Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Bipolar Disorder:

A Novel, Practical, Patient-Centered Guide for Clinicians

Michael J. Ostacher, MD, MPH, MMSc[a,b,*]; Rajiv Tandon, MD[c]; and Trisha Suppes, MD, PhD[a,b]

ABSTRACT

Objective: This report describes the 2014 update of the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Bipolar Disorder, intended to provide frontline clinicians with a simple, evidence-based approach to treatments for 3 phases of bipolar disorder: acute depression, acute mania, and maintenance.

Participants: The consensus meeting included representatives from the Florida Agency for Health Care Administration, pharmacists, health care policy experts, mental health clinicians, and experts in bipolar disorder. The effort was funded by the Florida Agency for Health Care Administration.

Evidence: The available published and nonpublished data from trials in the treatment of bipolar I disorder were reviewed. Evidence for efficacy and harm from replicated randomized clinical trials, systematic reviews and meta-analyses, or non-replicated randomized clinical trials was included. No recommendations were made with evidence from other sources.

Consensus Process: Decisions regarding the structure of the guidelines were made during a stakeholder meeting in Tampa, Florida, on September 20 and 21, 2013. Better proven and safer/more efficacious treatments were to be utilized before using those with less evidence and/or greater risk. Safety and risk of harm were balanced against potential benefit. Lower-quality evidence was recommended only if higher-level treatments were found to be ineffective or not tolerated, because of patient preference, or because of past treatment success. While respecting patient and clinician choice, the guidelines are structured to encourage evidence-based, safe prescribing first.

Conclusions: This iteration of the Florida guidelines for the treatment of bipolar disorder is a practical, simple, patient-focused guide to treatment for acute mania and acute bipolar depression and maintenance treatment that considers safety and harm in the hierarchy of treatment choices. While using strict evidence-based criteria for inclusion in recommendations, it eliminates expert opinion as a level of evidence while respecting clinician and patient choice in treatment decision-making.

J Clin Psychiatry
dx.doi.org/10.4088/JCP.15cs09841

[a]VA Palo Alto Health Care System, Palo Alto, California
[b]Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, California
[c]Department of Psychiatry, University of Florida College of Medicine, Gainesville
**Corresponding author:* Michael J. Ostacher, MD, MPH, MMSc, VA Palo Alto Health Care System, 3801 Miranda Ave, Mail Code 151-T, Palo Alto, CA 94304 (ostacher@stanford.edu).

Bipolar disorder is a complex disorder characterized by several different phases of illness that require different treatment approaches. It was not long ago that the established treatment options for bipolar disorder were limited (lithium, divalproex sodium, and chlorpromazine for acute mania; nothing for depression; and lithium for maintenance treatment), leaving clinicians mostly in the dark as how to treat their patients with bipolar disorder who did not respond to those treatments, could not tolerate them, or were depressed. Over the past 10 to 15 years, there has been a substantive increase in the number of treatments for each phase of bipolar disorder that have been well established in large, methodologically sound trials. During the same period, there has been great growth in the development of guidelines (expert-derived recommendations for treatment using existing evidence) and algorithms (formal, step-by-step recommendations for treatment) across all of medicine, although there is little guidance for clinicians about how to choose between competing guidelines and how to apply generic recommendations to individual patients.[1–9]

Because guidelines are generally expert-driven (with variable input from clinicians and other stakeholders), there has been a tendency for guidelines to use "expert opinion" and "clinical experience" to make treatment recommendations, but it is not clear that opinion (however informed) or clinical experience should be considered "evidence."[10] While the opinions of experts are clearly useful and the clinical experience of using treatments with patients an important aspect of clinical decision-making, it is important that opinion and anecdotal experience do not supersede actual medical evidence—and even more important that it remain clear that they are not a replacement for it. Many guidelines for the treatment of bipolar disorder, including the most recent iteration of the CANMAT guidelines (the 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),[11] codify both expert opinion and clinical experience into their levels of evidence. For CANMAT, the fourth level of evidence is "anecdotal reports or expert opinion."[11]

As more data from large trials and systematic reviews become available, the need for opinion and experience to fill gaps in knowledge has diminished, yet data remain incomplete. It is also generally the case that much good evidence comes from industry-funded trials that have been focused on assay sensitivity rather than generalizability, leading the exclusion from studies of the kind of complex patients often seen in actual clinical practice—and effective drugs are rarely compared head to head. In the real world, clinicians often conclude that the clinical needs of their

Clinical Points

- The diagnosis and treatment of bipolar disorder are complicated, and the evidence for best treatments for it is frequently changing.
- Clinical guidelines intended for front-line clinicians should be simple, easily implemented, and strongly evidence-based.
- Expert opinion and clinical experience, while important in treating patients, should not be a substitute for high-quality evidence.

patients quickly outstrip the available evidence addressing treatment management, leaving great uncertainty about how to proceed.

It is also important that evidence from small trials not be confused with replicated data from large samples, as we may be biased toward believing the results of positive, underpowered studies. As an example of this, CANMAT requires "clinical support for efficacy and safety" for a treatment to be recommended, but recommends against the use of a treatment only if there is level 1 or level 2 evidence demonstrating its lack of efficacy—in other words, recommending against a treatment only if it is definitely ineffective, rather than recommending against a treatment because evidence for it is inadequate or premature.[11]

Agencies responsible for the payment for and oversight of patient care have also become increasingly involved in establishing standards for the use of treatments and include the US Department of Veterans Affairs/Department of Defense VA/DoD), the government of the United Kingdom (National Institute for Health and Care Excellence),[12] and various states (beginning with Texas, where the Texas Medication Algorithm Project [TMAP] was developed).[7] Government-led guidelines tend to include more diverse stakeholders, be less subject to conflicts of interest, and be quite comprehensive, but sometimes leave the burdensome task of translating them into practice to the clinician.[3] It is important, then, that guidelines be independent from stakeholder bias (whether commercial or governmental), have fidelity to the published data, and respect clinician and patient choice while at the same time being simple and easily implemented in clinical practice.

To achieve this for the State of Florida, the Florida Legislature authorized the development of the Medicaid Drug Therapy Management Program for Behavioral Health (MDTMP),[13,14] whose purpose is "to improve the quality and efficiency of the prescribing of mental health drugs, and to improve the health outcomes of Medicaid beneficiaries with a mental illness."[15] Rather than using existing guidelines, however, Florida set about to develop new guidelines based on the needs of the "prescriber community" using the best available evidence. Because it was developed with a focus on front-line clinicians treating a generally socially disadvantaged and severely ill population, the guidelines have been designed to be straightforward and easy to use.

This most recent iteration of the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Bipolar Disorder has changes in several important areas that bring the guidelines in line with the most current evidence in bipolar disorder and consistent with changes in *DSM-5*.[16] As in previous versions, it is emphasized that patients with bipolar disorder need a careful initial diagnostic assessment to differentiate them from patients with other disorders, with a 2-pronged goal of minimizing the underdiagnosis of bipolar disorder while at the same time being careful not to mistakenly diagnose patients with bipolar disorder who actually have major depressive disorder or other illnesses. While these guidelines were developed by Florida Medicaid (the agency responsible for payment for drugs), the cost of the drugs themselves does not figure into the guidelines other than indirectly by discouraging the use of ineffective or unproven treatments.[15]

CONSENSUS PROCESS

This iteration of these guidelines was initiated as a biennial revision of existing Florida Medication Guidelines, previously distributed in 2012 (http://medicaidmentalhealth.org/_assets/file/Guidelines/FL_Best%20Practice_Adult%20Guidelines_20112013100712553256%20%281%293.pdf). As such, it became an opportunity to shift the focus of recommendations. The process for gaining consensus for these changes involved bringing together stakeholders in the guidelines for an in-person conference in Tampa, Florida, on September 20 and 21, 2013, to review data, discuss how the guidelines should be structured, and finalize the guidelines themselves. Stakeholders included content experts in bipolar disorder (Drs Ostacher and Suppes), schizophrenia (Dr Tandon), and major depression (Dr Yeung); leadership of Florida's Medicaid Drug Therapy Management Program for Behavioral Health; physicians and other professionals from community mental health centers and private practice; pharmacists; state participants; faculty from the Universities of Florida and South Florida; and representatives from managed care organizations. New evidence for the treatment of bipolar disorder and a review of existing evidence were presented, along with an overview of the changes. (A list of participants and the guideline document can be found at http://medicaidmentalhealth.org/ViewGuideline.cfm?GuidelineID=36.)

The levels of treatment utilized in these guidelines were based on available evidence for efficacy, available evidence for harm, prior history of response for a given patient, and patient preference. (There is currently no established method of placing treatments in different levels in published guidelines in psychiatry.) The basic premise of the guidelines is that better proven and safer/more efficacious treatments should be utilized before trying those with less evidence and/or greater risk. Treatments should start at the highest level (level 1) and move to lower levels only if the higher level treatments are found to be ineffective or not tolerated, because of patient preference, or because a patient has already

been treated successfully with lower level treatments. The first 3 levels contain evidence from replicated randomized clinical trials, systematic reviews and meta-analyses, or non-replicated randomized clinical trials. Recommendations in the guidelines for the treatment of all phases of bipolar disorder are made along 4 levels:

- Level 1A: Established efficacy without prominent safety concerns. These include drugs for which definitive, replicated, large randomized, placebo-controlled trials have been completed.
- Level 1B: Established efficacy (as in level 1A), but with prominent safety concerns for the treatments listed.
- Level 2: Established tolerability but with more limited data for efficacy (eg, meta-analyses with small effect sizes, smaller randomized trials, overall small effect sizes).
- Level 3: If levels 1 and 2 are ineffective or not tolerated. Treatments at this level have more limited efficacy data and/or more tolerability limitations than levels 1 and 2 (eg, small randomized trials, but with safety or tolerability concerns).
- Level 4: If levels 1–3 are ineffective or not tolerated. The treatments at this level do not have adequate evidence to support their use. At this level, treatments are listed if they do not have data to recommend them (or may have mixed study results) because stakeholders wanted to include treatments that were being used in the community. This level acknowledges clinical practice (eg, the use of standard antidepressants in bipolar disorder in spite of no clear efficacy and potential risk of harm) while categorizing the treatments as not being supported by evidence.

These guideline levels differ in some important ways from those published in the past. First, while they are based on evidence, they were made in conjunction with community stakeholders (eg, practitioners and funders). While there may not be evidence for certain treatments, community standards might suggest their use. For example, there is little evidence supporting the efficacy of antidepressants in bipolar disorder (and some evidence for harm), yet they are widely prescribed. The goal of this guideline is to reserve such treatments for use only after other treatments failed. While respecting patient and clinician choice, the guidelines are structured to encourage evidence-based, safe prescribing first. The guidelines thus serve both as an educational tool and as a hierarchically organized review of evidence.

Notably, the health consequences and adverse effects of any treatment are given great weight in these guidelines so that the guidelines are not solely based on efficacy. The balance in considering efficacy and harm reflects usual clinical decision-making that considers all aspects—both helpful and harmful—of a given medication. This follows the principle that efficacy has been overvalued relative to harms and that, in the context of shared responsibility for treatment decisions between patient and practitioner, the practitioner has greater access to information regarding potential harms of treatment. This was specifically discussed in regard to olanzapine, which was left at level 1 treatment for mania and maintenance treatment because of very strong, replicated efficacy data, but which led to the division of level 1 into A and B recommendations, with level 1B being recommended after level 1A only because of differentially larger safety concerns. Safety is different from tolerability, as disorder lipid or glucose metabolism is not something a patient "feels," as opposed to, for example, sedation, akathisia, or parkinsonism.

The guidelines for bipolar disorder remain divided (as in prior editions) into 3 sections: acute bipolar depression, acute mania, and maintenance treatment.

For all patients, careful assessment is stressed. Because bipolar disorder so often co-occurs with addictive disorders, including smoking, these comorbidities must be addressed at initial assessment and throughout the course of treatment. Increased mortality and morbidity due to medical illness must also be addressed, so care should be coordinated to improve access to medical treatment—and each contact with a patient with bipolar disorder who smokes should be considered an opportunity to engage in a discussion of behavioral change and smoking cessation. Patients should also be treated using measurement-based care, so symptom scales should be used at all visits if possible to determine whether treatment is working and whether continued treatment is merited given the inevitable side effects of medications. (A list of recommended scales can be found in the guidelines.) It should be the goal of all practitioners that they integrate rating scales, including patient self-rated assessments, into routine clinical practice.

These guidelines were also written and published during a period of transition from *DSM-IV-TR* to *DSM-5*. The category of major mood disorders was divided into 2 chapters, and bipolar disorder was explicitly separated from the depressive disorders.[17] What impact this has on practice is unclear, but there is now a further, formal distinction between the two, underscoring the need for careful assessment. In the definition of mania and hypomania, specific emphasis is placed on the symptoms of increased energy and activity, and both increased energy/activity and heightened or irritable mood are now necessary for a diagnosis of mania or hypomania (and hence, bipolar disorder itself). The *DSM-IV-TR* category of mixed episode was eliminated and was replaced by the use of a "mixed features" specifier for both episodes of mania and depression if symptoms of depression were present in the context of mania or symptoms of mania/hypomania were present in the context of major depression, respectively. The presence of mixed features has important implications for proper treatment selection, but because of the absence of evidence for treatments for mood episodes defined as such, no recommendations for the treatment of manic or hypomanic episodes with mixed specifier

Table 1. Consensus Guidelines for Acute Bipolar Depression

Level 1A—Established efficacy
- Quetiapine monotherapy (bipolar I and II disorder)
- Lurasidone monotherapy (bipolar I disorder)
- Lurasidone or quetiapine adjunctive to lithium or divalproex (bipolar I disorder)

Level 1B—Established efficacy, but with safety concerns*
- Olanzapine + fluoxetine (bipolar I disorder)

*Note: Tolerability limitations include sedation and weight gain.

Level 2—Established tolerability, but limited efficacy*

Consult specialist
- Lithium (bipolar I disorder)
- Lamotrigine adjunctive to lithium (bipolar I disorder)
- Lamotrigine (bipolar I disorder)
- 2-drug combination of above medications

*Note: Efficacy limitations include negative randomized controlled trials but positive meta-analyses.

Level 3—If levels 1 and 2 are ineffective or treatment not tolerated*
- Electroconvulsive therapy (ECT)

* Note: consideration merited due to clinical need, despite even greater efficacy/ tolerability limitations than level 1 and 2 treatments.

Level 4—If levels 1–3 are ineffective or treatment not tolerated
- Transcranial magnetic stimulation (TMS)
- Antimanic therapy + (US Food and Drug Administration–approved medication for major depression)*
- Pramipexole
- Adjunctive—modafinil, thyroid, or stimulants
- 3-drug combination

*Note: There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.

Table 2. Consensus Guidelines for Acute Mania

Level 1A—Established efficacy

Mild-to-moderate severity or not requiring hospitalization
- Lithium monotherapy
- Monotherapy with aripiprazole, asenapine, divalproex, quetiapine, risperidone, or ziprasidone

Severe or requiring hospitalization
- Lithium or divalproex plus aripiprazole, asenapine, quetiapine, or risperidone

Level 1B—Established efficacy, but with safety concerns*

Mild-to-moderate severity or not requiring hospitalization
- Monotherapy with haloperidol or olanzapine

Severe or requiring hospitalization
- Lithium or divalproex plus haloperidol or olanzapine

*Side effect concerns with these agents include weight gain, metabolic syndrome and extrapyramidal symptoms (EPS). Side effects warrant vigilance and close monitoring on the part of the clinician.

Level 2—If level 1A and 1B are ineffective or not tolerated
- 2-drug combination of lithium + divalproex
- Lithium or divalproex plus second-generation antipsychotic (non-clozapine)
- Paliperidone
- Carbamazepine

Level 3—If levels 1 and 2 are ineffective or not tolerated
- Electroconvulsive therapy (ECT)
- Clozapine
- Clozapine + lithium or divalproex
- Lithium + carbamazepine
- Divalproex + carbamazepine

Level 4—If levels 1, 2, and 3 are ineffective or not tolerated
- A 3-drug combination of level 1, 2, and 3. Drugs may include first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs) BUT NOT 2 antipsychotics. Example: lithium + (divalproex or carbamazepine) + antipsychotic.

are given in the current guidelines. We did not extend recommendations for bipolar I disorder to the treatment of bipolar II disorder as the evidence does not support doing so (even if it has become practice to do so), so it should be made clear that these guidelines are applicable only to patients who have previously had at least 1 manic episode except where specifically specified otherwise.

GUIDELINES

Acute Bipolar Depression

Unlike earlier guidelines, lurasidone, both as monotherapy and as an adjunct to lithium or divalproex, and quetiapine have the highest level (level 1A) recommendation for bipolar I disorder (with quetiapine the only specific treatment recommended for any phase of bipolar II disorder; Table 1). Two published 6-week randomized controlled trials submitted to the US Food and Drug Administration (FDA) have demonstrated the efficacy of lurasidone as monotherapy or as an adjunct to lithium or valproate in patients with acute bipolar I depression.[18,19]

Olanzapine + fluoxetine is a level 1B recommendation because of the safety concerns associated with olanzapine's metabolic effects. Some would argue that all atypical antipsychotics have metabolic effects, but we decided that the safety concerns with olanzapine were significantly great enough to separate it from the others with level 1 evidence.[20] Because olanzapine's benefit is well documented, however, its place in the guidelines remains high. Making olanzapine no longer a highest-tier and first-line treatment because of safety concerns is consistent with other recently published guidelines that take safety into consideration when comparing treatments.[8]

Lithium, lamotrigine, and the combination of lithium plus lamotrigine are level 2 recommendations because the evidence for them is not as strong as for those agents listed for level 1.[21] Electroconvulsive therapy (ECT) is a level 3 recommendation with good efficacy but with significant patient acceptability and safety concerns, as the cognitive side effects of ECT may be severe and enduring for some patients.[22] All other treatments or combinations currently in clinical use are on level 4 because there are simply not enough data to support a strong recommendation that they be used. Antidepressant medications, in spite of their frequent use in bipolar disorder for the treatment of depression, are now only on level 4 as there are insufficient data to suggest that they are helpful when added to antimanic treatment in the treatment of depression associated with bipolar I disorder.[23]

Notably, there were several studies of drugs that proved to be ineffective in the treatment of bipolar depression. Two 6-week trials of ziprasidone failed to find benefit for the drug in bipolar depression.[24] Three trials of armodafinil (references 25 and 26 and http://www.tevapharm.com/news/nuvigil_major_depression_associated_with_bipolar_disorder.aspx) also failed to find statistically significant benefit for this stimulant in acute bipolar depression.

It should also be noted that due to the overall limited available evidence base it is not possible to make

recommendations for the management of acute depression in patients with bipolar II disorder beyond the level 1A evidence given for quetiapine.

Acute Mania

The guideline recommendations for the treatment of acute mania have been updated and restructured (Table 2). Lithium is a prominent level 1A recommendation, whether as monotherapy or added to certain antipsychotics, as is treatment with divalproex monotherapy. Monotherapy or adjunctive antipsychotics at this level are limited to those that have evidence for their use and include aripiprazole, asenapine, quetiapine, risperidone, and ziprasidone. (It is important to note that adjunctive ziprasidone added to lithium or valproate did not add benefit for acute mania compared to placebo[27] and so cannot be recommended as an evidence-based treatment, although monotherapy for ziprasidone, as noted, remains at this level.)

Olanzapine and haloperidol, in spite of their efficacy, are now level 1B recommendations because of safety concerns due to metabolic or neurologic effects.

There had been no new studies of pharmacotherapies for acute mania published since the last update to these guidelines in 2012.

It must be noted that valproate should be used with care in women of childbearing potential because of the risk of teratogenicity, including developmental delay in children exposed to it in utero, and because of the high risk of unplanned pregnancy in women with bipolar disorder.[28] While it was not given a level 1B or level 2 recommendation for use in women of childbearing age in this iteration of the guidelines, it certainly can be argued that it should not be a level 1A treatment for such women. In any case, it is important that the potential harm to developing fetuses be discussed with women and their families, as well as the importance of the use of effective contraception.

Level 2 includes lithium combined with divalproex, lithium or divalproex combined with the antipsychotics not listed in level 1A or B, carbamazepine, and paliperidone.[29] Level 3 recommendations include ECT, clozapine, and carbamazepine combined with lithium or valproate/divalproex. Level 4 includes any 3-drug combination from levels 1, 2, and 3. Two-antipsychotic combinations cannot be recommended as there are not data for either their safety or efficacy in the treatment of acute mania.

Continuation/Maintenance Treatment

Several changes are apparent in the guidelines for maintenance treatment (Table 3). While lithium monotherapy remains a level 1A recommendation, monotherapy with valproate/divalproex is not recommended since there are no trials that have clearly shown it to be an effective monotherapy maintenance treatment. Monotherapy with quetiapine, aripiprazole, and long-acting injectable risperidone for the prevention of mania are in level 1A along with lamotrigine for the prevention of depressive recurrences in bipolar I disorder. Aripiprazole was superior to placebo when added to lithium or valproate for maintenance treatment up to 52 weeks.[30] A total of 337 patients were randomized to aripiprazole plus lithium or valproate (n = 168) or placebo plus lithium or valproate (n = 169). The Kaplan-Meier relapse rate at 52 weeks was 17% with adjunctive aripiprazole and 29% with adjunctive placebo, with significantly delayed time to any relapse compared; hazard ratio = 0.54.[30] Extended-release paliperidone (paliperidone ER) was superior to placebo in preventing recurrence of manic symptoms in subjects with bipolar I disorder who achieved stability on paliperidone ER treatment during a 12-week continuation phase treatment.[31] Median time to recurrence of any mood symptoms was 558 days for paliperidone ER compared to 283 days for placebo.[31] An earlier study of adjunctive paliperidone ER or placebo added to lithium or valproate for maintenance treatment, however, failed to demonstrate a benefit for paliperidone over placebo as an adjunctive treatment.[32]

Quetiapine and ziprasidone added to lithium or divalproex also are in level 1A, while olanzapine as monotherapy or adjunctive to lithium or divalproex is in level 1B (again because of safety, not efficacy, concerns.) As with the treatment of acute mania, and even more importantly because of long-term use, the safety concerns about the use of valproate in women of childbearing age should be discussed. Valproate is recommended as level 1A or 1B only when used as adjunctive treatment for maintenance or as level 2 as a continuation of acute treatment, but careful discussion about the risks of its use in women of childbearing potential must be part of treatment.

Level 2 recommends continued treatment of effective acute treatments (if not mentioned in level 1) and the combination of lithium and divalproex. Lamotrigine is a level 2 treatment when used to prevent mania in patients who have not had

Table 3. Consensus Guidelines for Continuation/Maintenance Treatment[a]

Level 1A—Established efficacy
• Lithium monotherapy
• Quetiapine monotherapy
• Aripiprazole or long-acting injectable risperidone monotherapy
• Quetiapine or ziprasidone adjunctive to lithium or divalproex
• Lamotrigine (evidence strongest for prevention of depression, usually as an adjunct)
Level 1B—Established efficacy, but safety concerns*
• Olanzapine monotherapy
• Olanzapine adjunctive to lithium or divalproex
*Side effect concerns with these agents include weight gain, metabolic syndrome and extrapyramidal symptoms (EPS). Side effects warrant vigilance and close monitoring on the part of the clinician.
Level 2—If level 1A and 1B are ineffective or not tolerated
• Continue effective and well-tolerated acute treatment(s) if not listed in level 1A or 1B
• Lithium and divalproex combination
• Lamotrigine monotherapy in patients without manic episode in past year
• Follow acute mania/bipolar depression guidelines to achieve remission or partial remission
Level 3—If level 1 and 2 are ineffective or not tolerated
• Adjunctive clozapine (not added to antipsychotics)

[a]Longer-term efficacy data are limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, electroconvulsive therapy (inconvenience/expense).

a manic episode in the last year. Lamotrigine is a level 1 treatment only when used to prevent depressive episodes. Adjunctive clozapine is the only level 3 recommendation.

There is no level 4 for maintenance treatment. We decided that we cannot recommend the use of maintenance treatments for which there are not adequately powered, replicated studies, primarily because of the unknown risk of long-term exposure to unproven agents. Acute agents that were effective (ie, the patient improved while treated with them) and well-tolerated that are continued beyond the period of acute treatment are recommended as level 2 treatments, but those agents (which include divalproex and carbamazepine, for example) are not recommended in the absence of an acute response to them. It is important to note that drugs that have worked acutely for one phase of the illness (eg, lurasidone for depression) and that are continued should not be used to prevent episodes of the other phases of the illness (eg, mania) without evidence for that use.

CONCLUSION

The 2014 iteration of the Florida Best Practice Psychotherapeutic Medication Guidelines for Adults with Bipolar Disorder is a relatively novel approach to clinician-focused treatment recommendations. First, it is strictly evidence-based, with (as much as is possible) a de-emphasis of expert opinion and anecdotal clinical experience in decision-making. What this means, in practical terms, is that unless there is published, quality evidence to support the use of a given treatment, it is not included in level 1–3 recommendations. This led to statements in the guidelines about the absence of evidence for certain long-held practices in bipolar disorder treatment, for example, that antidepressants cannot be recommended for the treatment of bipolar depression and that divalproex monotherapy cannot be recommended for first-line (level 1) maintenance treatment of bipolar disorder.

Second, a major change to the guidelines was to prioritize recommendations with the safety of treatments taken into consideration, something that other guidelines such as that developed by the VA/DoD have done.[8] Safety is defined as objective health-related negative effects of treatment. All drugs have adverse effects, with many treatments for bipolar disorder having significant burden in terms of tolerability. It is difficult to compare tolerability between drugs unless they are compared head to head, in part because subject selection and study design have an impact on how tolerability is reported and in part because patient-reported adverse effects are subjective in nature. When safety concerns—health effects that can be measured rather than subjectively reported tolerability—are taken into consideration, we decided that it is important to differentiate between the safety profiles of different drugs even if the cutoff point for determining safety is somewhat arbitrary. In contrast to safety, tolerability—that is, the extent to which patients report *subjective* adverse effects—is not used as a basis for treatment recommendations as it is not possible to be certain that one treatment is more tolerable than other in the absence of extensive head-to-head evaluation.

The ultimate goal in these recommendations is to provide a simple guide for clinical use for the careful evaluation and treatment of patients with bipolar disorder that relies on a hierarchy of scientific evidence that minimizes the use of conjecture and anecdote while allowing for the application of individual patient history and experience in shared decision-making for the treatment of this complex, chronic, and often debilitating illness. They are not meant to be the final and definitive word on the treatment of bipolar disorder, but are the work of a multidisciplinary group of different stakeholders who, at the time the guidelines were written, were aiming to produce a practical and easy to use document that maximizes benefit and minimizes harm to patients. It is hoped that these guidelines, as well as the other guidelines developed by the Florida Medicaid Drug Therapy Management Program for Behavioral Health, will easily complement the sources of information and heuristics for decision-making that prescribers in Florida are currently using to best treat their patients, and that they become a model for the development of patient-centered, easily implemented tools for the implementation of evidence into practice.

Submitted: January 30, 2015; accepted June 16, 2015.

Online first: September 15, 2015.

Drug names: aripiprazole (Abilify), armodafinil (Nuvigil and others) asenapine (Saphris), carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), levetiracetam (Keppra and others), modafinil (Provigil and others), olanzapine (Zyprexa and others), paliperidone (Invega), pramipexole (Mirapex and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

No trade: chlorpromazine, divalproex, haloperidol, lithium, lurasidone.

Potential conflicts of interest: **Dr Suppes** reports funding or medications for clinical grants from National Institute of Mental Health, Sunovion, Elan Pharma International Limited, and VA Cooperative Studies Program; consulting agreements/advisory board participation/speaking engagements with Astra Zeneca, Merck, and A/S H. Lundbeck; continuing medical education honoraria from Medscape Education and Global Medical Education; travel for AstraZeneca, A/S H. Lundbeck, and Merck; and royalties from Jones and Bartlett and Up-To-Date. **Drs Ostacher** and **Tandon** report no conflicts of interest.

Funding/support: The work was funded in part by Florida Medicaid Drug Therapy Management Program for Behavioral Health through the Florida Agency for Health Care Administration.

Role of the sponsor: The Florida Medicaid Drug Therapy Management Program for Behavioral Health through the Florida Agency for Health Care Administration. had no role in data analysis, data interpretation, or writing of the report. Dr Ostacher had final responsibility for the decision to submit for publication.

Disclaimer: The contents of this manuscript do not represent the views of the Department of Veterans Affairs or the United States Government.

Acknowledgments: The authors would like to acknowledge the assistance of the following people (all in Florida) who participated in the Expert Consensus Panel that developed these guidelines:

John T. Bailey, DO, Tallahassee, FL

Donald J. Baracskay II, MD, MBA—SalusCare

Mark Bloom, MD—Molina Healthcare of Florida

Marie Bruner, ARNP—Apalachee Center, Inc.

Jorge Dorta-Duque, MD—Peace River Center

Randolph Hemsath, MD—Boley Centers

Omar Howard, MD—Life Management of NW Florida

Beth Jones, PharmBSc, RPh—Florida Agency for Healthcare Administration

Khurshid A. Khurshid, MD—University of Florida

Marie McPherson, MBA—Florida Medicaid Drug Therapy Management Program for Behavioral Health

Rahul Mehra, MD—Mehra Vista Health

Lawrence Mobley, MD—Access Behavioral Health

J. David Moore, MD—Tri-County Human Services

Ruth Mulder, PharmD,– Lakeside Beh Healthcare

Hamsakumari Ramasubramaniam, MD—Henderson

Bhagirathy Sahasranaman, MD—Henderson

Radu V. Saveanu, MD—University of Miami

Albert S. Yeung, MD—Harvard Medical School

James E. Zenel, MD—James A. Haley VA Hospital

These individuals report no potential conflicts of interest relevant to the subject of this article.

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