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SAFER PRESCRIBING OF ANTIDEPRESSANT MEDICATION GUIDELINE

SCOPE: This Safer Prescribing of Antidepressant Medications Guideline is intended to offer antidepressant prescribing guidance for providers, clients and the interested general public to increase the effectiveness and safety of antidepressant use. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual.

INTRODUCTION: Antidepressant medications are prescribed for multiple conditions in mental health. They have a critical role in the treatment of major depressive disorder and other depressive disorders. Known as antidepressants, many of these medications are used to treat other mental disorders besides depression, including anxiety disorders, obsessive compulsive disorder, post-traumatic stress disorder and others. Although this class of medications is sometimes used in bipolar disorder, this treatment recommendation is complex and beyond the scope of this guideline. See introduction and treatment guidelines in the references and further reading section at the end of this document for suggested treatment algorithms for the use of these medications.

Antidepressant medications are often divided into families based upon mechanism of action or chemical structure: selective serotonin reuptake inhibitors (SSRIs) have their primary effect on modulating the neurotransmitter serotonin; serotonin norepinephrine reuptake inhibitors (SNRIs) modulate serotonin and norepinephrine; tricyclic antidepressants (TCAs) often have a chemical structure with three rings; monoamine oxidase inhibitors (MAOIs) inhibit the monoamine oxidase enzyme. There are other antidepressant medications both within these families as well as in other families with other mechanisms of action and chemical structures.

Antidepressants are primarily available in oral forms. One medication is available as a transdermal patch, one as a nasal spray and one is administered as a continuous IV infusion.

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 often include individualized treatment goal(s), client choice, history of past antidepressant medication trials, family history, side effect profile and other factors.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs):

Selective serotonin reuptake inhibitors, or SSRIs, work by inhibiting synaptic reuptake of serotonin in neurons, increasing serotonin availability and leading to downstream modulation of serotonin receptors. Vilazodone has also been identified as a partial agonist at the serotonergic 5-HT_{1A} receptor. Preliminary studies have suggested that this additional pharmacological property may impart enhanced benefit in treating anxiety symptoms compared with other SSRIs, but this has yet to be conclusively established in more robust clinical trials. 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 lowest effective dose (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. See Table 1 for more information about SSRIs.

SSRIs can take anywhere between 4-12 weeks to reach their full effect, with initial response likely in the first 2-6 weeks. 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.

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. See Appendix 4 for more information on antidepressant-related sexual dysfunction. SSRIs block serotonin transporter sites on platelets and osteocytes and are associated with increased risk of bleeding (particularly with NSAIDs/other antiplatelets or anticoagulants), bone resorption and hyponatremia.

TABLE 1: SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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 (IR); 12.5-62.5 (CR)	Sedating; Anticholinergic effects; Drug interactions; Short half-life
Sertraline	50-200 mg/day	Slightly activating; Fewer drug interactions
Vilazodone	10-40 mg/day	Nausea, anorexia, diarrhea

*See Appendix 1: Special considerations when using the SSRI citalopram

SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs):
Serotonin and norepinephrine reuptake inhibitors, or 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. Like SSRIs, SNRIs should be started at lower doses and titrated gradually. SNRIs should not be stopped abruptly due to discontinuation syndrome. See Table 2 for more information about SNRIs.

SNRIs, particularly duloxetine and venlafaxine, have been prescribed as non-opioid medications for chronic pain, and may be of particular benefit in clients with co-morbid depression and chronic pain. Duloxetine is FDA-approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.

Common side effects from SNRIs are diaphoresis, dizziness, headache, and nausea. Nausea tends to diminish over time and the medication may be better tolerated with food. Sexual dysfunction is common. Stimulation of norepinephrine receptors in the sympathetic nervous system leads to decrease in parasympathetic tone, leading to constipation, dry mouth, and urinary retention. Due to their serotonergic effect, SNRIs block serotonin transporter sites on platelets and osteocytes and have been associated with increased risk of bleeding, bone resorption and hyponatremia.

All SNRIs are associated with elevated blood pressure due to norepinephrine effects. Blood pressure should be evaluated prior to initiating SNRIs, and their use should be avoided in individuals with uncontrolled hypertension. Blood pressure should be monitored on a regular basis in individuals taking SNRIs. If necessary, antihypertensive treatment should be initiated or an alternative antidepressant agent should be used. (See *BHS Adult Blood Pressure Monitoring Guidelines* for more information).

TABLE 2: SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

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
Venlafaxine XR	75-225 mg/day	Sexual dysfunction, QTc prolongation; monitor blood pressure

TRICYCLIC ANTIDEPRESSANTS:

Tricyclic Antidepressants, or 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 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. TCAs should not be stopped abruptly due to discontinuation syndrome. Most TCAs are metabolized by the CYP450 2D6 and their levels can be altered by inducers/inhibitors of that enzyme.

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.

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 3 below for information about specific TCAs.

TABLE 3: TRICYCLIC ANTIDEPRESSANTS

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	150-300 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*	10-60 mg/day	Secondary

*Plasma level range is not well defined

MONOAMINE OXIDASE INHIBITORS:
Monoamine Oxidase Inhibitors, or MAOIs, irreversibly inhibit the monoamine oxidase enzymes, which are 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. See Table 5 below for names and dose ranges for MAOIs.

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.

As stated above, MAOIs inhibit the breakdown a tyramine which is a derivative of an amino acid found in aged and fermented foods. Consuming tyramine-containing foods while taking an MAOI can lead to dangerous increases in blood pressure and hypertensive crisis. See Table 4 below for details on dietary restrictions while taking on MAOI.

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.

TABLE 4: MAOI DIETARY RESTRICTIONS*

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	
Banana peel	Banana pulp, other fruit
Soy sauce, tofu	Peanuts

* 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.

TABLE 5: MONOAMINE OXIDASE INHIBITORS

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
Selegiline transdermal	6-12 mg/day	Transdermal patch- avoids first pass metabolism

NEFAZODONE AND TRAZODONE:
Nefazodone and trazodone weakly inhibit serotonin and norepinephrine reuptake, weakly antagonize alpha-1 receptors and are serotonin $5HT_2$ receptor antagonists. They are both FDA approved for the treatment of depression. Side effects include sedation, dry mouth, stomach upset and blurry vision.

Nefazodone has been associated with life-threatening hepatic failure and should not be used in anyone with active liver disease. If used, liver function tests should be monitored at baseline and every 3-6 months as clinically indicated. If aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels reach three times or greater the upper limit of normal, nefazodone should be discontinued. The dose range for nefazodone is 300-600 mg/day.

Trazodone is seldom used as an antidepressant due to its sedating effects. However, it is commonly used as a sleeping agent (refer to *BHS Non Sedative-Hypnotic Treatments of Insomnia Toolkit)*. It has the rare

potential to cause priapism, a painful, persistent and abnormal penile erection for which individuals should seek immediate emergency care. The dose range for trazodone is 25-100 mg at bedtime when used for sleep and 150-600 mg when used for depression.

BUPROPION:
Bupropion is a norepinephrine-dopamine reuptake inhibitor. It is commonly used for depression, smoking cessation and less commonly for Attention Deficit Hyperactivity Disorder. Bupropion can lower the seizure threshold and therefore is contraindicated in anyone who is prone to seizures, including individuals with a known seizure disorder, those with eating disorders or those withdrawing from alcohol or sedative-hypnotics. Similar to SSRIs, bupropion can take anywhere from 4-12 weeks for full antidepressant effect. Common side effects include insomnia, anxiety, headache and increase in sweating. It is less likely to cause sexual side effects compared to SSRIs, and may be used as augmentation to improve SSRI-related sexual dysfunction. See Table 6 for formulations and dosing information.

A combination of dextromethorphan (an uncompetitive *N*-methyl-*D*-aspartate [NMDA] receptor antagonist and sigma-1 receptor agonist) and bupropion was approved for the treatment of major depressive disorder in adults. Common side effects include dizziness, headache, diarrhea, somnolence, dry mouth, and increased sweating. There may be potential interactions with drugs that are substrates of CYP2D6; increased levels of those substrates may result from concomitant use of dextromethorphan-bupropion. See Table 6 for dosing information.

MIRTAZAPINE:
Mirtazapine works by inhibiting alpha$_2$ receptors which results in increased release of serotonin and norepinephrine. It also antagonizes serotonin receptors $5HT_2$, $5HT_3$, and the histamine receptor, H_1. It is used in the treatment of depressive disorders. Similar to SSRIs, mirtazapine can take 4-12 weeks for full antidepressant effect. It commonly causes increased appetite, weight gain and sedation and is thus useful when depressive symptoms include lack of appetite, weight loss and insomnia. It is less likely to cause sexual side effects compared to SSRIs. See Table 6 for dosing information. Lower doses tend to be more sedating than higher doses.

TABLE 6: BUPROPION AND MIRTAZAPINE

Generic Name	Dosage Range	Comments
Bupropion IR	100-450 mg/day	Three times daily; Single doses >150mg can decrease seizure threshold
Bupropion SR	150-400 mg/day	Twice daily
Bupropion XL	150-450 mg/day	Once daily
Dextromethorphan-Bupropion 45-105 mg	1-2 tablets daily (Dose not to exceed 2 tablets/day)	1 tablet once daily in the morning x3 days then 1 tablet twice daily (doses given at least 8 hours apart)
Mirtazapine	15-45 mg/day	Weight gain, increased appetite, sedating

VORTIOXETINE:
Vortioxetine is a newer antidepressant that works to inhibit reuptake of serotonin by inhibiting the 5HT transporter. Additionally, it acts as a $5HT_{1A}$ agonist, $5HT_{1B}$ partial agonist and $5HT_3$/$5HT_7$/$5HT_{1D}$ antagonist. It is approved for the treatment of depression in adults. It has also been studied for its effects on cognition. The dose range is 5-20mg/day. The dose should be adjusted for individuals who are CYP2D6 poor metabolizers or who are taking strong CYP2D6 inhibitors or inducers. Side effects are similar to those

of SSRIs/SNRIs and include nausea, dizziness, headache, diarrhea, dry mouth, constipation, vomiting, flatulence, pruritus, abnormal dreams and sexual dysfunction. Doses 15mg and above should be tapered down to 10mg for one week prior to stopping this medication in order to prevent discontinuation syndrome.

ESKETAMINE:
Esketamine is a non-competitive N-methyl D-aspartate receptor antagonist indicated for the treatment of treatment-resistant depression (TRD) in adults, in conjunction with an oral antidepressant. It is available only through a restricted REMS program because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. Prescribers, patients, pharmacies and health settings must all be registered within the REMS program to assure that all program requirements are met.

Esketamine is available as an intranasal spray. The dosing is described in Table 7 below. It must be administered under the direct supervision of a healthcare provider and patients must be observed for at least 2 hours after dosing to assure that they are clinically stable.

Potential adverse effects of esketamine include sedation, blood pressure changes, dissociation, perceptual changes, impaired attention and reaction speed and impaired ability to drive. It carries a risk of abuse and misuse and is a schedule III controlled substance. It can cause suicidal thoughts and behaviors in adolescents and young adults.

At this time, BHS is exploring the feasibility of using esketamine within the system, however, this medication is not yet available for administration at any BHS site per the REMS requirements. Providers wishing to access esketamine may refer individuals outside of BHS.

TABLE 7: ESKETAMINE DOSING

Phase	Frequency	Dose
Induction	Weeks 1 to 4: twice per week	Day 1: 56mg Subsequent doses: 56 or 84mg
Maintenance	Weeks 5 to 8: once per week Weeks 9 and after: once per week or once every 2 weeks*	56 or 84mg 56 or 84mg

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response

GABA-A MODULATORS:
Brexanolone is indicated for the treatment of postpartum depression in individuals 15 years and older. In 2019, it became the first drug approved for this specific disorder by the FDA. Its precise mechanism of action is not known. However, it is thought to fall in the class of GABA-A modulators as it is an aqueous formulation of the neuroactive steroid allopregnanolone which reduces neuronal excitability via GABA-A receptors. It is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires it to be administered as a continuous intravenous infusion at a certified health care facility under the close supervision of a health care provider. The infusion is given over 60 hours and is titrated to a maximum dose of 90mcg/kg/hour. Patients must be monitored for hypoxia and excessive sedation.

SPECIAL CONSIDERATIONS FOR USING ANTIDEPRESSANT MEDICATIONS IN CHILDREN AND ADOLESCENTS AND YOUNG ADULTS:
The use of antidepressant medication in children, adolescents and young adults merits special consideration and monitoring. See the related BHS guideline, *Safer Use of Psychotropic Medications in Children and Adolescents* for additional information about medication use in these specific age groups.

There has been some concern that the use of antidepressant medications themselves may induce suicidal behavior in youths. According to the National Institute of Mental Health (NIMH):

Following a thorough and comprehensive review of all the available published and unpublished controlled clinical trials of antidepressants in children and adolescents, the U.S. Food and Drug Administration (FDA) issued a black box label warning in October 2004 about an increased risk of suicidal thoughts or behavior (suicidality) in children and adolescents treated with SSRI antidepressant medications. In 2006, an advisory committee to the FDA recommended that the agency extend the warning to include young adults up to age 25.

More recently, results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested that the benefits of antidepressant medications likely outweigh their risks to children and adolescents with major depression and anxiety disorders. The study, partially funded by NIMH, was published in the April 18, 2007, issue of the Journal of the American Medical Association.

While the initial analyses demonstrated a doubling of the suicidality from ~2% in the control groups to the ~4% in the antidepressant groups, there were no completed suicides. Subsequent noncausal population associational studies demonstrated a temporal correlation between the release of the black box warning and decreasing antidepressant prescribing rates for depression (without concomitant increases in psychosocial intervention rates) and increasing suicide attempt rates. All this being said, the current standard of practice recognizes that generally the benefits outweigh the risks for antidepressant prescribing in depressed or anxious individuals 25 years old and younger but also there is a duty to warn prior to prescribing and monitor more closely for suicidality in this population especially during initiation of antidepressant pharmacotherapy and after dose increases.

There are six antidepressant medications FDA approved for the treatment of depression (MDD), generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD) in children and adolescents- see Table 8 for details. While it is recommended that these agents be used as first line, it is common in clinical practice to choose other agents, especially SSRIs or SNRIs based on clinical indicators (i.e. side effect profile, history of symptom response to a different agent, history of first degree family member or patient adverse reaction to these medications, history of other diagnoses that may contraindicate use of these agents).

A 2022 meta-analysis of RCT studies on the effect of antidepressants on the functioning and quality of life outcomes in children and adolescents with MDD showed positive effects on functioning in young people but not on quality of life measures. SSRIs, especially fluoxetine and escitalopram, as well as nefazodone improved functioning while TCAs did not.

TABLE 8: ANTIDEPRESSANTS WITH FDA APPROVAL FOR USE IN CHILDREN AND ADOLESCENTS

Generic Name	Dosage Range	Age (years)	Indication
Clomipramine	25-200mg/day (or 3mg/kg/day whichever is smaller)	10+	OCD
Duloxetine	30-120mg/day	7+	GAD
Escitalopram	5-20 mg/day	12+	MDD
Fluoxetine	10-60 mg/day	7+	MDD

			OCD
Fluvoxamine	25-300mg/day	8+	OCD
Sertraline	25-200mg/day	6+	OCD

†Note: Imipramine has an indication for enuresis in children six and older however it is not considered first line treatment and other agents should be tried prior to trying this medication.

Some young people respond to antidepressant medication after about two weeks, but for most, the full effect is not seen until four to six weeks or longer. During the first few weeks, the dose is usually increased gradually. For children, particular care should be given to start at the lowest possible dose and increase slowly unless the clinical symptoms or history indicate a different course. Children and families should be informed of the possible risks and side effects of medication and consent for medication must be signed by parents or guardians. Due to the need for more diligent safety observations regarding this black box warning, initial monitoring for children and adolescents starting antidepressant therapy is recommended by the FDA as follows in Table 9:

TABLE 9: FDA RECOMMENDED MONITORING PARAMETERS FOR CHILDREN AND ADOLESCENTS STARTING SSRI MEDICATION

Month 1	Patient seen once per week for the first four weeks. Some contacts may be by phone if deemed safe by prescriber. Telehealth appointments are reasonable if in-person visits are not an option and patient can tolerate them.
Month 2	Patient seen every 2 weeks. One contact may be by phone if determined safe by prescriber.
Month 3-12	Patient seen every 1-3 months if symptoms and dose stable. May be more frequent if clinically indicated.
Month 12-Beyond	After 12 months of medication treatment symptom re-assessment should be performed. If symptom free and no previous depressive episodes or extenuating clinical circumstances, consider possibility of medication taper if safe and clinically indicated.

SPECIAL CONSIDERATIONS FOR USING ANTIDEPRESSANT MEDICATIONS IN 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 in general due to diminished renal or hepatic function. In addition, older adults often have multiple medical comorbidities. As a result, they may be prescribed various medications, introducing the risk for drug interactions. The general approach is to initiate antidepressant therapy at a low dose and titrate to a therapeutic dose with careful monitoring.

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. These criteria recommend avoiding the use of TCAs (except doxepin when dosed <6mg/day) and paroxetine in older

adults due to the anticholinergic and sedating side effects when possible. Please refer to References and Further Reading section for additional details.

Older adults are at risk of developing hyponatremia, or low levels of sodium in the blood (<135 mEq/L), when using antidepressants. Symptoms of hyponatremia include increased thirst, weakness, lethargy, weight gain, headache and appetite loss. Rare but serious consequences include seizures, delirium and death. Mirtazapine and SSRIs (especially citalopram and escitalopram) are associated with the highest risk of hyponatremia compared to other antidepressants. Risk factors for hyponatremia include age 60+, female, low body weight (BMI <18.5), history of hyponatremia, concomitant use of other medications associated with hyponatremia, traumatic brain injury, malignancies, respiratory infections, multiple sclerosis and epilepsy. For mild, asymptomatic cases (Na >130 mEq/L) the offending medication dose should be reduced or gradually tapered off if clinically appropriate. For moderate and severe cases (Na <130 mEq/L or symptomatic) the offending agent should be immediately stopped and the individual should be medically treated. Full treatment recommendations are beyond the scope of this guideline. Baseline and periodic sodium monitoring may be considered for older adults with one or more risk factors for the development of hyponatremia when mirtazapine or SSRIs are used.

Several recent meta-analyses and cohort studies have demonstrated an association between SSRI use and bone loss/bone fractures in older adults. Serotonin receptors are located on all types of bone cells and may inhibit bone formation with chronic use. Other antidepressants may be implicated, but studies are lacking. A major confounding factor is that depression can increase the risk of fractures due to increased inflammation and cortisol, decreased gonadal steroids, behavioral risk factors like smoking and alcohol use, and less physical activity. If there are concerns about bone health, individuals should be referred for a DXA scan. Additionally, individuals should be counseled on ways to reduce osteoporosis such as performing regular weight bearing exercise, consume fruits and vegetables, ensure adequate dietary calcium and vitamin D, and avoid smoking and excess alcohol use.

SPECIAL CONSIDERATIONS FOR USING ANTIDEPRESSANT MEDICATIONS BEFORE AND DURING PREGNANCY:

The increased recognition of depression in pregnancy and post-partum periods as well as increased acceptance of mental health treatment in the general population necessitates the careful consideration for the use of antidepressants before, during and after pregnancy. Prospective RCTs cannot be conducted due to ethical concerns, so the breadth of data collected stems from observational cohort studies, many of which have large study populations from registry data collected over many years to generate the statistical power to identify small effect sizes for rare outcomes. A major bias of these studies is confounding by indication, recognizing that people who use antidepressants in pregnancy are different than those who do not. Therefore, decisions about antidepressant use should be individualized.

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: low birth weight, fetal growth retardation, pre-term delivery, increased risk of pre-eclampsia and increased risk of delivery complications. Women 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. Shared decision making between individuals and their providers is vital in the treatment of depression and anxiety disorders in individuals who may become pregnant. The decision of whether or not 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. The potential effects of antidepressants on fertility, pregnancy, and neonates are discussed below.

Effect on fertility: It is unknown whether most antidepressants can make it harder for an individual to become pregnant or whether they affect sperm quality or count. Fathers or sperm donors who take antidepressants are unlikely to increase risks of birth defects or pregnancy complications. See Table 10 for more information. Many antidepressants can contribute to sexual dysfunction which can make becoming pregnant more difficult. See Appendix 4 for more information on addressing antidepressant-induced sexual dysfunction.

Effect on risk of miscarriage: Some small studies have shown a slight increase in miscarriages for individuals taking certain antidepressants, however, most studies do not show an increased risk. Depression itself may increase the chance for a miscarriage which makes it hard to know if a medication, the condition it treats, or other factors are the cause of a miscarriage.

Teratogenic risk: 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. Recently published cohort studies suggest an association between venlafaxine and congenital cardiac malformations. Smaller studies on tricyclic antidepressants, bupropion, and mirtazapine have not shown increased risk of congenital malformations. All antidepressants that have been studied in pregnancy have been found to cross the placenta.

Pregnancy outcomes risk: 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. One cohort study found that TCA use during pregnancy was associated with an increased the risk of preeclampsia, and another study found an association between SNRI use and hypertensive disorders during pregnancy. The use of SSRIs during pregnancy does not appear to have an effect on weight gain during pregnancy or gestational diabetes.

Newborn Effects: 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. One systematic review found increased rates of neonatal seizures and hypoglycemia in newborns exposed to antidepressants in utero, although the absolute risk of these outcomes remains low (<1%). TCAs were associated with the highest rates of seizures and hypoglycemia. To date, studies following cohorts of children exposed to SSRIs or TCAs in utero as they grow older have not found associations with neurodevelopmental disorders or impacts on cognitive development, language or behavior.

SPECIAL CONSIDERATIONS FOR USING ANTIDEPRESSANT MEDICATIONS DURING BREASTFEEDING:

Antidepressants are considered relatively safe during breastfeeding. Data on SSRIs and TCAs suggest 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 woman responded well to a particular antidepressant in the past or during the course of her pregnancy, it would be reasonable to use that antidepressant while she is breastfeeding. See Table 10 for additional details regarding the use of antidepressants during pregnancy and lactation.

TABLE 10: ANTIDEPRESSANTS IN PREGNANCY AND LACTATION

Medication	Fertility Considerations	Pregnancy Considerations	Lactation Considerations
Bupropion	Unknown effects on ability to become pregnant or on sperm count/quality	Available data does not suggest risk of teratogenicity; no known associations with pregnancy complications	Doses of up to 300 mg daily produce low levels in breastmilk and are not expected to cause any adverse effects in most breastfed infants. Monitor infant for seizures and sedation if used. May reduce the amount of breastmilk produced in some individuals.
Escitalopram	Unknown effects on ability to become pregnant or on sperm count/quality	Available data does not suggest risk of teratogenicity; no known associations with pregnancy complications	Low levels found in breastmilk and has been detected in serum of some infants.
Desvenlafaxine/ Venlafaxine	Unknown effects on ability to become pregnant or on sperm count/quality	Desvenlafaxine is a major metabolite of venlafaxine. Venlafaxine has recently been associated with increased risk of cardiac malformations. Not preferred for first time treatment of MDD in females planning a pregnancy. If continued during pregnancy, fetal echocardiogram may be considered.	Present in breast milk. Monitor for excessive sedation and adequate weight gain if this drug is used during lactation.
Duloxetine	Unknown effects on ability to become pregnant or on sperm count/quality	Limited data	Limited data; low levels found in breastmilk. Not expected to cause any adverse effects in breastfed infants.
Fluoxetine	Unlikely to make it more difficult to become pregnant; may decrease sperm quality	Available data does not suggest risk of teratogenicity; no known associations with pregnancy complications	Higher levels found in breastmilk compared to other SSRIs; alternative treatments may be preferred
Fluvoxamine	Unknown effects on ability to become pregnant or on sperm count/quality	Less data compared to other SSRIs; If used, consider therapeutic drug monitoring in the 3rd trimester due to altered pharmacokinetics	Limited data; low levels found in breastmilk. Not expected to cause any adverse effects in breastfed infants.
Mirtazapine	Can increase	Limited data; no known	Low levels found in breast milk.

	prolactin levels which can make it harder to get pregnant; unknown effects on sperm	risk of congenital malformations	Not expected to cause any adverse effects in breastfed infants.
Paroxetine	Associated with increase prolactin levels which can make it harder to get pregnant; decreased sperm count in mice (no human studies)	Not recommended due to higher prevalence of malformations and neonatal complications	Low levels found in breast milk. One of the preferred antidepressants during breastfeeding
Sertraline	Unknown effects on ability to become pregnant or on sperm	Available data does not suggest risk of teratogenicity; no known associations with pregnancy complications	Low levels found in breast milk. One of the preferred antidepressants during breast feeding
Tricyclic antidepressants	Unknown effects on ability to become pregnant or on sperm count/quality	Do not seem to be associated with an increased risk of malformations. Not recommended as first-line depression treatment due to risk of neonatal complications.	Most are present in breastmilk at low levels. Imipramine and nortriptyline are considered best choices out of the TCAs for use during breastfeeding. Doxepin is not recommended for lactating women.

* MAOIs are not recommended in pregnancy due to insufficient data; there is minimal published information on their use during lactation
**Citalopram is not recommended due to general warnings of QT prolongation; Levomilnacipran, vilazodone and vortioxetine are not recommended in pregnancy due to insufficient data; there is minimal published information on their use during lactation

SPECIAL CONSIDERATIONS FOR RENAL AND HEPATIC IMPAIRMENT:
The metabolism of antidepressants may be compromised in individuals with renal or hepatic impairment. See Table 11 for general dose adjustment information. Refer to the package insert for additional details for each specific medication.

TABLE 11: RENAL AND HEPATIC IMPAIRMENT

Medication	Renal Impairment	Hepatic Impairment
Bupropion	GFR< 90 ml/min: Consider lower dose or giving less frequently	Child-Pugh A: Consider lower dose or giving less frequently Child-Pugh B/C: Max dose 75mg (IR), 100mg/day or 150mg every other day (SR), 150mg every other day (XL)
Citalopram	No dose adjustment	Max dose 20mg
Desvenlafaxine	CrCl 30-50ml/min: Max dose 50mg CrCl <30ml/min and ESRD: Max dose 25mg/day or 50mg every other day	Child-Pugh B/C: Max dose 100mg/day
Duloxetine	CrCl<30ml/min: Avoid use	Avoid use
Escitalopram	No dose adjustment	Max dose 10mg
Fluoxetine	No dose adjustment	Cirrhosis: administer lower dose or less

		frequent dosing interval (50% of normal dose in compensated cirrhosis without ascites)
Fluvoxamine	No dose adjustment	No dose adjustment (monitor closely)
Isocarboxazid	Avoid use in severe renal impairment	Avoid use
Levomilnacipran	CrCl 30-59ml/min: Max dose 80mg CrCl 15-29ml/min: Max dose 40mg ESRD: Avoid use	No dose adjustment
Mirtazapine	No dose adjustment	No dose adjustment
Nefazodone	No dose adjustment	Do not use in those with active liver disease or elevated baseline serum transaminases
Paroxetine	CrCl<30 mL/min: Max dose 40mg (IR), 50mg (ER)	Severe: Max dose 40mg (IR), 50mg (ER)
Phenelzine	Avoid use in severe renal impairment	Avoid use
Selegeline transdermal	No dose adjustment	No dose adjustment
Sertraline	No dose adjustment	Child-Pugh A: Reduce dose by 50% Child-Pugh B/C: Not recommended for use
Tranylcypromine	No dose adjustments, use caution	No dose adjustments, use caution
Tricyclic Antidepressants	No dose adjustments, use caution	No dose adjustments, use caution
Trazodone	No dose adjustment	No dose adjustment
Venlafaxine	CrCl<90ml/min: Consider dose reduction of 25-50%	Reduce dose by 50%
Vilazodone	No dose adjustment	No dose adjustment
Vortioxetine	No dose adjustment	No dose adjustment

*Child-Pugh classifications are used to assess the severity and prognosis of chronic liver disease. Child-Pugh A is the least severe, Child-Pugh B is moderately severe and Child Pugh C is the most severe; CrCl= creatinine clearance, used to measure kidney function; GFR= glomerular filtration rate, used to measure kidney function; ESRD= End stage renal disease

SEROTONIN SYNDROME:

Serotonin syndrome is a very rare though potentially life threating condition. It is estimated in a review of Veterans Health Administration records to have an incidence of 0.23%. All antidepressants, as well as numerous other medications (e.g. certain opioids, phentermine, lithium, fluconazole and others), plus some illicit drugs (cocaine, LSD, MDMA) can result in the condition, particularly when taken in combination. Sometimes called serotonin toxicity, the clinical presentation can range from mild symptoms (mild hypertension, tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus and hyperreflexia without increased temperature) to moderate (the above plus hyperthermia, hyperactive bowel sounds, horizontal ocular clonus, mild agitation, hypervigilance and pressured speech) to severe (all of the above, plus higher temperature, dramatic swings in pulse and blood pressure, delirium and muscle rigidity, death).

This condition usually becomes apparent within 24 hours of starting a new medication that affects serotonin, or after raising the dose of one currently being taken. Individuals who develop these symptoms should seek immediate emergency medical care. Treatment for serotonin syndrome is supportive. Treatment details are beyond the scope of this guideline.

WEIGHT GAIN AND METABOLIC RISKS ASSOCIATED WITH ANTIDEPRESSANT USE:

Antidepressant medications may lead to weight gain. There is increasing evidence that their use may also

be associated with the development of metabolic syndrome, a group of conditions associated with heart disease and diabetes. These conditions include:

- Hypertension (high blood pressure)
- Dyslipidemia (elevated cholesterol and triglycerides)
- Elevated blood glucose (high blood sugar)
- Weight gain

At this time there is no consensus on monitoring individuals taking antidepressant medications for conditions associated with metabolic syndrome. Providers should monitor clients as appropriate for each individual situation.

APPENDIX 1: SPECIAL CONSIDERATIONS WHEN USING THE SSRI CITALOPRAM

In 2011, the FDA updated the prescribing information for citalopram based on the risk of QT prolongation and potential to cause *torsades de pointes*. The use of citalopram is **not recommended** in individuals with the following characteristics:

- Congenital long QT syndrome
- Bradycardia (low heart rate)
- Hypokalemia (low potassium)
- Hypomagnesemia (low magnesium)
- Recent acute myocardial infarction (MI)
- Decompensated heart failure
- Taking other drugs that may prolong the QT interval.

ECG monitoring is recommended in those individuals if the use of citalopram is considered essential. If QTc is persistently > 500ms, FDA recommends discontinuation of citalopram. SFHN BHS recommends using an alternate SSRI in this population or ECG monitoring if citalopram is to be used.

The FDA recommends a **maximum dose of 20mg** for the following individuals: age >60 years, hepatic impairment, known CYP2C19 poor metabolizers, those taking CYP2C19 inhibitors. SFHN BHS recommends considering using no more than 20mg of citalopram in this population.

Individuals being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring.

APPENDIX 2: STRATEGIES FOR ADDRESSING TREATMENT RESISTANCE WHEN USING ANTIDEPRESSANT MEDICATIONS

MEDICATION ADHERENCE: Most antidepressants must be taken daily to be effective. Adherence to a medication regimen is challenging. Adherence difficulties are common and can significantly reduce the efficacy of antidepressant medication. Therefore, this should be carefully evaluated in all cases of less-than expected treatment response. Strategies to address this are varied and might include: weekly pill boxes or medi-sets, reminders by clients' significant others, and directly observed therapy. Strategies to address adherence should be individually customized for each client.

MAXIMIZING ANTIDEPRESSANT MEDICATION DOSE: Maximizing the antidepressant medication dose should be the first strategy employed for symptom reduction after it is determined that medication adherence is not a significant problem. Gradually increase the dose of the current medication to the maximum recommended dose or to the point where the client develops difficulty tolerating the medication, whichever comes first. This strategy should be considered for individuals who are able to tolerate their current antidepressant and have shown some response after a reasonable trial at the current dose.

SWITCHING ANTIDEPRESSANT MEDICATIONS: Switching should be considered in cases where individuals cannot tolerate their current antidepressant medication due to side effects, or when there is little to no response after a reasonable trial despite attempts to maximize the dose. Switching can be from one antidepressant medication to another in the same family or from an antidepressant in one family to one in another family. Sometimes during an antidepressant switch, the two medications should be cross-titrated, whereby the new antidepressant is added and the dose gradually raised while the old antidepressant dose is gradually tapered off. At other times, a wash-out period is necessary to prevent serotonin syndrome, as is the case when switching from a serotonergic agents (including SSRI, SNRI, TCAs) to MAOis. Cross titration is not necessary when switching within the family of SSRIs.

ANTIDEPRESSANT MEDICATION AUGMENTATION: Augmentation of an antidepressant is defined as adding a non-antidepressant medication to the treatment regimen of an individual taking an antidepressant medication with the goal of improving antidepressant response. There are several antidepressant augmentation medications that have demonstrated possible efficacy: lithium, L-triiodothyronine, buspirone, psychostimulants, and some second generation antipsychotic medications (see the related BHS publication, *Safer Prescribing of Antipsychotic Medications Guideline* for additional information on the use of antipsychotic medications). Current antipsychotic medications approved by the FDA as add on therapy in major depressive disorder include aripiprazole, brexpiprazole, and quetiapine ER. The combination medication, olanzapine/fluoxetine, is FDA approved for treatment resistant depression.

This strategy might be considered in individuals who have partially responded to the current antidepressant medication, have maximized its dose and in whom switching is contraindicated or not clinically appropriate.

ANTIDEPRESSANT COMBINATION THERAPY: Combining two antidepressant medications that each have a different mechanism of action is the final strategy to address treatment resistance. Some combination therapies that have evidence of efficacy include SSRIs/SNRIs with mirtazapine, and SSRIs/SNRIs with bupropion. Like with augmentation, this strategy might be considered in individuals who have partially responded to the current antidepressant medication, have maximized its dose, and in whom switching is contraindicated or not clinically appropriate.

APPENDIX 3: OTHER POTENTIAL THERAPIES

BRIGHT LIGHT THERAPY:

Bright light therapy has been shown to be effective in improving symptoms of major depressive disorder with seasonal pattern (also known as seasonal affective disorder). Bright light therapy is generally delivered via 10,000-lux commercial light boxes, placed 40-60 cm from the user's eyes, and administered in the early morning for at least 30 minutes. Treatment time may be increased in 15-minute increments to 60 minutes, based on response. Alternatively, treatment with a 2,500-lux light box is recommended for 1 to 2 hours. Light boxes should filter ultraviolet (UV) light, given that UV light is not necessary for the treatment effect and the potential harm caused by UV light.

Bright light therapy has also shown promising results in studies as an augmentation strategy with antidepressant treatment for non-seasonal major depressive disorder, as well as for the treatment of bipolar depression. In one study of adults with bipolar I or bipolar II disorder, who were experiencing a depressive episode, there was a significant antidepressant response in the group who received bright light therapy (7,000-lux bright white light, midday, titrated up to 60 minutes), and treatment was not associated with a switch into mania or hypomania.

CANNABIS: While there is some preliminary evidence of some possible positive effects on anxiety and depressive disorders, there is insufficient evidence to recommend the use of cannabinoid products such as cannabidiol (CBD) in the treatment of depressive or anxiety disorders. Cannabinoids can worsen psychiatric symptoms in some individuals. In general cannabinoids and cannabinoid metabolites inhibit CYP 450 enzymes and may interfere with metabolism of antidepressants. In particular, CBD inhibits the CYP2D6 hepatic enzyme and increase the blood levels of SSRIs and TCAs that are metabolized by this enzyme.

ELECTROCONVULSIVE THERAPY: Electroconvulsive therapy (ECT) is a procedure in which an electrical charge is applied to stimulate a seizure in the brain. It is an efficacious treatment for major depressive disorder, with 70-90% of individuals demonstrating improvement. Multiple practice guidelines recommend ECT for severe treatment resistant depression, including individuals who have psychotic or catatonic features, those who are acutely suicidal, and those who refuse food. ECT is contraindicated in those with recent myocardial infarction, active bleeding, or any cerebral lesions or hemorrhage. It is considered relatively safe during all trimesters of pregnancy. Side effects include confusion, impaired memory, headache and muscle aches; minimizing ECT dose and using unilateral electrode placement may minimize these side effects.

ECT is not currently available at any sites within the BHS system. UCSF Langley Porter Psychiatric Institute (LPPI), Alta Bates Medical Center, and Marin General Hospital have ECT services and may accept BHS client with Medicare. Clients with Medi-Cal or uninsured clients who need ECT will need a referral to the director of the private provider network (PPN). The current director of the PPN is Gloria Frederico, 415-255-3953, gloria.frederico@sfdph.org.

EXERCISE: Evidence exists for at least a modest improvement in symptoms of depression for people that engage in aerobic exercise or resistance training. The recommendation is at least 30 minutes of moderate exercise every day. Exercise for at least 180 minutes per week or more is moderately more effective than placebo, while exercise for 80 minutes per week or less has a similar effect to placebo. It is reasonable for an individual with mild depression to try exercise as an initial treatment for several weeks and then be re-evaluated. Physical activity can also be recommended as an adjunct to psychotherapy or medication(s).

HERBAL SUPPLEMENTS: In contrast to prescription medications, companies that manufacture dietary and herbal supplements do not have to seek FDA approval before putting their products on the market. They can state that their products address nutrient deficiencies, support health or are linked to body functions, as long as they include a disclaimer that the FDA has not evaluated the claim. Once an herbal supplement is on the market, the FDA is responsible for monitoring its safety. If a product is found to be unsafe, the FDA can take action against the company and may require the product to be removed from the market.

The regulations surrounding herbal supplements do not guarantee that they are effective or safe for anyone to use. Supplements should be reviewed for possible adverse effects and drug interactions before being cleared for patient use. Most insurance plans do not cover herbal supplements, so individuals may have to pay out-of-pocket if they wish to try them. Table 12 below describes some supplements with evidence for use in depressive disorders. Refer to *Safer Prescribing of Sedative-Hypnotics Guideline* for information on supplements with evidence for use in insomnia and anxiety disorders.

TABLE 12: DIETARY AND HERBAL SUPPLEMENTS

Supplement	Dose Range	Efficacy	Comments
Curcumin (*Curcuma longa*)	500-1000mg/day	Supportive evidence for monotherapy or adjunctive use in MDD; 1 meta-analysis (n= 531)	Potential adjuvant benefit in those with inflammatory disorders; no safety concerns identified
Lavender (*Lavandula officinalis*)	80-160 mg of essential oil per day (in the form of soft gels), or 500- 1500mg of dried flower (preferably in the form of standardized formulations), twice per day	3 small RCTs have shown supportive evidence for benefit in MDD as monotherapy or adjunctive treatment (n= 325)	No safety concerns identified; Standardized dosage forms advised over tea preparations
L-methylfolate (L-MTF)	15mg/day	Supportive evidence for use adjunctive to antidepressants; 1 meta-analysis (n= 966)	L-MTF is a "medical food" and requires a prescription; Folic acid has not shown benefit for depression; Consider checking for folic acid deficiencies
Omega-3 fatty acids: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)	1-2 grams/day EPA or EPA/DHA combination	Positive results seen in 1 meta-analysis and 5 RCTs (n= 1619) for use adjunctive to antidepressants	Adverse effects of gastrointestinal upset, diarrhea, constipation. Use caution with anticoagulants and prior to surgery.
Probiotics	1-10 billion units/day	Small but significant benefits for depression and anxiety when use as adjunct treatment; 1 meta-analysis (n= 302)	No evidence for benefit of prebiotics thus far; most data for *Lactobacillus* and *Bifidobacterium spp*. strains; more research is needed to identify which microbe(s)

			confer benefits
Saffron (*Crocus sativus*)	30mg given 1-3x/day depending on formulation	Supportive evidence for use as monotherapy or adjunctive to antidepressants; 1 meta-analysis (n= 620)	Extracts should be standardized and are quite expensive
S-Adenosyl Methionine (SAM-e)	Titrate up to 1600mg-3200mg/day	Weakly recommended- 1 RCT had positive results, 4 RCTs did not show benefit (n= 711)	Use caution in bipolar individuals- potential for causing mood cycling; Unstable compound- enteric coating and storage in blister packs under refrigeration may be advised; drug interactions with other antidepressants and dextromethorphan
St. John's Wort *(Hypericum perforatum)*	600- 1800 mg given 1-3x/day depending on the extract	Efficacious as monotherapy for MDD; 1 meta-analysis (n= 6993)	Drug interactions- use caution with oral contraceptives, warfarin protease inhibitors; Photosensitivity
Vitamin D	1500-4000 IU/day	Data is weak methodologically, but trends toward being supportive for adjunctive treatment of MDD; 1 meta-analysis and 2 RCTs (n= 7651)	Likely greater benefit in winter months; Unlikely to benefit those with sufficient skin exposure to sunlight or dietary intake
Zinc	25mg/day	Positive results in 1 meta-analysis (n= 124) for use adjunctive to antidepressants	May cause nausea on an empty stomach; certain chelations are more absorbable

KETAMINE: Ketamine acts primarily as an antagonist of the NMDA receptor. It is currently used in medical practice as an anesthetic agent and for acute post-operative pain management. It has also been used as a recreational drug of abuse as high doses produce a side effect of dissociation as well as visual and auditory hallucinations. In recent years there have been a number of studies indicating promising efficacy of intravenous infusions of ketamine in addressing symptoms of severe, treatment refractory depression. At this time, ketamine is not currently available within the BHS system for the treatment of depressive disorders.

TRANSCRANIAL MAGNETIC STIMULATION: Repetitive Transcranial Magnetic Stimulation (rTMS) is a somatic brain stimulation treatment effective and approved for treatment resistant depression in adults. An electromagnetic coil is non-invasively placed on the scalp above targeted cortical areas and a repetitive electromagnetic field is applied which alters neuronal activity without inducing seizures. Repeated treatments eventually alter network activity presumably contributing to the treatment's antidepressant effect. Side effects are generally mild to moderate and include headache, site scalp discomfort, tingling/spasm/twitching of facial muscles, and lightheadedness. These generally improve

shortly after an individual session and decrease over time with additional sessions. Serious side effects are rare and may include seizures, mania (in bipolar disorder), and hearing loss with inadequate ear protection during treatment. More study is needed to determine whether rTMS may have any long-term side effects. rTMS is available at UCSF to Medicare beneficiaries satisfying inclusion and exclusion criteria. A referral from a psychiatrist is necessary. For more information on the process, see https://psych.ucsf.edu/TMS.

VAGUS NERVE STIMULATION: Vagus nerve stimulation (VNS) is an FDA approved treatment for severe, recurrent unipolar or bipolar depression. It also has FDA approval for medication resistant epilepsy. VNS is thought to modulate the neural circuitry of depression by stimulating vagal afferent fibers in the neck, which carry impulses to the brain stem to target the locus ceruleus and dorsal raphe nucleus. The vagus stimulating device, an electrode, must be surgically implanted and wrapped around the left vagus nerve. Due to the location of the surgery, implantation carries several inherent risks and is cost-prohibitive for most. This treatment is not currently available within BHS. UCSF psychiatry does not offer VNS, and UCSF Neurology/Neurosurgery limits the availability of VNS for managing treatment-resistant epilepsy.

Several non-invasive, transcutaneous vagus nerve stimulating (tVNS) devices exist and purport to decrease depression, stress and anxiety as well as treat other conditions such as tinnitus, migraines and pain. These devices cost several hundred dollars, are not covered by insurance and do not have FDA approval for their use. Side effects are mild and include tingling and pain around the stimulation site as well as redness and itchiness. While several small studies show antidepressant effects from these devices, further studies are needed to validate their efficacy as well as determine optimal electrode types, stimulation sites/waveforms/intensity/frequency. BHS does not currently recommend the use of these devices.

APPENDIX 4: ANTIDEPRESSANT-RELATED SEXUAL DYSFUNCTION

Antidepressant-related sexual dysfunction, also called treatment emergent sexual dysfunction (TESD), can significantly impact quality of life, but frequently gets under-recognized. Estimates of its prevalence vary widely, for example, 25% to 73% in clients taking SSRIs and as much as 93% for those taking clomipramine.

As part of initiating and providing ongoing antidepressant therapy, providers should obtain a thorough sexual history and monitor for sexual dysfunction routinely at each visit. Asking specific questions about sexual interest, arousal, lubrication, erectile function, orgasm delay or anorgasmia is more likely to identify concerns compared to a broad general question about sexual dysfunction. A frank, non-judgmental approach is most effective.

Differentiating between sexual dysfunction due to depression, other physical/mental health issues versus TESD can be challenging. As much as possible, providers should try to clarify the cause(s) of sexual dysfunction.

Because TESD is common, the first approach is prevention. Whenever possible, providers should prescribe antidepressant therapy that has less likelihood to cause TESD. Medications like bupropion and mirtazapine have a low incidence of TESD. Serotonergic agents are more likely to cause dysfunction. However, if a serotonergic agent is deemed necessary, some evidence indicates fluvoxamine below a dose of 100mg/day, desvenlafaxine dosed under 100mg/day or vortioxetine between 10-15mg/day leads to less TESD.

Once identified, there are numerous strategies to address TESD. These approaches should be individually customized for each client. They are as follows:

1. Watchful waiting: Like with other antidepressant induced side effects (e.g. nausea, sedation), TESD may resolve with time. This can take months, which can be a significant drawback for some. It is estimated to be effective in only about 10% of people experiencing TESD.
2. Dose reduction or withdrawing antidepressant treatment: Decreasing the antidepressant dose by 50% can improve the sexual dysfunction in up to 75% of individuals. Stopping the medication will also resolve the problem. The main risk with this approach is recurrence of symptoms.
3. Medication augmentation: A variety of medications with varying mechanisms of action have been identified to treat TESD. These include buspirone, amantadine, dextroamphetamine, bupropion, mirtazapine, sildenafil, tadalafil, and aripiprazole. All of these can cause additional side effects. Few except for bupropion have robust evidence for their efficacy. See Table 13 for more information. Vaginal lubricants may be helpful for some women.
4. Treatment interruptions: This consists of withdrawing antidepressant therapy for two to three days before sexual activity and then restarting the medication following it. An alternative would be reducing the total antidepressant dose in half for two to three days prior to sexual activity. The main risks of this approach are recurrence of symptoms and the antidepressant withdrawal syndrome.
5. Switching antidepressant: In most cases, this would mean switching from a serotonergic agent to a non-serotonergic one. Bupropion and mirtazapine have the most evidence. One study suggests trazodone might be an effective alternative for an SSRI in individuals with TESD. Nefazodone could be considered though clients must be monitored for liver disease. Alternately, the partial serotonergic agents, desvenlafaxine or vortioxetine, as described above, might be considered.
6. Non-pharmacologic measures: Psychoeducation is critical for clients with depression and TESD as well as their sexual partner(s). Physical exercise may improve sexual desire and sexual satisfaction in women. It can improve depression in all clients.

TABLE 13: AUGMENTATION MEDICATIONS FOR TREATMENT EMERGENT SEXUAL DYSFUNCTION*

Drug	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
Amantadine	100mg daily x1 week then 100mg BID. Maximum 300mg/day	Limited human data – animal data suggest risk	Limited human data – potential toxicity	No dose adjustments	-CrCl 30-50 ml/min: max dose 100mg/day -CrCl 15-29 ml/min: max 100mg every other day -CrCl <15ml/min or hemodialysis: 200mg q7 days
Aripiprazole	2-20mg/day	Limited human data – animal data suggest risk	Drug and metabolite present in breast milk; lactation failure has been observed	No dose adjustments	No dose adjustments
Buspirone	5-60 mg/day	No adverse events seen in animal studies	Use not recommended	Severe: Use not recommended	Severe: Use not recommended

Drug	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
Amantadine	100mg daily x1 week then 100mg BID. Maximum 300mg/day	Limited human data – animal data suggest risk	Limited human data – potential toxicity	No dose adjustments	-CrCl 30-50 ml/min: max dose 100mg/day -CrCl 15-29 ml/min: max 100mg every other day -CrCl <15ml/min or hemodialysis: 200mg q7 days
Aripiprazole	2-20mg/day	Limited human data – animal data suggest risk	Drug and metabolite present in breast milk; lactation failure has been observed	No dose adjustments	No dose adjustments
Dextroamphetamine	5-40mg/day	Use not recommended	Use not recommended	No dose adjustments	No dose adjustments
Sildenafil	25-100mg taken 1 hour before sexual activity	NA	NA	Severe: Start at 25mg dose	CrCl <30 ml/min: Start at 25mg dose
Tadalafil	As needed: 5-20mg taken at least 30 minutes before sexual activity	NA	NA	Mild to moderate: max dose 10mg Severe: use not recommended	As needed: CrCl 30-50 ml/min: max dose 10mg not more frequently that every 48 hours; CrCl <30 ml/min: Max dose 5mg not more frequently than every 72 hours
	Once daily: 2.5mg/day				Once daily CrCl <30 ml/min: use not recommended

*This table contains off-label uses of medications
**Data from Briggs Drug in Pregnancy and Lactation

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