Florida Best Practice
Psychotherapeutic Medication Guidelines for Adults

medicaidmentalhealth.org
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Purpose of the Guidelines

Although some progress has been achieved in treating Florida Medicaid beneficiaries with mental illness since the first publication in 2006 of the Florida Psychotherapeutic Medication Guidelines for Adults, the delivery of high quality mental health services to the Florida Medicaid population continues to be fraught with many issues especially where the seriously mentally ill are concerned such as: uncoordinated care, barriers in accessing psychotherapy treatment and social services, a shortage of adult psychiatrists, lack of measurement tool utilization in clinical settings, unaddressed medication side effects, and inadequate screening and assessment of physical health problems. Against this background, we aim to provide Florida clinicians, who are treating Medicaid beneficiaries with behavioral health conditions, the most current information regarding the use of psychotherapeutic medications.

Purpose

The overreaching goals of the updated psychotherapeutic medication guidelines are to inform clinicians (specifically primary care clinicians on whom the care of patients with behavioral health conditions often falls) of the most current scientific evidence regarding the use of psychotherapeutic medications for the treatment of bipolar disorders, severe depression, and schizophrenia in adults.

The current updates were made by a panel of national and Florida experts comprised of academics, community mental health specialists, and primary care clinicians working in a variety of clinical settings. The names of the participating experts and presentations are available on the program website at http://medicaidmentalhealth.org.

In bringing together this diverse group of stakeholders with a variety of clinical experience and views, we sought to produce a document that is sensitive to the practice realities, and yet provides care recommendations relevant to both clinicians and patients. In its recommendations, the expert panel also incorporated the revisions made in the DSM-5. It is, therefore, our hope that the decisions made by clinicians will be grounded on reliable evidence and account for individual variations and patient needs in treating complex and challenging conditions.
Organization and Disclaimer

Organization

In this updated version of the Florida Best Practice Psychotherapeutic Medications Guidelines for Adults, the guidelines underwent a thorough review of the most relevant literature by the expert panel, are scientifically valid, and incorporate a grading system for displaying the quality of the evidence and strength of the recommendations. The recommendations are prioritized in order of importance and with the most solid evidence. When empirical information is uncertain, it is noted, explained, and cautioned.

The decision was made to categorize options in different levels rather than creating an algorithm where specific options are mandatory, have to be used first, or diagrammatically look like they have to be used first. This categorization takes into account the individuality of the patients and presenting symptoms. The levels are based upon the strength of the science and expert consensus regarding a particular agent or treatment options. The panel weighed both safety and efficacy issues when assigning particular options to a level. For example, Level 1 treatment options have stronger evidence and consensus than Level 2 and higher.

The panel chose this approach with an understanding that using a particular option at any level would depend upon clinical judgment, patient individual symptoms, needs and preferences. Therefore, the number of iterations at each level and adjunctive treatment(s) should be determined by clinician judgment and patient needs. While moving sequentially through the levels is encouraged, the treatment choices should be dictated by past and current history, and patient/clinician preferences.

Disclaimer

The Florida Best Practice Psychotherapeutic Medication Guidelines for Adults reflect the current state of knowledge at the time of publication on effective and appropriate care, as well as clinical consensus judgments when research is lacking. The inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revisions will be needed. These guidelines may not apply to all patients; therefore, each guideline must be adapted and tailored to the individual patient. Proper use, adaptation, modifications, or decisions to disregard these or other guidelines, in whole or in part, are entirely the responsibility of the clinician who uses the guidelines. The authors bear no responsibility for the use of these guidelines by third parties.
Principles of Practice

**COMPREHENSIVE ASSESSMENT**

- Careful differential diagnostic evaluation.
- Risk for suicide and violence must be carefully assessed and addressed.
- Psychiatric co-occurring disorders and physical comorbidities must be carefully assessed.
- Substance-related abuse and addictive disorders, including tobacco use/abuse, must be evaluated and addressed.
- Potential bipolar disorder must be assessed in patients presenting with depression.
- Serious mental health conditions are chronic in nature; therefore, emphasis on an on-going management plan of chronic conditions is essential.
  - Measurement-based care to measure symptoms, side effects, and adherence.
  - Integration of psychiatrists and primary care providers.
  - Collaborative/shared treatment decision-making with patients and family/caregivers.
  - Psychosocial assessment.
  - Assess social support system (housing, family, other caregivers).
  - Evaluate threats to continuity of care (access to medication, adherence, etc.).

**ADJUNCTIVE PSYCHOSOCIAL TREATMENTS (AS INDICATED)**

- Individual and family psychoeducation
- Cognitive behavior therapy
- Family-focused therapy
- Interpersonal and social rhythm therapy
- Group psychoeducation (especially for bipolar disorder)
- Social skills training (especially in schizophrenia)
**Principles of Practice (continued)**

**COLLABORATIVE/SHARED DECISION-MAKING**

Shared decision making is the collaborative process between patients and providers in reaching treatment decisions. The clinician should inform patients of all treatment options and the potential harms and benefits of each treatment. Patients should be able to make treatment decisions based on expert advice coupled with their own values and preferences regarding treatment. Shared decision making involves open, supportive communication and deliberation ultimately to ensure the patient’s treatment decisions are well-informed and self-directed. Shared decision making enhances treatment adherence, health outcomes, and patient satisfaction with care.

**INTEGRATION OF PRIMARY AND SPECIALTY CARE**

Facilitating access to routine primary care services and referrals to specialty care can result in improved outcomes, more effective/efficient care, increased patient functioning/productivity, and improved patient satisfaction. Therefore, it is extremely important for patients with serious mental illnesses (SMI) to have access to primary and specialty care providers. Ideally, all providers should communicate in order to improve the quality of patient care.
Measurement-Based Care

Questionnaires and rating scales are useful tools for diagnostic assessment and evaluation of treatment outcomes, and such instruments can be helpful in providing supplemental information to the clinician's clinical judgment. The integration of measurement scales into routine clinical practice is suggested for each of the conditions covered in this document. Clinicians should use rating scales to assess symptom severity during the initial evaluation/treatment, when medication changes are implemented, and/or when the patient reports a change in symptoms.

- Treatment targets need to be precisely defined.
- Effectiveness and safety/tolerability of medication treatment must be systematically assessed by methodical use of appropriate rating scales and side-effect assessment protocols.

Brief Psychiatric Rating Scale (BPRS) - [www.priory.com/psych/bprs.htm](http://www.priory.com/psych/bprs.htm)

Clinical Global Impression Scale (CGI) - [http://miksa.ils.unc.edu/unc-hit/media/CGI.pdf](http://miksa.ils.unc.edu/unc-hit/media/CGI.pdf)

Hamilton Rating Scale for Depression (HAM-D) - [http://healthnet.umassmed.edu/mhealth/HAMD.pdf](http://healthnet.umassmed.edu/mhealth/HAMD.pdf)

Montgomery Asberg Depression Rating Scale (MADRS) - [www.opapc.com/images/pdfs/MADRS.pdf](http://www.opapc.com/images/pdfs/MADRS.pdf)


Quick Inventory of Depression Symptoms (QIDS) - [www.ids-qids.org/translations/english/QIDS-SREnglish2page.pdf](http://www.ids-qids.org/translations/english/QIDS-SREnglish2page.pdf)


## Measures

<table>
<thead>
<tr>
<th>Measures</th>
<th>Bipolar-Acute Depression</th>
<th>Bipolar-Acute Mania</th>
<th>Bipolar I-Cont/Main Therapy</th>
<th>Major Depression Non-psychotic</th>
<th>Major Depression Psychotic</th>
<th>Schizophrenia</th>
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<tbody>
<tr>
<td>Brief Psychiatric Rating Scale (BPRS)</td>
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<td>Clinical Global Impression Scale (CGI)</td>
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<tr>
<td>Hamilton Rating Scale for Depression (HAM-D)</td>
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<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
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<td>Patient Health Questionnaire (PHQ-9)</td>
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<tr>
<td>Positive and Negative Symptom Subscale (PANSS)</td>
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<tr>
<td>Quick Inventory of Depression Symptoms (QIDS)</td>
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<tr>
<td>Young Mania Rating Scale (YMRS)</td>
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<tr>
<td>Beck Depression Inventory (BDI)</td>
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</table>
Principles of Practice (continued)

Treatment with Antipsychotic Medications

In the context of dementia, anxiety disorders, and impulse control disorder:

- Antipsychotics have at best, modest and variable benefits:
  - Risks are not insignificant.
  - No difference in efficacy between first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs).
  - FGAs and SGAs are heterogeneous within the class and differ in many properties:
    - Efficacy
    - Side-effects
    - Pharmacology

- Carry EPS (extrapyramidal symptoms) liability and metabolic effects.

- For these conditions antipsychotic utilization should be:
  - Targeted
  - After other alternative treatments have been tried
  - Generally short-term
  - Monitored with periodic re-evaluation of benefits and risks
  - Prescribed at the minimal effective dose

- Selection of antipsychotic medication with well-informed patients made on the basis of prior individual treatment response, side-effect experience, medication side-effect profile, and long-term treatment planning.
Principles of Practice (continued)

AchEiving Optimum OuTcomes with Curently AvailablE Antipsychotics

STEP 1 – Considerations in selecting the best antipsychotic for a particular patient:

✦ Equivalent efficacy across agents.
✦ Individual variability in response.
✦ No good predictor of individual response to different agents.
✦ Different agents have different side-effects.
✦ Different patients have different vulnerabilities and preferences.

STEP 2 – Proper antipsychotic trial sequence:

✦ Begin with systematic 6 to 10 week trial of one antipsychotic with optimal dosing.
✦ If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration.
✦ If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic.
✦ Follow with a trial of clozapine, if not tried before.
✦ Only then consider other strategies (e.g., antipsychotic polypharmacy).

STEP 3 – Good practice guidelines for ongoing antipsychotic treatment:

✦ Measurement-based individualized care.
✦ Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales).
✦ Careful assessment of adverse effects.
✦ Care consistent with health monitoring protocols.
✦ Standard protocols customized to individual vulnerabilities/needs and specific agent.
✦ Ongoing collaboration with patient in decision-making.

Adapted from: Tandon, R., Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice found on page 28.
**Principles of Practice (continued)**

Provided is a list of national and local resources for adults with serious mental illnesses (SMI). This list does not infer endorsement of the following websites.

**National Resources**

- National Depressive and Manic Depressive Association (NDMDA) – [http://www.dbsalliance.org/site](http://www.dbsalliance.org/site)

**Local Resources**

# Treatment of Acute Bipolar Disorder - Depression

The primary goals of bipolar disorder care are remission, maintenance of response, and prevention of relapse.

- Selection of acute treatment should take maintenance treatment goals into account.
- Be aware of safety and tolerability concerns, evidence for maintenance use, and acute efficacy.

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Consider psychiatric consultation, if possible, prior to psychotherapeutic treatment.

<table>
<thead>
<tr>
<th>Level 1A - Established efficacy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Quetiapine monotherapy (bipolar disorder I &amp; II)</td>
</tr>
<tr>
<td>♦ Lurasidone monotherapy (bipolar disorder I)</td>
</tr>
<tr>
<td>♦ Lurasidone or quetiapine adjunctive to lithium or divalproex (bipolar disorder I)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 1B - Established efficacy, but with safety concerns*</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Olanzapine + fluoxetine (bipolar disorder I)</td>
</tr>
</tbody>
</table>

*Note. Tolerability limitations include sedation and weight gain.

<table>
<thead>
<tr>
<th>Level 2 - Established tolerability, but limited efficacy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult specialist</td>
</tr>
<tr>
<td>♦ Lithium (bipolar disorder I)</td>
</tr>
<tr>
<td>♦ Lamotrigine adjunctive to lithium (bipolar disorder I)</td>
</tr>
<tr>
<td>♦ Lamotrigine (bipolar disorder I)</td>
</tr>
<tr>
<td>♦ 2 drug combination of above medications</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Level 3 - If levels 1 and 2 are ineffective or treatment not tolerated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Electroconvulsive therapy (ECT)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Level 4 - If levels 1 - 3 are ineffective or treatment not tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Transcranial Magnetic Stimulation (TMS)</td>
</tr>
<tr>
<td>♦ Antimanic therapy + (FDA approved medication for major depression)*</td>
</tr>
<tr>
<td>♦ Pramipexole</td>
</tr>
<tr>
<td>♦ Adjunctive – modafinil, thyroid, or stimulants</td>
</tr>
<tr>
<td>♦ 3 drug combination</td>
</tr>
</tbody>
</table>

*Note. There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.
The primary goals of bipolar disorder care are remission, maintenance of response, and prevention of relapse.

- Selection of acute treatment should take maintenance treatment goals into account.
- Be aware of safety and tolerability concerns, evidence for maintenance use, and acute efficacy.

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Consider psychiatric consultation, if possible, prior to psychotherapeutic treatment.

### 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 - Establish 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 extra pyramidal 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

- Two-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 three-drug combination of level 1, 2, and 3. Drugs may include first generation antipsychotic (FSA) or second generation antipsychotics (SGA) BUT NOT 2 antipsychotics. Example: lithium + (divalproex or carbamazepine) + antipsychotic.
### Bipolar I Disorder Continuation/Maintenance Therapy

#### 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 extra pyramidal 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)

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*Note. Longer-term efficacy data limited for the following: divalproex monotherapy, carbamazepine (drug interaction risk), antidepressants, electroconvulsive therapy (inconvenience/expense).*
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>In acute mania: 1200-2400 mg/day (serum level 0.8 – 1.2 mEq/L)</td>
<td>Initial titration for tolerability – start 600-900 mg/day, increase 300 mg/day every 5 days. Check levels 5 days after initiation/dose change. Check levels frequently if clinical toxicity. Monitor renal and thyroid functions. Lower doses/levels may be necessary in non-manic compared to manic patients. For maintenance, some patients require serum levels of 0.8 to 1.2 mEq/L, others can be maintained with lower levels, but not below 0.6 mEq/L. In elderly, start with lower lithium dose, titrate more slowly, and require lower serum lithium levels.</td>
</tr>
<tr>
<td>Divalproex</td>
<td>In acute mania: 5-60 mg/kg/day; 1000-2500 mg/day (serum level 85 -125 µg/mL)</td>
<td>Initial loading may be tolerated, but some patients need initial titration for tolerability. Check levels 48 hours after initiation and adjust dose accordingly. Side effects (especially gastrointestinal) more evident above 100µg/mL. More teratogenic than other mood stabilizers. Lower doses/levels may be necessary in non-manic compared to manic patients.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>In acute mania: 200 – 1600 mg/day (serum level 6-12 µg/mL)</td>
<td>Initial titration for tolerability due to hepatic auto-induction: Start 200-400 mg/day and increase 200 mg/day every 3 days. Lower doses/levels may be necessary in non-manic compared to manic patients. Monitor for blood dyscrasias and serious rash. Screen Asians for HLA-B*1502 (serious rash risk indicator). Decreases serum levels of multiple other drugs.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>In bipolar maintenance: 100 – 400 mg/day</td>
<td>Initial titration to reduce risk of serious rash (Stevens-Johnson syndrome): Start 25 mg/day (12.5 mg/day if taken with divalproex). Increase by 25mg/day (12.5 mg/day if taken with divalproex) after 2 and 4 weeks and weekly thereafter. Initial target dose 200 mg/day, but final doses may be 100-400 mg/day. May be used in some patients with acute bipolar depression (despite acute efficacy limitation) due to good tolerability and depression prevention efficacy.</td>
</tr>
</tbody>
</table>
# Second Generation Antipsychotics & Antidepressants – Recommendations for Bipolar Disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Second Generation Antipsychotics (SGA)</strong></td>
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</tr>
<tr>
<td>In acute mania:</td>
<td>• Aripiprazole: 15-30 mg/day&lt;br&gt;• Asenapine: 10-20 mg/day&lt;br&gt;• Olanzapine: 6-20 mg/day&lt;br&gt;• Quetiapine: 400-800 mg/day&lt;br&gt;• Risperidone: 2-6 mg/day&lt;br&gt;• Ziprasidone: 80-160 mg/day</td>
<td>Initial titration may be necessary for tolerability. Lower doses may be necessary in depressed patients (e.g. quetiapine 300 mg/day). Ziprasidone should be taken with food. Asenapine is sublingual. Monitor for side effects, including sedation (especially with quetiapine and clozapine), weight gain (especially with olanzapine and clozapine), akathisia (especially with aripiprazole and ziprasidone), and EPS (especially with risperidone). Monitor weight and BMI at each visit and laboratory metabolic indices at baseline, 3 months, and yearly thereafter.</td>
</tr>
<tr>
<td>In acute bipolar depression:</td>
<td>• Quetiapine: 200-600 mg&lt;br&gt;• Olanzapine/Fluoxetine: 3mg/12.5 mg – 12 mg/50 mg&lt;br&gt;• Lurasidone: 40-120 mg&lt;br&gt;• Clozapine: 50-400 mg/day (if treatment resistant)</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>In acute bipolar depression:</td>
<td>Larger trials have not found a benefit of antidepressants when added to mood stabilizers/antimanics for bipolar depression (other than olanzapine/fluoxetine combination). May be used in combination with antimanic drugs in some patients with acute bipolar depression, but should not be prescribed as monotherapy in patients with bipolar I disorder due to manic switch risk. SNRIs and TCAs may have greater manic switch risk. Increased suicidality risk in pediatric and young adult patients. May be continued in patients who are on them and have stable mood.</td>
</tr>
<tr>
<td>As dosed for major depression. (No specific dosing recommendations can be given in bipolar depression.)</td>
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SNRI = Serotonin-norepinephrine reuptake inhibitor  
TCA = Tricyclic antidepressant
INTRODUCTION

The Florida Medicaid Drug Therapy Management Program guidelines for the treatment of bipolar disorder were first published in 2005 and have since been updated on a biennial basis. This fifth update, like the previous iterations, was based on a comprehensive review of the literature and its critical evaluation by a panel of academic and community clinicians. As in previous editions, three related but separate guidelines were developed for the pharmacological treatment of acute bipolar depression, acute bipolar mania/hypomania, and continuation/maintenance treatment of bipolar disorder, respectively. Beginning with recommendations for elements of a good diagnostic assessment, treatment options were categorized at different levels based on the strength of the evidence and clinical considerations of comparative efficacy and safety.

COMPREHENSIVE ASSESSMENT AND PRINCIPLES OF TREATMENT

With the introduction of the DSM-5 in 2013, revisions in the diagnostic assessment became necessary in order to be consistent with changes made in the DSM-5 treatment of bipolar disorder. The category of major mood disorders was split into two chapters and bipolar disorder was explicitly separated from the depressive disorders. In the definition of mania/hypomania, increased emphasis was placed on the symptom of increased energy and activity, and both increased energy/activity along with heightened mood are necessary for a diagnosis of mania or hypomania. Particular care in the distinction of bipolar depression from unipolar depression is important for appropriate treatment planning and the use of the Mood Disorders Questionnaire (MDQ) was recommended for this purpose. The DSM-IV category of bipolar disorder-mixed was eliminated because of the rarity of its utilization in clinical practice and was replaced by the use of a “mixed features” specifier for both 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.

Since bipolar disorder is often co-morbid with addictive disorders, including smoking, these must be addressed at initial assessment and over the course of treatment. Increased mortality and morbidity due to medical illness must be addressed in this population, and therefore these need to be carefully assessed at initial presentation and on an ongoing basis. Since patients with bipolar disorder are at an increased risk for suicide and violent behavior, these need to be specifically monitored at initial presentation and during the course of treatment. Good pharmacological treatment needs to be combined with appropriate psychosocial care. Since treatment response varies across patients, careful assessment of symptomatology and side-effects is essential in the course of treatment. The use of appropriate rating scales is highly recommended.

PHARMACOLOGICAL TREATMENT OF ACUTE BIPOLAR DEPRESSION

For acute bipolar depression, one important change was the addition of lurasidone as a therapeutic agent at Level 1. Lurasidone was found to be effective and safe in the treatment of bipolar depression in two large-scale clinical trials and was consequently approved by the Food and
Drug Administration (FDA) for the treatment of acute bipolar depression, both as monotherapy and as an adjunct to lithium or divalproex. It joins quetiapine as the Level 1a recommendation for bipolar I disorder, with quetiapine also recommended for bipolar II disorder. Despite its approval by the FDA for treatment of bipolar depression, the combination of [olanzapine + fluoxetine] remained as a Level 1b recommendation because of the metabolic safety concerns associated with the use of olanzapine. In the absence of an adequate response to level 1 treatment, it is recommended that a psychiatrist consultation be obtained. Level 2, level 3, and level 4 treatment recommendations were provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

**Pharmacological Treatment of Acute Bipolar Mania**

For the pharmacotherapy of acute mania, updated treatment recommendations are provided, although the changes are relatively minor. Lithium is significantly underutilized in the treatment of acute mania in clinical practice and its prominent position as a level 1a recommendation, as monotherapy or in combination with certain antipsychotics, is re-emphasized. There are important distinctions between different antipsychotic agents with regards to their utility in the treatment of mania and this is explicitly reflected in the new treatment guidelines. For example, the use of olanzapine or haloperidol, in spite of their proven efficacy, is now relegated to a Level 1b recommendation because of metabolic and EPS safety concerns, respectively. Level 2, level 3, and level 4 treatment recommendations are provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

**Continuation and Maintenance Pharmacological Treatment of Bipolar Disorder**

Several changes are apparent in the guidelines for maintenance treatment of bipolar disorder. Lithium remains a strong level 1a recommendation but divalproex is no longer recommended at this level since there are trials that have found it to be a less effective monotherapy maintenance treatment. Monotherapy with quetiapine, aripiprazole, long-acting injectable risperidone, and lamotrigine are recommended at level 1a, with distinctions made between the first three and lamotrigine with regards to utility in the prevention of manic episodes and depressive episodes, respectively. Despite its proven efficacy, olanzapine has been relegated to Level 1b because of metabolic safety concerns. Level 2 and level 3 treatment recommendations are provided on the basis of declining evidence of efficacy and/or increasing risk of safety concerns or poor tolerability.

**References**


**Treatment of Adult Major Depressive Disorder - Nonpsychotic**

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Most importantly assess for bipolarity, comorbidities (e.g. substance abuse, anxiety disorders), and clinical features (psychosis, suicidality).

<table>
<thead>
<tr>
<th>Level 1 – Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Discuss treatment options, including evidence-based psychotherapy [Cognitive behavior therapy (CBT)/Interpersonal psychotherapy (IPT)]</td>
</tr>
<tr>
<td>✦ Monotherapy 4-8 week trial at adequate dose and evaluate:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>✦ If no response at 4 weeks go to Level 2</td>
</tr>
<tr>
<td>✦ If partial response at 4 weeks may continue for another 4 weeks or go to Level 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Switch to different monotherapy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>✦ Dose increase</td>
</tr>
<tr>
<td>✦ Augment prior monotherapy with:</td>
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</tr>
</tbody>
</table>
Treatment of Adult Major Depressive Disorder - Nonpsychotic (continued)

**Level 3**
- Seek psychiatric consultation
- Electroconvulsive therapy (ECT)
- TCA, MAOI
- SSRI or SNRI + L-methylfolate, T3, lithium
- SSRI or SNRI + aripiprazole or quetiapine
- Fluoxetine + olanzapine (tolerability concerns)
- Augmentation after partial response with agent from different class (SSRI, SNRI, mirtazapine, bupropion, TCA)
- Transcranial magnetic stimulation

**Level 4**
- Re-evaluate diagnosis if patient has failed to respond to two or more treatments
- Augment antidepressant with Vagal Nerve Stimulation (VNS)
- MAOI augmentation (AVOID CONTRAINDICATED COMBINATIONS)
- Triple drug combination (little evidence exists supporting or refuting this strategy):
  - SSRI or SNRI + mirtazapine + bupropion
  - SSRI or SNRI + mirtazapine + lithium
  - SSRI or SNRI + bupropion + second generation antipsychotic (SGA)
- If no response, try a different two or three drug combination.

SSRI = Selective serotonin reuptake inhibitor
SNRI = Serotonin-norepinephrine reuptake inhibitor
TCA = Tricyclic antidepressant
MAOI = Monoamine oxidase inhibitor
**Treatment of Adult Major Depressive Disorder - Psychotic**

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Most importantly assess for bipolarity, comorbidities (e.g. substance abuse, anxiety disorders), and clinical features (psychosis, suicidality).

<table>
<thead>
<tr>
<th>Level 1 - Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Discuss treatment options, including evidence-based psychotherapy [Cognitive behavior therapy (CBT)/Interpersonal psychotherapy (IPT)]</td>
</tr>
<tr>
<td>✦ Antidepressant + antipsychotic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2 - If level 1 is ineffective or not well tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Antipsychotic + SSRI or SNRI</td>
</tr>
<tr>
<td>✦ Electroconvulsive therapy (ECT) with patient consent (if severe)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3 - If levels 1 and 2 are ineffective or not well tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Other drug combinations</td>
</tr>
<tr>
<td>✦ Electroconvulsive therapy (ECT) with patient consent if not attempted earlier</td>
</tr>
<tr>
<td>✦ Antidepressant (any including tricyclic) + antipsychotic (including perphenazine)</td>
</tr>
<tr>
<td>✦ Re-evaluate diagnosis if the patient has failed to respond to two or more treatments.</td>
</tr>
</tbody>
</table>

SSRI = Selective serotonin reuptake inhibitor  
SNRI = Serotonin-norepinephrine reuptake inhibitor
Approaches to Treatment Resistant Depression (TRD): An Update Focusing on Studies Published in 2011-2013

Albert Yeung, M.D., ScD
Associate Professor of Psychiatry
Harvard Medical School

This is a summary of a review of approaches to treatment resistant depression (TRD), which refers to when a patient has received an adequate dose of a medication for an adequate duration and yet has not experienced an acceptable level of symptomatic response.

In treating patients with TRD, it is recommended that the clinician should first assess the accuracy of the diagnosis of depression, whether it is unipolar or bipolar, and whether there are psychiatric and medical comorbidities involved. The clinician should also assess if the treatment offered was adequate in dose and duration, whether treatment was well tolerated, and whether patient has been adherent to treatment. After the clinician has done that, pharmacological approaches to TRD include: Dose increase, switching, combination of more than one antidepressant, and the use of an augmentation psychotropic agent to enhance the effect of the antidepressant. Neuromodulation approaches have also shown promise for treatment of TRD.

**Switching:** Inoue et al. (2012) examined the long-term effectiveness and safety of switching to sertraline from other selective serotonin reuptake inhibitors (SSRIs) in the treatment of TRD. They concluded that switching from paroxetine or fluvoxamine to sertraline might be effective and well-tolerated in patients with non-remitted or treatment-intolerant major depressive disorder.

**Comments:** Switching from one SSRI which has inadequate response to another SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) has been reported to be an effective approach for TRD, not limited to switching to sertraline.

**Combination:** Holt et al. (2011) analyzed anonymous data to compare outcomes of patients who received augmentation therapy with either mirtazapine or atypical antipsychotics. They concluded that patient with mirtazapine combination, compared to those who received atypical antipsychotics augmentation, resulted in better discharge rates and reduction in suicidality.

**Comments:** Mirtazapine and bupropion are frequently used to combine with SSRIs/SNRIs for treatment of TRD with evidence supporting their efficacy.

**Augmentation Strategies:**

1. **Pramipexole:** Cusin et al. (2013) investigated the antidepressant efficacy of a flexible dose of the dopamine agonist pramipexole as an adjunct to standard antidepressant treatment in an 8-week, randomized, double-blind, placebo-controlled trial. They found a modest but statistically significant benefit for pramipexole (P = .038), and augmentation with pramipexole was well-tolerated, with no serious adverse effects identified.

**Comments:** There is limited data on pramipexole augmentation of major depressive disorder (MDD) treatment. Pramipexole is associated with 3 rare but serious side effects: sleep attacks, compulsive behaviors and pathological gambling, and psychosis.

2. **Stimulants:** Trivedi et al. (2013) evaluated the efficacy and safety of lisdexamfetamine dimesylate augmentation for MDD in escitalopram nonremitters. They conclude that lisdexamfetamine dimesylate augmentation reduced depressive symptoms in participants with inadequate escitalopram response.

**Comments:** Studies using stimulants to augment antidepressants have mostly shown negative outcomes.
3. **Atypical antipsychotics**: Spielmans et al. (2013) performed a meta-analysis to compare the outcomes of adjunctive antipsychotic medication to placebo for TRD in adults. They concluded that atypical antipsychotic medications for the adjunctive treatment of depression are efficacious in reducing observer-rated depressive symptoms, but effect sizes of the benefits were small-to-moderate, and quality of life or functional impairment did not improve. The authors warned about the abundant evidence of potential treatment-related harm.

   **Comments**: Strong evidence suggesting that newer antipsychotics, particularly quetiapine and aripiprazole augmentation improves depression symptoms, but they may cause serious adverse events.

4. **Use of glutamatergic agents**: Ketamine. Murrough et al. (2013) studied the use of ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, for treating patients with TRD. They reported that the ketamine group had greater improvement as soon as 24 hours after treatment.

   **Comments**: Ketamine demonstrated rapid antidepressant effects in this study. More studies are needed to replicate the findings, and more information on response durability and safety is required before implementation in clinical practice.

5. **Anticholinergic, antimuscarinic drugs**: Scopolamine. Khajavi et al. (2012) conducted a randomized clinical trial to evaluate the antidepressant effect of oral scopolamine as an adjunct to citalopram and showed that augmentation with scopolamine was safe and significantly more effective than placebo.

   **Comments**: As side effect potential for this agent includes confusion and delirium, safety remains a serious concern if scopolamine in any form is used in clinical practice.

6. **Mood Stabilizers**:

   a. **Lamotrigine**: Barbee et al. (2011) performed a large randomized clinical trial to examine the use of lamotrigine as an antidepressant augmentation agent in patients with TRD. They reported that patients with TRD failed to detect a statistically significant difference between lamotrigine and placebo given for 10 weeks.

   **Comments**: Existing data do not support the efficacy of lamotrigine to augment treatment of TRD.

   b. **Topiramate**: Mowla and Kardeh (2013) designed an 8-week randomized, placebo-controlled, double-blind study on 53 TRD patients. Patients were randomized to receive a flexible dose of topiramate (100-200 mg/day) or placebo beside their current antidepressant medication for a period of eight weeks. They showed that topiramate augmentation potentiate the efficacy of SSRIs in treatment of resistant MDD.

   **Comments**: This is a preliminary study with a small sample size. Data on topiramate is limited.
7. **Supplements:**
   
a. **L-Methylfolate:** Papakostas et al. (2012) conducted two multicenter sequential parallel comparison design trials to investigate the effect of L-methylfolate augmentation in the treatment of patients with TRD. They concluded that adjunctive L-methylfolate at 15 mg/day may constitute an effective, safe, and relatively well tolerated treatment strategy for patients with MDD who have a partial response or no response to SSRIs.
   
   **Comments:** The positive evidence accumulated for using L-methylfolate to augment depression treatment and its great safety profiles make it a favorable candidate for augmentation treatment of TRD.

b. **Omega 3:** Gertsik et al., (2012) studied 42 subjects in the efficacy of treatment with citalopram plus omega-3 fatty acids versus citalopram plus placebo in the treatment of individuals with MDD. They demonstrated that patients who received combination therapy had significantly greater improvement in depression symptoms. Lespérance et al. (2011) performed a randomized, controlled, 8-week study to investigate the effects of taking 8-weeks of 1,050 mg/d of eicosapentaenoic acid (EPA) and 150 mg/d of docosahexaenoic acid (DHA) or placebo. The intervention group showed a non-significant trend in the improvement of depression outcomes. For patients without comorbid anxiety disorders (n = 204), omega-3 supplementation was superior to placebo.
   
   **Comments:** Existing studies show different outcomes. Stronger evidence is needed to support the use of omega 3 as an augmentation agent for the treatment of depression.

c. **Creatine:** Lyoo et al. (2012) randomized 52 women with MDD who were enrolled in an 8-week clinical trial to receive escitalopram in addition to either creatine (5 g/day, N=25) or placebo (N=27). They reported that patients receiving creatine augmentation showed significantly greater improvements in depression as early as week 2 of treatment.
   
   Nemets and Levine et al. (2013) performed a pilot study on 14 TRD women and treated them with a 4-week, double-blind, parallel augmentation study where creatine monohydrate 5 or 10 g was given daily or a placebo was added to ongoing antidepressant treatment. They found that, overall; there was no difference between creatine administered at 5 or 10 g daily and its corresponding placebos.
   
   **Comments:** Data on efficacy of creatine for TRD augmentation is limited.

8. **Tumor Necrosis Factor (TNF) Antagonist Infliximab:** Raison et al. (2013) administered three infusions of the TNF antagonist infliximab (5 mg/kg) (n = 30) or placebo (n = 30) to outpatients with MDD who were on either a consistent antidepressant or medication free. They reported no overall difference in change of depression outcomes between treatment groups was found.
   
   **Comments:** TNF antagonism may not have generalized efficacy in TRD, but may improve depressive symptoms in patients with high baseline inflammatory biomarkers.
approaches to treatment resistant depression (trd): an update focusing on studies published in 2011-2013 (continued)

9. **Neuromodulation:** High-Frequency Repetitive Transcranial Magnetic Stimulation (HF-rTMS). Berlim et al. (2013) performed a meta-analysis study and selected all randomized, double-blind, and sham-controlled trials on the use of HF-rTMS as an accelerating (add-on) strategy to antidepressants for MDD, and concluded HF-rTMS is a promising strategy for accelerating clinical response to antidepressants in MDD, providing clinically meaningful benefits.

   **Comments:** The technology of neuromodulation is promising for SSRI augmentation. More evidence from well-designed clinical trials is needed.

10. **Psychosocial Treatments:** Cognitive Behavioral Therapy (CBT). Wiles et al. (2013) randomized 469 patients with TRD in primary care settings to receive either CBT augmentation or usual care. The intervention group performed significantly better than the control group.

   **Comments:** This study has provided robust evidence that CBT is an effective adjunctive treatment for TRD.

11. **Exercise:** Trivedi et al. (2011) randomized 126 patients with TRD to augmentation treatment with either 16 kcal per kg per week (KKW) or 4 KKW of exercise for 12 weeks while SSRI treatment held constant. They reported a trend for higher remission rates in the higher-dose exercise group (p < .06), suggesting high exercise dose is an effective adjunctive treatment.

   **Comments:** Existing evidence supports that exercise is an effective adjunctive treatment of TRD.

**References**


Holt C, Butler S, Agius M, Zaman R. An audit to compare patient factors (age, sex, social background & associated physical diagnoses) in people with refractory depression in a Bedfordshire Community Mental Health Team (BCMHT) being augmented with (A) mirtazapine, (B) atypical antipsychotics or (C) both. *Psychiatr Danub*. September 2011; 23 Suppl 1: S166-70.


### Treatment of Schizophrenia

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Most importantly assess social support system (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

<table>
<thead>
<tr>
<th>Level 1 - Initial treatment</th>
<th>Level 2 - If level 1 is ineffective or not tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Monotherapy with an oral antipsychotic other than clozapine*</td>
<td>♦ Consider long-acting injectable for non-adherence</td>
</tr>
<tr>
<td>♦ If initial trial of antipsychotic monotherapy unsuccessful try monotherapy with another antipsychotic.</td>
<td>♦ Highly recommended to consider clozapine when lack of efficacy</td>
</tr>
</tbody>
</table>

*Balance efficacy, side-effects, individual vulnerabilities and preferences.

<table>
<thead>
<tr>
<th>Level 3 - If levels 1 and 2 are ineffective or not well tolerated</th>
<th>Level 4 - If levels 1, 2, and 3 are ineffective or not well tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Diagnostic review and/or consultation</td>
<td>♦ Augmentation of antipsychotic with anticonvulsant</td>
</tr>
<tr>
<td>♦ Clozapine if not tried earlier</td>
<td>♦ Other antipsychotic combinations (not augmentation; if partial response with one agent)</td>
</tr>
<tr>
<td>♦ Antipsychotic + ECT</td>
<td></td>
</tr>
<tr>
<td>♦ Augmentation of clozapine with second antipsychotic if partial response to clozapine</td>
<td></td>
</tr>
</tbody>
</table>

Note. Consider Clozapine after 2-3 failed antipsychotic trials. Assess other causes of non-response such as substance abuse, concurrent use of other medication or physical illness.

Note. There is suggestive evidence to support the use of high-potency agents.

<table>
<thead>
<tr>
<th>1</th>
<th>Relatively equivalent efficacy of different antipsychotic agents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Significant differences in side-effect profiles across agents.</td>
</tr>
<tr>
<td>3</td>
<td>Individual differences in sensitivity to different side-effects.</td>
</tr>
<tr>
<td>4</td>
<td>Dosing strategies optimal for each agent.</td>
</tr>
<tr>
<td>5</td>
<td>Olanzapine has a significantly greater risk of metabolic side-effects.</td>
</tr>
<tr>
<td>6</td>
<td>Monitor, record, and address the potential side effects of treatment such as extrapyramidal side effects including akathisia, metabolic side effects (weight gain) and other unpleasant experiences.</td>
</tr>
</tbody>
</table>
### Recommended Medications for the Treatment of Schizophrenia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Chlorpromazine Equivalents</th>
<th>Acute Therapy</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation Antipsychotics (FGA)</strong></td>
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<td></td>
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<tr>
<td><strong>Phenothiazines</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fluphenazine HCl</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>5-15 mg/day</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>NA</td>
<td>NA</td>
<td>6.25-50 mg/2wks</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8</td>
<td>16-80 mg/day</td>
<td>16-64 mg/day</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>300-1,000 mg/day</td>
<td>300-600 mg/day</td>
</tr>
<tr>
<td><strong>Butyrophenone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>5-20 mg/day</td>
<td>6-12 mg/day</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>NA</td>
<td>NA</td>
<td>50-200 mg/4wks</td>
</tr>
<tr>
<td><strong>Second Generation Antipsychotics (SGA)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>NA</td>
<td>150-600 mg/day</td>
<td>150-600 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>NA</td>
<td>2-8 mg/day</td>
<td>2-8 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>NA</td>
<td>10-30 mg/day</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>NA</td>
<td>300-800 mg/day</td>
<td>300-800 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>NA</td>
<td>120-240 mg/day</td>
<td>120-160 mg/day</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>NA</td>
<td>10-30 mg/day</td>
<td>10-30 mg/day</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioprophene</td>
<td>5</td>
<td>15-50 mg/day</td>
<td>15-30 mg/day</td>
</tr>
<tr>
<td>Molindone</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10</td>
<td>30-100 mg/day</td>
<td>30-60 mg/day</td>
</tr>
</tbody>
</table>

*Consider lower doses for 1st episode due to higher sensitivity to medications in pharmaceutically naïve patients.

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1. Approximate dose equivalent to 100mg of chlorpromazine (relative potency); it may not be the same at lower vs. higher doses. Chlorpromazine equivalent doses are not relevant to the second generation antipsychotics and therefore are not provided for these agents.

2. Fluphenazine decanoate dosage recommendations are based on an empirical rule suggested by Kane (1996) (25 mg every 3 weeks of decanoate is equivalent to 665 chlorpromazine equivalents per day). These are theoretically determined values and should be interpreted as approximations only (Baldessarini et al., 1988).

3. Haloperidol decanoate dosage recommendations are based on the following rule: 5 mg oral haloperidol (250 chlorpromazine equivalents) per day is equivalent to 50 mg haloperidol decanoate every month. Olanzapine has been found to cause more weight gain and related metabolic side effects than other SGAs (Newcomer, 2005).

4. Drug-drug interactions (DDIs) can impact dosing. Maintenance dose should generally be no less than half of the initial clinically effective dose, as that can result in reduced effectiveness of relapse prevention.
Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice

Rajiv Tandon, M.D.
Professor of Psychiatry
University of Florida College of Medicine

SUMMARY

The primary objectives in the treatment of schizophrenia are to reduce frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, prevent relapses, and improve functional capacity and quality of life. Treatment includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia. The twenty antipsychotics available in our country have traditionally been classified into two major groups: first-generation (conventional) agents (FGAs) and second-generation (atypical) agents (SGAs), although this dichotomization can be misleading. Whereas the efficacy of these antipsychotic agents in the treatment of schizophrenia is broadly similar (with the exception of clozapine’s greater efficacy in otherwise treatment-refractory patients), there are significant differences in their side-effect profiles. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of the nature of schizophrenia (multiple pathological dimensions, remitting and relapsing course), knowledge about the similarities and differences between available antipsychotic treatments, and awareness of how to use these treatments most effectively (targeted, measurement-based, individualized). In this paper, recent advances in antipsychotic therapy are summarized and basic principles of the Florida Medicaid Drug Therapy Management Program for the treatment of schizophrenia are articulated.

PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA: WHAT DO ANTIPSYCHOTICS DO?

Schizophrenia is characterized by positive (reality distortion and disorganization), negative, cognitive, and mood symptoms, with the types and severity of symptoms differing among patients and over the course of the illness. With its typical onset in early adulthood, schizophrenia tends to be a chronic illness with a relapsing and remitting course. Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. In addition to reducing symptoms in the acute psychotic phase of the illness, antipsychotic medications are very effective in reducing the likelihood of psychotic relapses in stable patients. Antipsychotics are most effective in ameliorating positive and disorganization symptoms, but ineffective in treating negative and cognitive symptoms. They can help but also worsen mood symptoms (eg., neuroleptic dysphoria) and motor symptoms (eg., neuroleptic malignant syndrome). In the DSM-5, the distinction between the different psychopathological dimensions of schizophrenia is explicitly catalogued and a simple scale for measurement of each dimension in the context of treatment is provided. The use of this scale is strongly recommended.

COMPARATIVE EFFICACY

Although it was formerly believed that FGAs are less effective than SGAs, recent trials have refuted this belief. Clozapine is the only antipsychotic agent that is found to be more effective than other antipsychotic agents in treating positive symptoms and reducing suicidality in otherwise refractory patients. All other agents are found to be about equally effective, although different degrees of ease of use lead to minor differences in efficacy being observed in routine clinical practice. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia,
without any consistent differences among agents. Since medication non-adherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates.

**SAFETY AND TOLERABILITY**

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in adverse-effect profiles. Compared with the FGAs, the SGAs have generally been believed to have a lower risk of EPS but a higher risk of metabolic adverse effects. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Thus, no categorical distinction can be made between so-called FGAs and SGAs with regard to these risks. The 20 antipsychotic medications available in the United States also differ in their propensity to cause other side effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs and the SGAs for each of these effects, without any definitive categorical separation between the two classes. Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, in combination with what other agents), and the patient’s vulnerability.

**OPTIMIZING INDIVIDUAL OUTCOMES**

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. It is not currently possible to predict which antipsychotic may be optimal for a given patient. There is no best agent or best dose for all patients, although dose ranges for optimal effectiveness do appear to exist. Decisions about antipsychotic therapy therefore often entail a trial and error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary. To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatments in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.

The Florida Medicaid Drug Therapy Management Program (MDTMP) guidelines for the pharmacological treatment of schizophrenia were developed on the basis of our current understanding of what they do and how they compare and a clinician-friendly elaboration of key principles. Markers of unusual (less evidence-based) practices were also developed on the basis of an extensive review of data and a critical consideration of current challenges.
Pharmacological Treatment of Schizophrenia: Antipsychotic Update and Guidance for Best Practice (continued)

Clinical Guidance

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine’s superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by 1) the extent to which reduction in positive symptoms brings about improvement in these other domains and 2) the extent to which extrapyramidal side effects (EPS) and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yields multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice.

References


Guideline References


References (continued)


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