are presented in the Gary Sachs approach of 'menu of reasonable choices.'

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General Principles

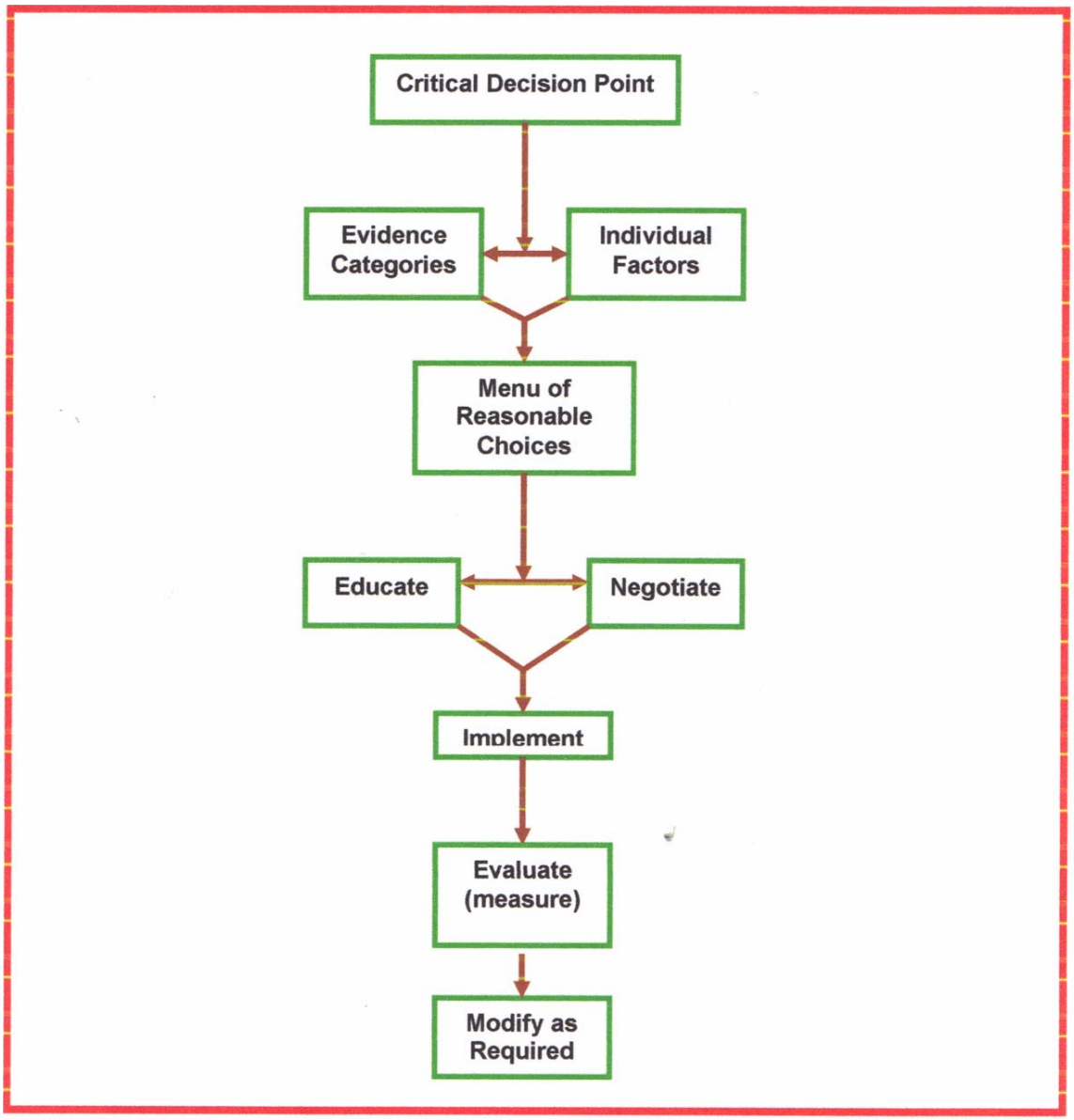
The general approach for decision making in treatment of bipolar patients is presented in Figure 1 (Sachs 2006). In this scheme, an initial Critical Decision Point arises due to illness factors (e.g., onset of a mode episode, or resolution of a mood episode). The clinician integrates both evidence-based choices with individual patient factors that may modify those choices or help determine which is the most reasonable choice. The patient is then presented with the choice or possible choices, educated regarding the evidence, and a collaborative decision is reached. The choice is implemented and outcome measured in a mutually agreed on predetermined method (e.g., target symptoms). Ongoing evaluation of how these goals are being met determines ongoing treatment decisions.

Quality of data supporting clinical decisions is based upon study design. The rating system for quality of studies is presented in Table 1 (based on Sachs 2006)

Table 1. Rating of quality of evidence (A is highest, F is lowest) (Sachs 2006)

Rating	Definition
A	More than 1 placebo controlled study
B	Blinded active comparator study
C	Open comparator study
D	Uncontrolled observations (e.g., case series)
E	No published evidence or single case reports
F	Negative evidence

Figure 1. Scheme for decision making in the treatment of bipolar illness.



Diagnostic Issues

The diagnosis of bipolar illness is difficult and the disease is both underdiagnosed and overdiagnosed (Hirschfeld et al 2003; Lish et al. 1994; Stewart and El-Mallakh 2007). It is important to understand that evidence-based practice only works if the clinical diagnosis is made in the same fashion as the research diagnosis. Thus, the current treatment guidelines are only useful if the clinician diagnosis strictly follows DSM-IV criteria. Patients whom the clinician believes have bipolar illness, but do not meet strict DSM-IV criteria should be defined as Bipolar NOS.

Since data are only available for type I and type II bipolar illness, those illnesses will be the only ones presented with any detail.

Bipolar I: Mania

There are multiple agents available for the treatment of mania associated with bipolar illness. Regardless of the severity of mania the menu of reasonable choices is similar. Table 2 presents reasonable options of both euphoric or dysphoric mania. **Antidepressant discontinuation** has never been studied, but since antidepressants can induce mania, discontinuation is recommended.

Table 2. Menu of reasonable choices for mania

Intervention	Quality of Supportive Evidence	Comment
Lithium, carbamazepine, divalproex (i.e., mood stabilizer) monotherapy	A	Divalproex and carbamazepine may be better for mixed mania
Haloperidol, chlorpromazine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole monotherapy	A	
Combination mood stabilizer (lithium, divalproex, carbamazepine [with the exception of carbamazepine + risperidone]) + antipsychotic (olanzapine, risperidone, quetiapine, aripiprazole [no evidence for ziprasidone])	A »	Carbamazepine induces 3A4 and reduces levels of other agents such as risperidone and aripiprazole, and may be useful with higher doses of antipsychotic.
Clonazepam monotherapy	B	Based on a single study
ECT	B	
Oxcarbazepine	D	
Antidepressants	E	
Gabapentin, lamotrigine, toparimate	F	Gabapentin may worsen mania

Bipolar I: Depression

Depression in bipolar illness is less well studied, but a fair amount of data exists nonetheless. Menu of reasonable choices in presented in Table 3.

Table 3. Menu of reasonable choices of the treatment of bipolar I depression

Intervention	Quality of Supportive Evidence	Comment
Lithium, quetiapine, lamotrigine monotherapy, and olanzapine/fluoxetine combination (OFC)	**A**	**Lamotrigine and lithium are preferred. Long-term safety of quetiapine and OFC has not been established**
Pramipexole	**A**	**Added to mood stabilizer**
Psychotherapy added to mood stabilizer (CBT, IPRT, psychoeducation)	**A**	
ECT	**B**	
Divalproex	**D**	**Small placebo controlled studies have been both positive and negative with a small effect size**
Olanzapine	**D**	**Double-blind placebo controlled study positive but only a subset of depressive symptoms improve**
Methylphenidate	**D**	**Added to mood stabilizer**
Oxcarbazepine	**D**	
Antidepressants	**D**	**Negative studies when antidepressants added to mood stabilizer. Positive clinical experience and positive studies when added to antipsychotic (e.g., OFC)**

Bipolar I: Relapse Prevention

There are very few true relapse prevention studies in bipolar illness. Most available evidence utilizes maintenance designs. Maintenance designs frequently utilize enriched samples (i.e., people who have already benefited from the acute medication). Such study designs are useful clinically, but less informative regarding true relapse prevention efficacy. The menu of reasonable choices presented in Table 4 does not distinguish relapse prevention from maintenance designs. Most treatment guidelines separate recommendations based on patients' most recent episode (mania vs. depression), however, since there is little evidence that this is predictive regarding response, the current guidelines combine them.

Table 4. Menu of reasonable choices for relapse prevention

Intervention	Quality of Supportive Evidence	Comment
Lithium, lamotrigine, Olanzapine, aripiprazole monotherapy	A	Divalproex relapse prevention study positive with enriched analysis
Olanzapine plus lithium or divalpoex	A	
Psychotherapy (CBT, psychoeducational, family, IPRT) added to phamracotherapy	B	
Antidepressants	F	Antidepressants do not reduce likelihood of depressive relapse

Bipolar II: Hypomania

There are no studies that have been done to treat hypomania in bipolar II illness. Antidepressant **discontinuation** has never been studied, but since antidepressants can induce hypomania, discontinuation is recommended.

Bipolar II: Depression

There are several studies examining short term treatment of depression in type II illness. The menu of reasonable choices in Table 5.

Table 5. Menu of reasonable choices for the treatment of depression in type II bipolar subjects.

Intervention	Quality of Supportive Evidence	Comment
Quetiapine	A	
Antidepressant monotherapy	A «	Despite several studies documenting short term efficacy of antidepressant monotherapy, this is generally not recommended. Addition of a mood stabilizer is preferred. There are no long term trials with antidepressants either in monotherapy or combination.
Psychotherapy (CBT, psychoeducational, family, IPRT) added to phamracotherapy	C	
Lithium, carbamazepine, divalproex	C	

Bipolar II: Relapse Prevention

Divalproex and **lithium** are the only agents examined in randomized comparison trials **(B)** and appear to be equally effective.

Rapid Cycling

There is only one blinded, placebo controlled study of rapid cycling **(A)** which showed that **lamotrigine** was superior to placebo for type II patients. There is one randomized, blinded comparison of monotherapy with lithium or divalproex versus combination snowing that combination was superior in both type I and II patients. However, drop out rates were so high (>80%) that data utility is questionable. **Antidepressant discontinuation** has never been studied, but since antidepressants can induce cycling, discontinuation is recommended.

Bipolar NOS

There are studies of NOS bipolar illness. Recommendation is to apply data from type I or type II studies. **Antidepressant discontinuation** has never been studied, but since antidepressants can induce a bipolar-like picture, discontinuation is recommended.

References

Hirschfeld RM, 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. J Clin Psychiatry 2003; 64: 161-174.

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