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Abbreviated Class Update: Antidepressants (First and Second Generation)

Month/Year of Review: September 2014 **End date of literature search:** June 1, 2014

Current Status of Voluntary PDL Class:

- Preferred Agents: BUPROPION HCL TABLET/TABLET ER, CITALOPRAM TABLET/SOLUTION, FLUOXETINE CAPSULE/SOLUTION/TABLET, FLUVOXAMINE, MIRTAZEPINE TAB RAPDIS/TABLET, PAROXETINE TABLET, SERTRALINE ORAL CONC/TABLET, VENLAFAXINE TABLET, VENLAFAXINE ER
- Non Preferred Agents: BUPROPRION XL, DESVENLAFAXINE (PRISTIQ ER), DULOXETINE (CYMBALTA®), ESCITALOPRAM, FLUOXETINE DF (PROZAC® WEEKLY), NEFAZODONE, PAROXETINE HCL (PAXIL CR®), SELEGILINE PATCH (ENSAM®), VILAZODONE (VIIBRYD®), OLANZAPINE/FLUOXETINE (SYMBYAX®), VORTIOXETINE (BRINTELLIX®), LEVOMILNACIPRAN (FETZIMA®)

Research Questions:

- What is the comparative efficacy of first and second generation antidepressants in the treatment of major depressive disorder?
- How do first and second generation antidepressants differ in type and incidence of adverse events?

Conclusions:

- There is low quality evidence that shows there are minimal differences in efficacy between first and second generation antidepressants. While some meta-analyses show a trend towards greater improvement with TCAs compared to SSRIs, TCAs are no longer favored when only higher quality studies are considered.
- The safety profiles of antidepressants vary by class, and there is no comprehensive analysis that directly compares the rate and type of adverse events between first and second generation antidepressants. There is low quality evidence to show that SSRIs are more tolerable than TCAs, as a larger proportion of patients treated with TCAs withdrew treatment due to adverse events compared to those treated with SSRIs. MAOIs are associated with more drug-drug and food-drug interactions than any other class of antidepressants.

Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.
- Recommend including first generation antidepressants to the voluntary PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions. Also maintain nefazodone as non-preferred due to hepatic safety concerns.

Reason for Review:
To understand where first generation antidepressants fit on the PDL. Currently, all antidepressants are available without restriction and are not subject to prior authorization. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs, such as prior authorization. Thus, the mental health PDL is strictly voluntary. Second generation antidepressants have been reviewed for clinical efficacy and safety and specific agents have been chosen as clinically preferred. The advantage of this is the elimination of a copay. Reviewing the first generation agents and adding clinically appropriate agents to the PDL would reduce the copay burden to the client, while improving access to these medications.

Previous P&T conclusions and recommendations (May 2014):
- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder.
- There is moderate quality evidence that vortioxetine is safe and effective for the treatment of major depressive disorder (MDD) based on short-term placebo-controlled trials. There is insufficient evidence to determine the most effective treatment dose.
- There is moderate quality evidence that vortioxetine is not superior to duloxetine 60 mg daily or venlafaxine XR 225 mg daily in efficacy.
- There is low quality evidence that levomilnacipran is safe and effective for the treatment of MDD based on short-term placebo-controlled trials.
- There is insufficient evidence to determine the effectiveness of either vortioxetine or levomilnacipran in the maintenance treatment of MDD, as well as in pediatric patients or patients with severe hepatic impairment.
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Background:
The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines major depressive disorder (MDD) as having one or more major depressive episodes (MDE) and the lifetime absence of mania and hypomania. An MDE is defined as having five of nine symptoms during a two week period. To qualify as an MDE one of the following symptoms must be present (1) depressed mood or (2) loss of interest or pleasure in usual activities that lasts for ≥ 2 weeks. This coincides with other symptoms of MDD which include: significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or excessive or inappropriate guilt nearly every day, diminished ability to think or concentrate or indecisiveness nearly every day, or recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan for committing suicide. These symptoms must cause significant distress or impairment, not be attributable to a substance or medical condition, and cannot be better explained by a psychotic disorder.[1]

Depression is a very common disorder throughout the world with an estimated lifetime prevalence of 12%.[2] The lifetime prevalence in the US is estimated at 17%, which reflects the variation of the disease.[3] The average age of onset for MDD in the United States is 32 years old.[4] Women are 70% more likely to experience depression at some point in their life than men.[4] Before the late 1980s, the pharmacologic treatment of Axis I psychiatric disorders (such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders) was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).[5] Antidepressant medications are generally broken down in into two categories; first-generation and second generation. TCAs and MAOIs are often referred to as traditional or first-generation antidepressants. While these medications often are effective they are associated with more side effects than the second-generations. Common side effects of TCAs include classic anticholinergic effects including dry mouth and eyes, urinary retention, and constipation.

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The original MAOIs are rarely used do to their potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine.[5] Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters.[5] In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then several other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, escitalopram, and vilazodone. The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine.[5] Other agents used for treatment of MDD include bupropion, levomilnacipran, mirtazapine, and nefazodone.

Due to the heterogeneity and unknown definitive cause of depression, determining successful treatment in clinical trials can be difficult. The FDA has accepted primary success as improvement between a baseline score and a post-treatment score using commonly used observer-administered depression rating scores. The most widely used observer-administered depression rating scales are the Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions (HAMD24 and HAMD17, respectively), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician Global Impressions-Severity of Illness (CGI-S) scale. The The HAMD scores patients on a scale of 0-5 on 24 items associated with major depression. MADRS uses a range of 0-6 on 10 items associated with major depression. The CGI-S measures disease severity on a 7-point scale which scores the clinician's global assessment of the patient rather than individual aspects of the disease state. Clinically meaningful changes on these scales are not well defined, yet these scales are still considered the gold standard in clinical trials for antidepressants.

Defining consensus outcomes has been described in previous papers.[6,7] The term 'response' is used to describe a clinically significant degree of depressive symptom reduction following treatment initiation.[6,7] Those who no longer have depressive symptoms are considered to be in remission.[6] The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).[6] Trials have used various changes in depression scales to define response and remission, but the most widely accepted cutoffs for response is a ≥50% reduction from baseline (both MADRS and HAMD), and a specific threshold for remission. For the HAMD17 a score of ≤7 on the HAMD17 is widely accepted, while some argue a score of ≤5 be used, but there are differing recommendations for remission using MADRS.[7] A HAMD17 score of ≤7 corresponds to a MADRS score of ≤9, but others recommend a MADRS score of ≤5 to define remission, while most clinical trials use a score of ≤10.[7] This variance has led to disagreements in the scientific community but represents the best method for defining pharmacological treatment success.

Methods:
A Medline literature search ending June 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing first generation antipsychotics to second generation antipsychotics. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Systematic Reviews/Meta-analyses:
The relative efficacy and safety of first and second generation antidepressants for the treatment of major depressive disorder were evaluated in a 2012 meta-analysis. The analysis included studies that were randomized, double-blind, placebo-controlled trials in adults with acute, apparently unipolar, major depressive

episode, based on DSM-III, III-R, or –IV, ICD-9 or -10, or RDC diagnostic criteria, and had at least 20 subjects per arm.[8] Antidepressants must have been studied as a monotherapy. Trials were excluded from the review if they evaluated drugs that were not FDA-approved for the treatment of acute episodes of major depressive disorder. The primary outcome measure was 'response,' which was defined as ≥50% reduction in initial depression rating-scale scores. Ratings were typically based on the HAMD or MADRS Depression Rating Scales. When these measures were not available, scores were based on the CGI ratings.[8]

In total, 107 trials met the inclusion criteria with 27,127 total subjects (17,059 randomized to one of 19 different antidepressants, 9,925 randomized to placebo). The antidepressants studied were: imipramine, fluoxetine, venlafaxine, paroxetine, amitriptyline, duloxetine, bupropion, desvenlafaxine, sertraline, R,S-citalopram, S-citalopram, mirtazapine, selegiline, desipramine, clomipramine, nortriptyline, phenelzine, tranylcypromine, and trazodone. The frequency of studies by antidepressant types is as follows: SSRIs [52 trials (36.6%)], TCAs [38 (26.8%)], SNRIs [33 (23.2%)], atypical agents (bupropion, mirtazapine, trazodone) [14 (9.9%)], and MAOIs [5 (3.5%)].[8]

The pooled responder rate ratio (RR) for all agents was 1.42 (CI 1.38-1.48) compared to placebo. Overall, phenelzine ranked the highest in terms of efficacy, and trazodone the lowest. However in addition to tranylcypromine and clomipramine, these four drugs were ranked as outliers among the other antidepressants, as each drug only had one related study included in the meta-analysis. When only drugs with greater than one trial are considered, amitriptyline is ranked highest and bupropion the lowest. All confidence intervals overlap, indicating the need for cautious interpretation of trial data. Authors also compared classes of antidepressants using response rate ratios (RRs), and found TCAs to be the most effective, followed by SNRIs, MAOIs, SSRIs, and atypicals, in order of decreasing efficacy. For the outcome of responder rate differences, the classes were ranked in order of decreasing efficacy: TCAs, SNRIs, SSRIs, MAOIs, atypicals. Adverse events, discontinuation rates, and other safety outcomes were not included in this analysis.[8]

This comprehensive meta-analysis found that the differences between antidepressants and placebo were moderate, yet statistically significant, and that differences in efficacy among the different agents are minimal. These findings are similar to results from previous meta-analyses, but differ in that TCAs demonstrated clear statistical superiority over the other classes of antidepressants. The authors propose that this is a reflection of evolving clinical trial design that has occurred over the last three decades, including increasing size and complexity, greater heterogeneity in diagnostic and clinical assessments, inclusion of patients with less severe depression, and increasing trial length. These factors may have contributed to an increase in placebo-response rate or a decline in antidepressant-response rate, so further research is needed to determine the optimal trial design for evaluating antidepressants.

Two different meta-analyses evaluated TCAs and SSRI's for depression, specifically in the primary care setting. Each study included randomized, placebo-controlled trials using TCAs or SSRIs in adults who had a diagnosis of depression and received treatment in the primary care setting, but the studies differed in primary endpoints. In the meta-analysis by Arrol et al., the primary endpoint was the efficacy of TCAs and SSRIs in comparison with placebo, calculated using the weighted mean difference in studies where the same outcome scale was used. Where there were dichotomous outcomes, the relative risk was calculated. Patient-reported adverse events were evaluated as a secondary outcome.[9] In the meta-analysis by MacGillivray et al., the primary endpoint was the relative efficacy of TCAs compared to SSRIs, measured by the mean difference of final mean depression scores and relative risk of response using the CGI score.[10]

Arrol et al. found that both TCAs and SSRIs were statistically superior to placebo, for both continuous and dichotomous outcomes. In total, 12 studies with 2,753 participants (596 using TCAs, 890 using SSRIs, and 1,267 using placebo) were evaluated. The relative risk for improvement was 1.26 (95% CI 1.12-1.42) with TCAs and 1.37 (95% CI 1.21-1.55) with SSRIs. The numbers needed to treat for one improved patient was 3-4 and 6, for TCAs and SSRIs, respectively. Comparative efficacy of TCAs and SSRIs was not evaluated in this analysis. The relative risk for withdrawal due to adverse events was 2.35 (95% CI 1.59-3.46) for TCAs and 2.01

(95% CI 1.1-3.7) for SSRIs with a number needed to harm range of 5-10 and 21-94, respectively. All the studies included were of short duration (6-8 weeks), and all of the SSRI studies had commercial involvement.[9]

The analysis conducted by MacGillivray et al. included 11 studies with 2,954 total participants (1,607 using an SSRI and 1,347 using a TCA). Six studies contributed to the overall efficacy analysis and found that the standardized weighted mean difference on depression rating scales was 0.07 (95% CI -0.02-0.15). Though TCAs and SSRIs were not statistically significantly different, the data trended in favor of TCAs. When evaluators only considered the three studies that were deemed to be higher quality, TCAs are no longer favored, with a standardized mean difference of -0.03 (95% CI -0.2- 0.14). There was also no difference between TCAs and SSRIs for the endpoint of CGI improvement [relative risk 1.11 (95%CI 0.86-1.43)]. Fewer patients treated with SSRIs withdrew treatment due to an adverse event [11.6% (9.9%-13.3%)] compared to those treated with TCAs [17% (14.8%-19.1%)]. The results of this trial indicate that there is no difference in efficacy between TCAs and SSRIs, and that SSRIs may be better tolerated than TCAs. This is consistent with meta-analyses that have conducted similar comparisons of efficacy in patients of all care settings, however data is conflicting on the relative tolerability of the two classes. It appears that SSRIs may be marginally more tolerable, however high quality, long-term trials are needed to confirm this assertion.[10]

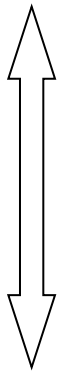
Table 1. Summary of meta-analysis comparing first and second generation antidepressants

<table>
<tr><th>Reference</th><th>Population</th><th>Primary Endpoint</th><th>Results</th></tr>
<tr>
<td>Underraga 2012[8]

Meta-analysis of all FDA-approved antidepressants</td>
<td>Adults with major depression

107 trials

Antidepressants: n=17,059

Placebo: n=9,925</td>
<td>Pooled rate ratios (RRs) of responder rates based on HDRS, MADRS, or CGI rating scales. Response: ≥ 50% reduction in rating-scale scores.</td>
<td>
Most effective
 
Least effective
<table>
<tr><th></th><th>Relative response rates for drugs with >1 trial (95% CI, p-value)</th><th></th><th>Relative response rates for drugs by class (95% CI, p-value)</th></tr>
<tr><td>Amitriptyline</td><td>1.74 (1.5-2.01), p≤0.001</td><td rowspan="3">TCAs</td><td rowspan="3">1.62 (1.47-1.78), p=0.0001</td></tr>
<tr><td>Mirtazapine</td><td>1.73 (1.26-2.36), p≤0.001</td></tr>
<tr><td>Imipramine</td><td>1.58 (1.37-1.83), p≤0.001</td></tr>
<tr><td>Citalopram</td><td>1.48 (1.24-1.76), p≤0.001</td><td rowspan="3">SNRIs</td><td rowspan="3">1.40 (1.3-1.51), p=0.0001</td></tr>
<tr><td>Desipramine</td><td>1.45 (1.07-1.96), p≤0.001</td></tr>
<tr><td>Venlafaxine</td><td>1.45 (1.35-1.56), p≤0.001</td></tr>
<tr><td>Paroxetine</td><td>1.44(1.26-1.66), p≤0.001</td><td rowspan="2">MAOIs</td><td rowspan="2">1.39 (1.11-1.48), p=0.0001</td></tr>
<tr><td>Desvenlafaxine</td><td>1.41 (1.16-1.72), p≤0.001</td></tr>
<tr><td>Escitalopram</td><td>1.33 (1.2-1.48), p≤0.001</td><td rowspan="4">SSRIs</td><td rowspan="4">1.37 (1.27-1.48), p=0.0001</td></tr>
<tr><td>Sertraline</td><td>1.33 (1.2-1.47), p≤0.001</td></tr>
<tr><td>Selegiline</td><td>1.33 (1.07-1.65), p≤0.001</td></tr>
<tr><td>Fluoxetine</td><td>1.31 (1.07-1.60), p≤0.001</td></tr>
<tr><td>Duloxetine</td><td>1.29 (1.09-1.52), p≤0.001</td><td rowspan="2">Atypicals</td><td rowspan="2">1.25 (1.15-1.35), p=0.0001</td></tr>
<tr><td>Bupropion</td><td>1.23 (1.14-1.33), p≤0.001</td></tr>
<tr><td>Pooled</td><td colspan="3">1.42 (1.38-1.48), p<0.0001</td></tr>
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<tr>
<td>Arroll 2005[9]

Meta-analysis comparing TCAs and SSRIs to placebo</td>
<td>Adults with major depression, receiving care in the primary care setting

TCAs: n=596
SSRIs: n=890
Placebo: n=1,267</td>
<td>Response, measured by HAMD, MADRS, or CGI rating scales</td>
<td>
<table>
<tr><th></th><th>Events (treatment)</th><th>Events (placebo)</th><th>Relative risk (95% CI)</th></tr>
<tr><td colspan="4">Efficacy endpoint: Response on depression rating scales (definition of response varied by scale)</td></tr>
<tr><td>TCAs vs. Placebo</td><td>323/535 (60.4%)</td><td>216/460 (47.0%)</td><td>1.26 (1.12-1.42)</td></tr>
<tr><td>SSRIs vs Placebo</td><td>310/552 (56.2%)</td><td>231/562 (41.1%)</td><td>1.37 (1.21-1.55)</td></tr>
<tr><td colspan="4">Safety endpoint: Adverse events leading to withdrawal</td></tr>
<tr><td>TCAs vs. Placebo</td><td>81/692 (11.7%)</td><td>30/578 (5.2%)</td><td>2.35 (1.69-3.46)</td></tr>
<tr><td>SSRIs vs Placebo</td><td>30/576 (5.2%)</td><td>15/573 (2.6%)</td><td>2.01 (1.10-3.69)</td></tr>
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<tr>
<td>MacGillivray 2003[10]</td>
<td>Adults with major depression, receiving</td>
<td>Standard mean difference of final mean depression scores</td>
<td>Standardized mean difference in final mean depression scores: 0.07 (-0.02, 0.15), in favor of TCAs.</td>
</tr>
</table>

Meta-analysis comparing TCAs to SSRIs	care in the primary care setting TCAs: n=1,347 SSRIs: n=1,607		Relative risk of treatment withdrawal due to drug related adverse events: 0.73 (0.60, 0.88), in favor of SSRIs.

HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scales; CGI: Clinical Global Impression rating scale; HAMD: Hamilton Depression rating scale

2. Guidelines – Major Depressive Disorder:

The 3rd edition of the Practice Guideline for the Treatment of Patients with Major Depressive Disorder where released in 2010 by the American Psychiatric Association. Recommendations fell into one of three categories:[11]

[I] Recommended with substantial clinical confidence

[II] Recommended with moderate clinical confidence

[III] May be recommended on the basis of individual circumstances

For the acute phase of treatment, clinicians may use pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies to achieve a full return to the patient's baseline level of functioning. The guidelines recommend an antidepressant medication for the initial treatment for patients with mild to moderate major depressive disorder [I] and definitely should be used in severe major depressive disorder unless ECT is planned [I]. The guidelines state that because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g. half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [I]. The guideline's preferred agents for most patients are SSRIs, SNRIs, mirtazapine, or bupropion [I]. MAOIs should be restricted to patients who do not respond to other treatments [I], due to the necessity for dietary restrictions and drug-drug interactions. For patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [III] or St. John's wort [III] might be considered although evidence of efficacy is modest at best.[8]

After starting a medication, the rate at which it is titrated to the full therapeutic dose depends on age, the treatment setting, the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [I]. During the early phase of treatment patients should be closely monitored on the response and to identify side effects [I]. The frequency of patient monitoring should be determined on patient factors including symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [II]. If side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [I].[11]

If at least moderate improvement in symptoms is not observed within 4-8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [I]. Therapeutic alliance and treatment adherence should also be addressed [I]. For antidepressant medications the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. For some TCAs a drug blood level can help with dose adjustments [I]. For patients who require a change in treatment plan, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the

antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to something within the same pharmacological class or to one from a different class [II]. Patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or second-generation antipsychotic [II]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a non-selective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline can also be considered [II].[11]

During the continuation phase patients should have systematic assessment of symptoms, side effects, adherence, and function status [I]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4-9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline.[11]

If it is decided to proceed to the maintenance phase of therapy, considerations including whether the patient has additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II].[11]

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks to minimize the likelihood of discontinuation symptoms [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II].[11]

A patient's co-occurring medical conditions can contribute to what therapy a patient should receive. In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., ECG with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [I]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individuals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [I]. Some antidepressant drugs reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [II]. Serotonergic agents can worsen Parkinson's disease symptoms [II] and selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [I]. For patients being treated following a stroke, consideration should be given to potential interactions with anticoagulation medications [I]. The side effect of weight gain should be considered when choosing an agent. Patients who have undergone bariatric surgery should reconsider the pharmacokinetics and pharmacodynamics of medications [I]. Drug interactions with HIV medications should be considered [I]. Interferon can exacerbate depressive symptoms, making close monitoring important [I]. Patients receiving tamoxifen who are going to be started on an antidepressive medication, should be treated with an agent that has minimal effect on the P450 2D6 isoenzyme [I]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [II].[11]

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37. Nefazodone Prescribing Information. at <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_11_Serzone-Label.pdf>

38. Trazodone Prescribing Information. at <http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022411lbl.pdf>

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

DOSE & AVAILABILITY

MEDICATIONS	USUAL DOSAGE	INDICATIONS
Tricyclic Antidepressants (TCAs)		
Amitriptyline, generic[12]	75-150 mg/day in divided doses	• Depression
Amoxapine, generic[13]	100-400 mg/day; Doses > 300mg should be divided	• Depression
Desipramine, generic[14]	100-200 mg/day	• Depression
Doxepin, generic[15]	25-300 mg/day	• Depression • Insomnia
Imipramine, generic[16]	50-150 mg/day	• Depression • Childhood enuresis
Maprotiline, generic[17]	25-225 mg/day (Max of 150mg in most patients)	• Depression
Nortriptyline, generic[18]	50-100 mg/day	• Depression
Protryptiline, generic[19]	15-60 mg/day in divided doses	• Depression
Trimipramine, generic[20]	50-150 mg/day	• Depression
Monoamine Oxidase Inhibitors		
Isocarboxazid, generic[21]	20-60 mg/day	• Depression
Phenelzine, generic[22]	15mg (every other day)-60 mg/day	• Depression
Selegiline patch, generic[23]	6-12mg/24 hours patches	• Depression
Tranylcypromine, generic[24]	30-60 mg/day	• Depression without melancholia
Selective Serotonin Reuptake Inhibitors		

Citalopram, generic[25]	20-40 mg/day	• Depression
Escitalopram, generic[26]	10-20 mg/day	• Depression • Generalized anxiety disorder
Fluoxetine, generic[27]	10-60 mg/day	• Depression • Acute and maintenance treatment of obsessive compulsive disorder age 7-17 • Treatment of Bulimia Nervosa in adult patients • Acute treatment of Panic Disorder in adult patients
Paroxetine, generic[28]	20-50 mg/day	• Depression • Panic disorder • Obsessive compulsive disorder • Social anxiety disorder • Generalized anxiety disorder • Post-traumatic stress disorder • Premenstrual dysphoric disorder
Sertraline, generic[29]	50-200 mg/day	• Depression • Obsessive compulsive disorder • Panic disorder • Post-traumatic stress disorder • Premenstrual dysphoric disorder • Social anxiety disorder
Vilazodone (Viibryd)[30]	10-40 mg/day	• Depression
Serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Desvenlafaxine, generic[31]	50 mg/day	• Depression
Duloxetine, generic[32]	40-60 mg/day	• Depression • Generalized anxiety disorder • Diabetic peripheral neuropathic pain • Fibromyalgia • Chronic musculoskeletal pain
Levomilnacipran (Fetzima)[33]	40-120 mg/day	• Depression
Venlafaxine, generic[34]	37.5-225 mg/day	• Depression • Social anxiety disorder

Atypical antidepressants		
Bupropion, generic[35]	IR: 200-450 mg/day in divided doses SR: 150-400 mg/day in divided doses ER: 150-450 mg/day once daily	• Depression • Seasonal affective disorder • Adjunct in smoking cessation
Mirtazapine, generic[36]	15-45 mg/day	• Depression
Nefazodone, generic[37]	200-600 mg/day in two divided doses	• Depression
Trazadone, generic[38]	150-600 mg/day in divided doses Extended Release: 150mg once daily up to 375 mg/day	• Depression
Vortioxetine (Brintellix)[39]	5-20 mg/day	• Depression

SAFETY[12-40]

Black box warnings:

- All antidepressants
    - Suicidality/suicidal thoughts and behaviors – antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adults, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Nefazodone
-
    - Life threatening liver failure – Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000-300,000 patient-years of treatment. Treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases.

Contraindications:

- All antidepressants
    - Concomitant use of non-MAOIs with MAOIs
- TCAs: Nortriptyline, trimipramine, protryptiline, maprotiline
    - Acute recovery period after myocardial infarction
- TCAs: Doxepin
    - Urinary retention
    - Narrow-angle glaucoma
- MAOIs (all)
    - With pheochromocytoma
    - Congestive heart failure
    - Severe renal impairment or renal disease
    - History of liver disease or abnormal LFTs
    - With sympathomimetic drugs
    - Foods high in tyramine or dopamine/Food restrictions with high doses of selegilene patch
    - Do not use in combination with dextromethorphan or CNS depressants. Do not use with meperidine. Do not use multiple MAOIs together
    - Do not use in combination with buspirone
    - General anesthesia, spinal anesthesia. MAOIs should be stopped at least 10 days prior to procedure
    - Drug interactions – all medications should be checked before starting an MAOI or adding a new medication
- SSRIs – citalopram, escitalopram, fluoxetine, paroxetine, sertraline
    - Do not use with pimozide
- SSRIs –fluoxetine, paroxetine (sertraline, escitalopram, citalopram – double check PI),
    - Do not use with thioridazine
- SNRIs – duloxetine
    - Use in patients with uncontrolled narrow-angle glaucoma
- Atypicals – bupropion
    - Seizure disorders
    - Current or prior diagnosis of bulimia or anorexia
    - If undergoing abrupt discontinuation of alcohol or sedatives
- Atypicals – nefazodone
    - If previous use has caused liver injury
    - Avoid combining with triaozlam in most patients
    - Coadministration of terfenadine, astemizole, cisapride, pimozide, or carbamazepine
    - In the recovery phase of an MI

DOSE ADJUSTMENTS

MEDICATIONS	RENAL ADJ	HEPATIC ADJ	Pediatric	Elderly	OTHER DOSING CONSIDERATIONS

			Dose	Dose	
Tricyclic Antidepressants (TCAs)					
Amitriptyline, generic[12]	None specified	None specified	Not recommended in under 12 years of age	50 mg/day in divided doses	Sedative effect may be apparent before the antidepressant effect is noted, but therapeutic effect may take up to 30 days to develop.
Amoxapine, generic[13]	None specified	None specified	Not discussed	50-300 mg/day	Hospitalized patients refractory to antidepressant therapy may be cautiously titrated to 600 mg/day in divided doses
Desipramine, generic[14]	None specified	None specified	20-100 mg/day	20-100 mg/day	Higher doses should be initiated administered in hospitals
Doxepin, generic[15]	None specified	Use a lower dose and adjust gradually.	Not discussed	10-75 mg/day	A single dose should not exceed 150mg, select patients may respond to 25-50 mg/day.
Imipramine, generic[16]	None specified	None specified	Not to exceed 100 mg/day	Not to exceed 100 mg/day	If hospitalized, max dose is 250-300mg/day
Maprotiline, generic[17]	None specified	None specified	Not discussed	50-75 mg/day	Long half-life so initial doses should be maintained for 2 weeks.
Nortryptiline, generic[18]	None specified	None specified	No data on its use	30-50 mg/day	
Protriptyline, generic[19]	None specified	None specified	Adolescents: 15-20 mg/day	15-20 mg/day	
Trimipramine, generic[20]	None specified	None specified	Not discussed	50-100 mg/day	Hospitalized patients may receive 100 mg/day up to 200 mg/day in a few days up to a maximum of 300 mg/day
Monoamine Oxidase Inhibitors					
Isocarboxazid, generic[21]	Contraindicated in renal dysfunction	Contraindicated in liver disease	Not discussed	See adult dosing	Many drug and food interactions Doses of the selegiline patch <9 mg/24 hours do not have dietary restrictions.
Phenelzine, generic[22]	None specified but use caution	None specified but use caution	Not discussed	Use doses on the lower end	
Selegiline patch, generic[29]	No adjustment	No adjustment	Not discussed	6mg/24 hour patch	
Tranylcypromine,	None specified	None specified	Not discussed	See adult dosing	

generic[24]					
Selective Serotonin Reuptake Inhibitors					
Citalopram, generic[25]	No change for moderate renal impairment; use with caution in severe renal impairment.	Maximum 20 mg/day	10-40 mg/day for obsessive-compulsive disorder	Maximum recommended dose is 20 mg/day.	Doses greater than 40 mg/day are not recommended due to risk of QT prolongation and failure to show additional efficacy.
Escitalopram, generic[26]	Use with caution in severe renal impairment	10 mg/day	Age ≥12 10-20 mg/day	5-10 mg/day	
Fluoxetine, generic[27]	No adjustment	Lower and less frequent dosage should be used in patients with hepatic impairment	10-20 mg/day	Use adult dosing	
Paroxetine, generic[28]	10-40 mg/day	10-40 mg/day	Not discussed	10-40 mg/day	
Sertraline, generic[29]	No adjustment	Lower dose and less frequent dosing should be used	25-50 mg/day (for OCD)	25-100 mg/day	
Vilazodone (Viibryd)[30]	No adjustment	No adjustment	Not approved for pediatric use	No adjustment	Reduce dose if co-administered with a strong inhibitor of CYP3A4
Serotonin and norepinephrine reuptake inhibitors					
Desvenlafaxine, generic[31]	CrCl 30-50 mL/min – max dose 50 mg/day End-stage renal disease – 50 mg every other day	Max dose 50 mg/day	Safety and effectiveness not established	Increased incidence of orthostatic hypotension	No additional benefit was seen at doses greater than 50 mg/day and increased adverse reactions.
Duloxetine, generic[32]	Not recommended for patients with end-stage renal disease or severe renal impairment (CrCl <30 ml/min)	Avoid use	Efficacy not demonstrated Not studied in age <7	No adjustment	
Levomilnacipran	Do not exceed 80	No adjustment	Not studied	No adjustment	

(Fetzima)[33]	mg/day for moderate impairment. Max 40 mg/day for severe impairment.				
Venlafaxine, generic[34]	Reduce dose by 25-50% Reduce by 50% in hemodialysis	Reduce dose by 50% in mild to moderate impairment.	Not approved for pediatric use	No adjustment	
Other Antidepressants					
Bupropion, generic[35]	Use with caution, elimination is reduced, consider lowering frequency in IR formulations	Use with extreme caution in sever hepatic cirrhosis, low doses only	Not studied for depression	IR: 75-300 mg/day in divided doses	Doses given are for hydrochloride salt formulation. See package insert for dose conversions to hydrobromide salt.
Mirtazepine, generic[36]	Be aware that plasma levels increase in renal impairment	Be aware that plasma levels increase in hepatic impairment	Not studied	Use with caution due to decreased clearance in the elderly.	Do to the long half-life, dose changes should only be done every 1-2 weeks.
Nefazodone, generic[40]	Non provided, however it is partially cleared by the kidney	Contraindicated in patients with hepatic impairment	No information given	Initial dose of 100 mg/day in two divided doses	
Trazadone, generic[38]	None specified	None specified	Age 6-12: Initial 1.5-2 mg/kg/day in divided doses with maximum of 6 mg/kg/day in 3 divided doses	Short acting: 25-150 mg/day ER: Use caution	
Vortioxetine (Brintellix)[39]	None specified	None specified	Not studied	Not addressed	Maximum recommended dose is 10 mg/day for known CYP2D6 poor metabolizers. Reduce dose in half if strong CYP2D6 strong inhibitor is started.