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# Antidepressant Prescribing Practice Guidelines

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| **Effective Date** | 06/28/2023 | DocuSigned by: Dr. Georgina Yoshioka 7DE8077EEA674B3... |
| **Revised Date** | 06/28/2023 | Georgina Yoshioka, DSW, MBA, LCSW, Director |

**Policy**

It is the policy of the San Bernardino County (County) of Department of Behavioral Health to establish practice guidelines for the use of antidepressants in the provision of client treatment.

**Purpose**

The DBH Antidepressant Prescribing Practice Guidelines are intended to provide guidance for providers, to increase the effectiveness and safety of antidepressant use. These Guidelines are not intended to be comprehensive in scope and are not a substitute for clinical judgment. In making decisions about client care physicians must carefully consider the clinical characteristics and circumstances of each individual.

**Introduction**

Antidepressant medications are prescribed for multiple mental health conditions and play a critical role in the treatment of major depressive disorder and other depressive disorders. Antidepressant medications are used to treat other mental health disorders besides depression including anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder.

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# Antidepressant Prescribing Practice Guidelines, Continued

**Use and Indications**

The selection of a specific antidepressant medication, form of administration, dose and duration of treatment is a complex decision-making process involving multiple factors. These factors include individualized treatment goals, client choice, history of past antidepressant medication trials, family history, side effect profile, and other factors. The tables below identify disorders for which antidepressants may be indicated:

| Depressive and Related Disorders Where Antidepressants May Be Indicated (*SOME are off-label indications) |
|---|
| • Major Depressive Disorder<br>• Persistent Depressive Disorder (Dysthymia)<br>• Premenstrual Dysphoric Disorder<br>• Substance/Medication-Induced Depressive Disorder<br>• Depressive Disorder Due to Another Medical Condition<br>• Other Specified Depressive Disorder<br>• Unspecified Depressive Disorder<br>• Bipolar and Related Disorders<br>• Anxiety Disorders<br>• Obsessive-Compulsive and Related Disorders |

| Non-Depressive Disorders Where Antidepressants May Be Indicated (*ALL are off-label indications) |
|---|
| • Neurodevelopmental Disorders<br>• Schizophrenia Spectrum and Other Psychotic Disorders<br>• Bipolar and Related Disorders<br>• Trauma- and Stressor-Related Disorders<br>• Dissociative Disorders<br>• Somatic Symptom and Related Disorders<br>• Feeding and Eating Disorders<br>• Elimination Disorders<br>• Sleep-Wake Disorders<br>• Sexual Dysfunctions<br>• Gender Dysphoria<br>• Disruptive, Impulse-Control, and Conduct Disorders<br>• Substance-Related and Addictive Disorders<br>• Neurocognitive Disorders<br>• Personality Disorders<br>• Paraphilic Disorders |

**Antidepressant Classification**

Antidepressant medications are divided into groups based upon mechanism of action or chemical structure. The information blocks below provide information about different types of antidepressants.

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**Selective Serotonin Reuptake Inhibitors (SSRIs)**

SSRIs work by inhibiting synaptic reuptake of serotonin in neurons, increasing serotonin availability, which leads to downstream modulation of serotonin receptors. SSRIs are first line for the treatment of major depressive disorder, anxiety disorders, trauma-related disorders, and obsessive-compulsive disorder. When prescribing SSRIs, one should begin at the low end of the dosage range and gradually titrate up to the FDA-maximum dose, if clinically warranted. Due to genetic variability, some individuals are very sensitive to SSRI adverse effects and may require even lower starting doses. The table below outlines SSRIs dosage ranges:

| Generic Name | Dosage Range | Comments |
|---|---|---|
| Citalopram | 10-40 mg/day | Well tolerated; QTc prolongation and FDA warning for abnormal heart rhythms; Fewer drug interactions |
| Escitalopram | 5-20 mg/day | Well tolerated; QTc prolongation; Fewer drug interactions |
| Fluoxetine | 10-80 mg/day | Most activating (insomnia, diarrhea, initial increase in anxiety); More drug interactions; Least likely to cause discontinuation syndrome; QTc prolongation |
| Fluvoxamine | 50-300 mg/day | Most sedating |
| Paroxetine | 10-60 mg/day | Sedating, anticholinergic effects; Drug interactions |
| Sertraline | 50-200 mg/day | Slightly activating; Fewer drug interactions |
| Vilazodone | 10-40 mg/day | Nausea, anorexia, diarrhea |

**Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)**

SNRIs, work by blocking presynaptic serotonin and norepinephrine transporter proteins, thus inhibiting reuptake of these neurotransmitters and increasing stimulation of postsynaptic receptors. The effect of SNRIs on serotonin and norepinephrine reuptake is dose dependent. For example, venlafaxine acts like an SSRI at low doses, but at 150 mg daily and above, it has a significant effect on norepinephrine reuptake. Duloxetine affects serotonin and norepinephrine reuptake at all doses. The effect of SNRIs on serotonin and norepinephrine reuptake is dose dependent. For example, venlafaxine acts like an SSRI at low doses, but at 150 mg daily and above, it has a significant effect on norepinephrine reuptake. Duloxetine affects serotonin and norepinephrine reuptake at all doses. Similar to SSRIs, SNRIs should be started at lower doses and titrated gradually.

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**Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)**, continued

The table below outlines SNRIs dosage ranges:

| Generic Name | Dosage Range | Comments |
|---|---|---|
| Desvenlafaxine | 50-100 mg/day | Monitor blood pressure |
| Duloxetine | 60-120 mg/day | Monitor blood pressure; Avoid in chronic liver disease or those with substantial alcohol use |
| Levomilnacipran | 40-80 mg/day | Orthostatic hypotension; monitor blood pressure |
| Venlafaxine | 75-375 mg/day | Sexual dysfunction, QTc prolongation; monitor blood pressure |
| Milnacipran | 100-200 mg/day | Blurred vision, dizziness, headaches, sweating, hypertensive crisis |

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**Tricyclic Antidepressants (TCAs)**

TCAs, work by inhibiting serotonin and norepinephrine transporters, thereby inhibiting presynaptic serotonin and norepinephrine reuptake, and increasing concentrations of these neurotransmitters in synaptic clefts. Secondary amines have greater affinity for the norepinephrine transporter, while tertiary amines have greater affinity for the serotonin transporter. In general, secondary amine TCAs are better tolerated than tertiary amines. TCAs should not be stopped abruptly due to discontinuation syndrome. Most TCAs are metabolized by the cytochrome P450 2D6 enzyme, and levels can be altered by inducers/inhibitors of that enzyme.

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**Tricyclic Antidepressants (TCAs)**, continued

The table below outlines TCAs dosage ranges:

| Generic Name | Dosage Range | Comments |
|---|---|---|
| Amitriptyline | 50-300 mg/day | Tertiary; Active metabolite is nortriptyline; Plasma level range: 100-250ng/mL (amitriptyline + nortriptyline) |
| Clomipramine | 25-250 mg/day | Tertiary; Plasma level range: 230-450ng/mL (clomipramine + norclomipramine) |
| Desipramine | 25-300 mg/day | Secondary; Plasma level range: 50-300ng/mL |
| Doxepin | 10-300 mg/day | Tertiary; Lower doses used for insomnia; Plasma level range: 30-150ng/mL |
| Imipramine | 50-300 mg/day | Tertiary; Active metabolite is desipramine; Plasma level range: 150-250ng/mL (imipramine + desipramine) |
| Nortriptyline | 25-150 mg/day | Secondary; Plasma level range: 50-150ng/mL |
| Protriptyline* | 10-60mg/day | Secondary |

**Monoamine Oxidase Inhibitors (MAOIs)**

All MAOIs, currently approved for use in the United States, irreversibly inhibit the monoamine oxidase enzymes (MAO-A and MAO-B). These enzymes ware responsible for the metabolism of serotonin, norepinephrine, dopamine, tyramine, and other amines. They work by increasing the concentration of serotonin, norepinephrine, and dopamine in the synapse. Tranylcypromine also inhibits norepinephrine and dopamine transporters. Start MAOIs at low doses, and titrate to therapeutic responses, to help minimize adverse effects. The table below outlines MAOIs dosage ranges:

| Generic Name | Dosage Range | Comments |
|---|---|---|
| Phenelzine | 45-90 mg/day | Irreversible, non-selective inhibitor of MAO-A and MAO-B |
| Tranylcypromine | 30-60 mg/day | Irreversible, non-selective inhibitor of MAO-A and MAO-B; Inhibits dopamine and norepinephrine transporters |
| Isocarboxazid | 20-60 mg/day | Irreversible, non-selective inhibitor of MAO-A and MAO-B |
| Phenelzine | 45-90 mg/day | Irreversible, non-selective inhibitor of MAO-A and MAO-B |
| Selegiline transdermal | 6-12 mg/day | Transdermal patch- avoids first pass metabolism, selective for MAO-B |

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**Monoamine Oxidase Inhibitors (MAOIs)**, continued

***Note:*** Outside the United States, moclobemide is marketed as a selective and *reversible* inhibitor of MAO-A. Because of its reversibility, it is much safer in overdose, has fewer anticholinergic side effects, and will not cause a potentially large rise in blood pressure when taken with tyramine-containing foods, compared to irreversible MAOIs.

**Serotonin Modulators and Stimulators (SMS)**

The table below provides the generic name of SMS:

| Generic Name |
|---|
| Vilazodone |
| Vortioxetine |

**Serotonin Antagonists and Reuptake Inhibitors (SARIs)**

The table below provides the generic name of SARI's:

| Generic Name |
|---|
| Nefazodone – withdrawn/discontinued in most countries. |
| Trazodone |

**Norepinephrine Reuptake Inhibitors (NRIs)**

The table below provides the generic name of SARI's:

| Generic Name |
|---|
| Atomoxetine - an NRI approved to treat ADHD |
| Reboxetine |
| Teniloxazine – also a 5-HT2A receptor antagonist |
| Viloxazine |

**Norepinephrine –Dopamine Reuptake Inhibitors (NDRIs)**

The table below provides the generic name of SARI's:

| Generic Name |
|---|
| Bupropion – weak NDRI |

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**Tetracyclic Antidepressants (TeCAs)**

The table below provides the generic name of TeCA's:

| Generic Name |
|---|
| Amoxapine |
| Maprotiline |
| Mianserin |
| Mirtazapine |
| Setiptiline |

**Combination Products**

The table below provides the generic name of combination products; no dosage or comments are included:

| Generic Name |
|---|
| Amitriptyline/perphenazine – TCA and typical antipsychotic combination |
| Olanzapine/fluoxetine – SSRI and atypical antipsychotic combination – specifically approved as a monotherapy for depressive episodes in bipolar disorder and treatment-resistant depression. |

**Atypical Antipsychotics FDA approved for treating Depressive Disorders**

The table below provides the generic name of atypical antipsychotics FDA approved for treating depressive disorders; no dosage or comments are included:

| Generic Name |
|---|
| Aripiprazole – specifically approved as an adjunct for major depressive disorder. |
| Brexpiprazole – specifically approved as an adjunct for major depressive disorder. |
| Lurasidone – specifically approved for depressive episodes in bipolar disorder. |
| Olanzapine – specifically approved as an adjunct for major depressive disorder. |
| Quetiapine – approved as an adjunct for both major depressive disorder and depressive episodes in bipolar disorder. |

**Other Medications used as an adjunct for depression**

The table below provides the generic name of other medications used as an adjunct treatment for depressive disorders; no dosage or comments are included:

| Generic Name |
|---|
| Buspirone – 5-HT1A receptor partial agonist – not specifically approved for depression (used off-label). |
| Lithium – mood stabilizer (mechanism of action unknown/unclear) – not specifically approved for depression (used off-label). |
| Thyroxine (T4) – thyroid hormone (thyroid hormone receptor agonist) – not specifically approved for depression (used off-label). |
| Triiodothyronine (T3) – thyroid hormone (thyroid hormone receptor agonist) – not specifically approved for depression (used off-label). |

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| | |
|---|---|
| **Prescribing Precautions** | There are precautions to consider when prescribing antipsychotic medications including risks and side effects. The information blocks below provide information about precautions and special considerations. |
| **Black Box Warning** | The FDA requires all antidepressants to include a black box warning indicating they are associated with an increased risk of suicidal thinking, feeling, and behavior in young people. |
| **Older Adults** | Aging may increase the risk of developing side effects from antidepressant medications that otherwise would likely be well-tolerated by a younger adult. This may be due to an enhanced sensitivity to common side effects associated with these drugs; particularly anticholinergic, hypotensive, and sedating effects, and a decreasing capacity to metabolize and eliminate medications due to diminished renal or hepatic function. Additionally, older adults often have multiple medical comorbidities. As a result, they may be prescribed various medications, introducing the risk for drug interactions.<br><br>The general approach is to initiate antidepressant therapy at a low dose and titrate to a therapeutic dose with careful monitoring.<br><br>The American Geriatrics Society periodically releases updates to the Beers criteria for potentially inappropriate medication use in older adults; the most recent version was released in 2019. Please refer to *References* block for additional details. |
| **Pregnancy** | Discontinuing antidepressants before or during pregnancy increases the risk of symptom relapse. Untreated depression and anxiety are associated with a variety of adverse pregnancy outcomes including low birth weight; fetal growth retardation; pre-term delivery; increased risk of pre-eclampsia, and increased risk of delivery complications. Patients with untreated mental illness are less likely to receive adequate prenatal care and are more likely to use alcohol, tobacco, and other substances known to adversely affect pregnancy outcomes. The decision whether to continue antidepressants during pregnancy should be carefully considered and individualized, weighing both the risk of untreated mental illness, and risks from fetal medication exposure.<br><br>In 2014 the FDA changed the labeling system of rating safety of medications taken during pregnancy in the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the “Pregnancy and Lactation Labeling Rule” (PLLR). |

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**Pregnancy**, continued

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant and nursing patients who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated.

The most well studied antidepressants during pregnancy are SSRIs. Meta-analyses on SSRI exposure do not demonstrate an increased risk in congenital malformations in children. However, there have been some reports of an association between first trimester paroxetine exposure and congenital heart defects. Smaller studies on tricyclic antidepressants, bupropion, venlafaxine, and mirtazapine have not shown increased risk of congenital malformations. Maternal SSRI use has been associated with a 1% risk of persistent pulmonary hypertension of the newborn in one report, although subsequent studies demonstrated lower risk or no association.

Some studies have suggested that use of SSRIs near the time of delivery may be associated with pre-term birth and poor perinatal outcomes; in particular, tremor, restlessness, increased muscle tone, and increased crying in about 25% of newborns. These symptoms usually resolve within 1-4 days after delivery.
It is unclear whether SSRI use during pregnancy can cause persistent pulmonary hypertension of the newborn (PPHN), because the available data are conflicting. It is well documented in the medical literature that SSRIs are used during pregnancy. In general, most epidemiology studies show that adverse events in pregnant patients are similar to those in non-pregnant patients, and many studies find no major fetal abnormalities in excess of the 1-3% found in the general population. The association between persistent pulmonary hypertension of the newborn (PPHN) and SSRI use during pregnancy is unclear. Some studies suggest an association between PPHN, and SSRI use in pregnancy and other studies do not.

At present, FDA does not find sufficient evidence to conclude that SSRI use in pregnancy causes PPHN, and therefore recommends that health care providers treat depression during pregnancy as clinically appropriate.

FDA will update the SSRI labels as any new data regarding SSRI use and PPHN become available.

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**Breastfeeding**

Antidepressants are considered relatively safe during breastfeeding. Data on SSRIs such as fluoxetine, paroxetine, and sertraline and on TCAs suggests that breastfeeding infants have very low to non-detectable amounts of these drugs in their serum. While there have been a small number of case reports of breastfeeding infants experiencing jitteriness, irritability, sleep disturbance, excessive crying, and feeding problems, a causal link between medication exposure and these symptoms has been difficult to establish. Serious side effects related to antidepressant exposure in breast milk have not been reported. When selecting an appropriate antidepressant, one should consider choosing an antidepressant for which there are data to support its safety during breastfeeding. However, if a patient responded well to a particular antidepressant in the past or during the course of the pregnancy, it would be reasonable to use that antidepressant while breastfeeding. In depth information about specific medications are available on LactMed, a free database available online supported by the National Institute of Health (NIH).

**Class Specification Prescribing Precautions**

The following outlines precautions by class:

| Selective Serotonin Reuptake Inhibitors (SSRI) Precautions |
|---|
| **Side Effects:**<br>• Common initial side effects from SSRIs include headaches, nausea, and gastrointestinal effects (constipation, diarrhea, vomiting). These effects are usually mild and tend to dissipate in 1-2 weeks. Some individuals experience an initial increase in anxiety. This too tends to improve over time. SSRIs occasionally cause bruxism (teeth grinding) and an increase in sweating. Sexual dysfunction may occur with SSRI treatment. The most common types of dysfunctions are delayed ejaculation and anorgasmia. Sexual side effects do not tend to improve over time. SSRIs block serotonin transporter sites on platelets and osteocytes and are associated with increased risk of bleeding, bone resorption, and hyponatremia.<br>• SSRIs can take anywhere between 4-12 weeks for their full effect. Sudden cessation of SSRIs can lead to discontinuation syndrome, consisting of flu-like symptoms, sleep disturbances, imbalance, tremors, dizziness, electric-shock sensations, agitation, and confusion. When stopping SSRI treatment, prescribers should gradually taper the dose to minimize the risk of discontinuation syndrome.<br>• Do not take SSRIs with certain other medicines:<br>  ○ Monoamine Oxidase Inhibitors (MAOIs)<br>  ○ Thioridazine<br>  ○ Orap<br>• Patients should talk to their doctors about the risks of taking Paroxetine during pregnancy. |

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**Class Specification Prescribing Precautions**, continued

| Tricyclic Antidepressant (TCA) Precautions |
|---|
| **Side Effects:**<br>• TCAs commonly cause sedation, weight gain, sexual dysfunction, and anticholinergic effects including blurry vision, urinary retention, dry mouth, constipation, cognitive impairment, and delirium. They should be used with caution in individuals with a history of glaucoma. They can lower the seizure threshold in individuals prone to seizures.<br>• Individuals taking TCAs should be monitored for cardiovascular side effects. TCAs are contraindicated in individuals with a recent myocardial infarction. They are lethal in overdose due to their cardiotoxic effects. They should be used cautiously in individuals with cardiovascular disease or family history of sudden death. Ingesting TCAs with alcohol or sedatives increases the risk of accidental overdose. They are also known to cause orthostatic hypotension, tachycardia and right bundle branch block. ECG monitoring should be performed at baseline and as clinically indicated when TCAs are used in children, in adults over the age of 40, and in those with cardiovascular disease.<br>• TCAs have a narrow therapeutic index and high inter-individual variability. Plasma concentration levels can be used to monitor for adherence and toxicity, although they are less helpful in guiding therapy. See Table 4 below for information about specific TCAs.<br>• Do not take tricyclic antidepressants if you are also taking MAO Inhibitors (MAOIs).<br>• Do not take tricyclic antidepressants if you have narrow-angle glaucoma. |

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**Class Specification Prescribing Precautions**, continued

**Monoamine Oxidase Inhibitors (MAOI) Precautions**

**Side Effects:**

- Side effects of MAOIs include postural hypotension, dry mouth, upset stomach, constipation, weight gain, and sexual dysfunction. Starting at a low dose and titrating to therapeutic response may help minimize adverse effects.
- MAOIs are contraindicated in pheochromocytoma, cardiovascular or cerebrovascular disease, hypertension or use of hypertensives, and hepatic impairment. They interact with virtually all other classes of antidepressants by causing serotonin syndrome and should never be used in combination with them. One should stop all other antidepressants and allow at least two weeks to elapse (five weeks for fluoxetine) prior to starting treatment with an MAOI. MAOIs should be discontinued at least 10 days before an elective surgery because of concerns with concurrent use with general anesthesia. MAOIs interact with some opioid analgesics that have serotonin reuptake inhibitor activity such as meperidine, tramadol, methadone, and dextromethorphan, increasing the risk of serotonin syndrome. MAOIs also interact with stimulants and over-the-counter sympathomimetic decongestants such as pseudoephedrine and phenylephrine; the combination may cause increased blood pressure and should be used with great caution.
- Patients taking MAOIs must be advised to not eat certain foods like certain cheeses, wine, and meats that have been aged or any food containing tyramine.

| Foods to Avoid | Foods Allowed |
|---|---|
| All matured or aged cheeses | Fresh cottage cheese, cream cheese, ricotta cheese, processed cheese slices, sour cream, yogurt, ice cream |
| Dried, aged, smoked, fermented, spoiled or improperly stored meat, poultry and fish | Fresh or processed meat, poultry and fish, properly stored pickled or smoked fish |
| Tap and unpasteurized beer | Canned or bottled beer and alcohol |
| Broad bean pods, fava beans | All other vegetables and beans |
| Marmite concentrated yeast extract | Brewer's and baker's yeast |
| Sauerkraut, kimchee | N/A |
| Banana peel | Banana pulp, other fruit |
| Soy sauce, tofu | Peanuts |

***Note:*** Adapted with permission from Grady MM, Stahl SM. Practical guide for prescribing MAOIs: debunking myths and removing barriers. CNS Spectrums. 2012;17(1):2-10.

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# Antidepressant Prescribing Practice Guidelines, Continued

**Atypical Antidepressant Warnings**

The following outline atypical antidepressant warnings apply to the following medications:

| Medication Type | Warning |
|---|---|
| Trazodone, Maprotiline, Nefazodone | • Do not take tricyclic antidepressants if you are also taking MAO Inhibitors (MAOIs).<br>• Use caution if you drink alcohol or take barbiturates while taking this medicine.<br>• Be careful if you have cardiovascular disease |
| Bupropion | • Use caution if you drink alcohol while taking this medicine.<br>• Use caution if you take Levodopa.<br>• Use caution if you have seizures or take medicines that raise your chance of having a seizure. |

**Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) - Warnings**

The following outline atypical antidepressant warnings apply to the following SNRI's:

| Medication Type | Warning |
|---|---|
| Duloxetine | • Do not take with MAO Inhibitors (MAOIs).<br>• Do not take if you have narrow-angle glaucoma.<br>• Do not use with Fluvoxamine.<br>• Use with care if you have liver or kidney problems. |
| Desvenlafaxine | • Do not take Desvenlafaxine if you have taken a MAOI medicine within the last 14 days.<br>• Tell your doctor if you have any health problems especially seizures, mania, bipolar disorder, and heart, liver or kidney problems. |

**Disclaimers**

- The Antidepressant Prescribing guidelines are intended to offer guidance for providers and increase the effectiveness and safety of antidepressant use. The guidelines are not intended to be comprehensive in scope. These Guidelines are not a substitute for sound clinical judgment and treatment decisions must incorporate the individual patent's clinical characteristics and circumstances.

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**Disclaimers**, continued

- **Documentation:**
  - When a medication is ordered for an indication NOT approved by the FDA, the prescribing physician shall document the following in the Physician note:
    1. Rationale for the use of the particular medication.
    2. Summary of past medications and response.
    3. Reasoning for choosing the particular medication being prescribed
       a. The specific target symptoms by which the treating physician is treating and using to assess whether or not the medication is effective.
       b. Follow up notes shall be written documenting efficacy, non-efficacy, side effects, and rationale to continue use or discontinue medication.

***Note:*** As guidelines can change the prescriber is advised to refer to the current prescribing FDA guidelines, indications, and warnings. The prescriber is advised to consult the FDA's pharmaceutical prescribing medication website. DBH's Medical Services Division will review these guidelines every twenty-four (24) months.

**Related Policy or Procedure**

DBH Standard Practice Manual:

- Sedative Hypnotics Prescribing Guidelines (MDS2037)
- Mood Stabilizer Prescribing Guidelines (MDS2038)
- Antipsychotic Treatment Practice Guidelines (MDS2039)

**Reference(s)**

Clinical Practice Guidelines for the management of Depression