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VETERANS HEALTH ADMINISTRATION PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), CENTER FOR MEDICATION SAFETY (VAMedSAFE), OFFICE OF MENTAL HEALTH SERVICES (OMHS), & OFFICE OF THE NATIONAL DIRECTOR OF CARDIOLOGY

UPDATED GUIDANCE: CITALOPRAM HYDROBROMIDE (CELEXA®) AND DOSE-DEPENDENT QT INTERVAL PROLONGATION

On August 23, 2011, FDA issued a drug safety communication stating that citalopram **should no longer be used at doses greater than 40 mg per day** because it can cause abnormal changes in the electrical activity of the heart. And for the same safety concerns, 20 mg per day is the maximum recommended dose for patients with hepatic impairment, who are greater than 60 years of age, who are CYP 2C19 poor metabolizers, or who are taking concomitant cimetidine. A National PBM Bulletin was distributed on August 31, 2011, reiterating the FDA communication. Since that time, representatives from PBM, VAMedSAFE, OMHS, and the Office of the National Director of Cardiology have been in communication with FDA, and internal discussions on additional guidance can be provided.

Based on these discussions the following is recommended:

1) When possible, providers should refrain from prescribing citalopram in doses that exceed those in its label.
2) When possible, providers should attempt to reduce doses in patients whose current dose exceeds that in its label to those within its labeling.
3) VHA does recognize some patients require higher doses (off-label) of citalopram. In these cases the following should be observed:
    a. The provider has decided that the benefits outweigh the risk of harm (QTc prolongation, Torsade de Pointes) and has discussed this with the patient or caregiver.
    b. The above (a) has been documented in CPRS by the provider. (*a* and *b* apply to current and future patients.)
    c. For patients **already** on higher (off-label) doses of citalopram, an ECG will be done to document that the QTc is less than 500 msec. Prior to increasing citalopram to higher off-label doses, an ECG has been obtained and read prior to initiating the higher dose of citalopram. *(An ECG obtained within the previous 3months is acceptable.)*
    d. For **future** patients, an ECG is to be obtained and read prior to initiating the higher dose of citalopram. *(An ECG obtained within the previous 3months is acceptable.)*
    e. Serum potassium and magnesium concentrations have been obtained and abnormal concentrations corrected prior to initiating the higher dose of citalopram.
    f. That periodic ECG and labs will be obtained during the course of therapy and prior to any additional dose increases.
    g. If at any time the patient's QTc is greater than 500 msec *or if other risk factors for QTc prolongation are present (e.g., another drug that prolongs QTc is required)*, the dose will be reduced or citalopram will be discontinued.
    h. The patient's need for a higher dose should be assessed periodically and consider dose a reduction if appropriate.
4) Providers are to report adverse events to the VA's adverse drug event reporting surveillance system (VADERS).

VISN Mental Health leads are responsible for implementation and monitoring of this guidance within their VISNs.

ORIGINAL NATIONAL PBM BULLETIN *(issued August 31, 2011)*:

I. ISSUE [1]

The Food and Drug Administration (FDA) states that citalopram hydrobromide (Celexa®) **should no longer be used at doses greater than 40 mg per day** as higher doses have lead to abnormal changes in the electrical activity of the heart. Revised product labeling updates the new drug dosage and usage recommendations including information about the potential for QT interval prolongation and Torsade de Pointes.

II. BACKGROUND [1]

Citalopram causes dose-dependent QT interval prolongation and FDA no longer recommends using doses above 40 mg per day.

- Post-marketing reports submitted to FDA document cases of QT interval prolongation and Torsade de Pointes associated with branded and generic citalopram.
- FDA evaluated a randomized, multi-center, double-blind, placebo-controlled, crossover study, assessing the effects of 20-mg and 60-mg doses of Citalopram versus placebo on the QT interval in adults. Results showed maximum mean QT interval prolongations of 8.5, 12.6, and 18.5 milliseconds (ms) for 20 mg, 40 mg, and 60 mg citalopram, respectively.
- Other studies revealed no improvement in symptoms of depression at doses greater than 40 mg citalopram per day, although previous product labeling permitted use of 60 mg per day in certain patients. Typically, higher doses of selective serotonin reuptake inhibitors (SSRIs) are most commonly used for anxiety disorders where there is dose-response.

Risk factors for developing QT interval prolongation with the administration of citalopram include:

- Congestive heart failure
- Brady arrhythmias
- Hypokalemia
- Hypomagnesemia

A search in the VA Adverse Drug Event Reporting System (VA ADERS) from March 2006 until August 25, 2011 showed:

- Out of 2109 reports involving citalopram (as either the primary or secondary suspect drug) and 3165 symptoms, QT prolongation was documented in 4 cases with citalopram 20mg (1 mild, 2 moderate, 1 severe); 1 case with citalopram 40mg (moderate); 2 cases with citalopram 60mg (1 mild and 1 moderate); 1 case with citalopram 80mg (moderate); and 2 cases with unreported dosages (both severe).
- Dosages per day are not required in VA ADERS reporting, but for those that specified, citalopram >40mg/day (as either the primary or secondary suspect drug) was identified in 58 reports documenting 93 symptoms, out of which 3 involved QT prolongation per electrocardiogram (2 moderate and 1 mild in severity) as reported above.

III. PROVIDER RECOMMENDATIONS [1]

- Continue citalopram within new FDA recommended dosing ranges, i.e., dose reductions, and with new FDA monitoring parameters:
  - Monitor electrolyes as needed and correct for any hypokalemia or hypomagnesemia prior to citalopram therapy.
  - Perform electrocardiograms (ECG) in patients with congestive heart failure, bradyarrhythmias, or those taking concomitant medications that prolong the QT interval.
  - A maximum dose of 20 mg per day is recommended for the following patients due to increased blood levels of citalopram and consequent greater risk of QT interval prolongation as well as Torsade de Pointes :
    - Hepatic impairment,
    - Age greater than 60 years,
    - CYP 2C19 poor metabolizers, OR
    - Receiving concomitant cimetidine (Tagamet®).
  - Mild or moderate renal impairment - No dose adjustment needed.
- Consider an alternative agent in cases of:
  - Suboptimal response (despite confirmed compliance) with citalopram 40 mg per day or maximum tolerated dose (See Table 1).
- Consider augmentation if partial response on lower dose of citalopram (See VA/DoD Major Depressive Disorder Clinical Pracatice Guidelines (http://www.healthquality.va.gov/).
- Consider referral to a mental health specialist for psychotherapy or pharmacotherapy.
- Providers should continue to report any adverse events with citalopram by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Facilities should continue to report adverse events into VA ADERS and to the FDA (as appropriate).

TABLE 1. AGENTS INDICATED FOR MAJOR DEPRESSIVE DISORDER: DOSE RANGES AND POSSIBLE ADVERSE EVENTS [2-12]

CLASS/AGENT	DAILY DOSE RANGE (mg/day) FOR MAJOR DEPRESSIVE DISORDER	COMMON ADVERSE EVENTS	CYTOCHROME P450 INHIBITION	DRUG INTERACTIONS
SSRI Citalopram	20mg-40mg	*Citalopram:* Ejaculation disorder, erectile dysfunction	*Citalopram:* 2D6 (mild)	*Citalopram:* Drugs that prolong the QT interval; Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) – possible serotonergic syndrome; CNS drugs and alcohol – increased CNS depression; MAOIs– severe or fatal reactions (i.e., confusion, nausea, double vision, hypomania, hypertension, tremor, serotonin syndrome); Drugs that interfere with

				homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding; Cimetidine – increased citalopram concentration; Pimozide - increase in QTc interval; Sumatriptan – weakness, hyperreflexia, incoordination; Carbamazepine – may increase clearance of citalopram; TCAs – possible increase in TCA concentrations with symptoms of TCA toxicity.
Escitalopram	10mg-40mg	*Escitalopram:* Insomnia, ejaculation disorder, erectile dysfunction, nausea, increased sweating, fatigue, somnolence	*Escitalopram:* 2D6 (mild)	*Escitalopram:* Same as Citalopram (above).
Fluoxetine **Fluoxetine weekly**	20mg-80mg 90mg-90mg weekly	*Fluoxetine:* Nausea, anorexia, somnolence, tremor, sweating, ejaculation disorder, erectile dysfunction	*Fluoxetine:* 2C9/10, 2D6 (substantial); 2C19 (moderate); 1A2, 2B6, 3A4 (mild to moderate)	*Fluoxetine*: MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); CNS acting drugs – increased CNS depression; Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) – possible serotonergic syndrome; Tryptophan – agitation, restlessness, poor concentration, nausea; Drugs that interfere with homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding; Pimozide - increase in QTc interval; Thioridazine – fluoxetine-induced inhibition of metabolism → dose related prolongation of QT interval; Drugs metabolized by P450 CYP2D6 - fluoxetine inhibits CYP2D6 → increased drug concentrations (i.e., TCAs, antipsychotics, antiarrhythmics); TCAs – increased concentration of TCAs; Alprazolam – increased plasma concentrations and half-life of alprazolam →increased psychomotor impairment; Haloperidol - increased haloperidol concentrations → increased extrapyramidal side effects; Carbamazepine – increased concentration of carbamazepine → carbamazepine toxicity; Phenytoin – increased concentration of phenytoin and symptoms of phenytoin toxicity; Lithium – neurotoxicity → confusion, ataxia, dizziness, tremor, absence seizures; β-adrenergic blockers – increased metoprolol concrentration → bradycardia, heart block.
Paroxetine **Paroxetine CR**	20mg-50mg 25mg-62.5mg	*Paroxetine:* Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculation disorder, erectile dysfunction, other male genital disorders	*Paroxetine:* 2D6, 2B6 (substantial)	*Paroxetine*: MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) – possible serotonergic syndrome; Drugs that interfere with homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding; Cimetidine – increased paroxetine concentrations; Drugs metabolized by P450 CYP2D6 - paroxetine inhibits CYP2D6 → increased drug concentrations (i.e., TCAs, antipsychotics, antiarrhythmics); TCAs – increased concentration of TCAs; CNS acting drugs (i.e., alcohol) – increased CNS depression; Digoxin – levels decreased in the presence of paroxetine; Procyclidine – increased concentration → anticholinergic effects; Theophylline – elevated levels in treatment with paroxetine; fosamprenavir/ritonavir – decreased levels of paroxetine.
Sertraline	50mg-200mg	*Sertraline:* Ejaculation disorder, erectile dysfunction, increased sweating, somnolence, tremor, diarrhea, dyspepsia, nausea	*Sertraline:* 2D6 (dose-dependent); 2B6, 2C19 (moderate); 1A2, 3A4 (mild)	*Sertraline:* Drugs highly bound to plasma proteins – displacement of drugs bound to protein by sertraline or vice versa → increased concentrations of drugs highly bound to protein; Cimetidine – increased concentrations of sertraline; Pimozide - increase in QTc interval; CNS acting drugs (i.e., alcohol) – increased CNS depression; MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); Drugs metabolized by P450 CYP2D6 – sertraline inhibits CYP2D6 → increased drug concentrations (i.e., TCAs, antipsychotics, antiarrhythmics); Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) – possible serotonergic syndrome; Sumatriptan – weakness, hyperreflexia, incoordination; TCAs – possible increase in TCA concentrations with symptoms of TCA toxicity; Tolbutamide – decrease in tolbutamide clearance; Drugs that interfere with homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding.
SNRI **Duloxetine**	40-60mg	*Duloxetine:* Nausea, dry mouth, fatigue, somnolence,	*Duloxetine:* 2D6 (moderate)	*Duloxetine:* Inhibitors of CYP1A2 (fluvoxamine, cimetidine, quinolone antimicrobials)– increased duloxetine concentration; Inhibitors of CYP2D6 (fluoxetine, quinidine) – increased duloxetine concentration; Dual inhibition of CYP1A2 and CYP2D6 (fluxoxamine) - increased duloxetine concentration;

		constipation, dizziness, increased sweating		Drugs that interfere with homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding; Drugs that affect gastric acidity – enteric coating dissolves in acidic conditions; Drugs metabolized by CYP 1A2 (i.e., theophylline) – increase in theophylline concentration; Drugs metabolized by CYP 2D6 (i.e., desipramine) – increase in desipramine level; MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) – possible serotonergic syndrome; CNS acting drugs (i.e., alcohol) – increased CNS depression; Drugs highly bound to plasma proteins – displacement of drugs bound to protein by duloxetine or vice versa → increased concentrations of drugs highly bound to protein.
Venlafaxine IR **Venlafaxine XR**	75-375mg 75-225mg	*Venlafaxine:* Sexual dysfunction, nausea, dry mouth, anorexia, constipation, flatulence, dizziness, somnolence, abnormal dreams, insomnia, nervousness, tremor, sweating, abnormal vision, hypertension, vasodilatation	*Venlafaxine:* 2D6 (mild)	*Venlafaxine:* Cimetidine – Reduced clearance of venlafaxine; Haloperidol – decreased haloperidol clearance → increased haloperidol concentration, but no change in half-life; Drugs that interfere with homeostasis (NSAIDS, ASA, Warfarin) – increased bleeding; Drugs inhibited by P450 CYP2D6 – increased venlafaxine concentrations; Ketoconazole – increased concentrations of venlafaxine; Drugs inhibited by P450 CYP3A4 –increased venlafaxine concentrations; Metoprolol – increased metoprolol concentrations → bradycardia and possible heart block; Indinavir – decrease in indinavir concentration; MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); CNS acting drugs (i.e., alcohol) – increased CNS depression; Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) → serotonergic syndrome.
DNRI **Bupropion IR** **Bupropion SR** **Bupropion XR**	200-450mg 150-400mg 150-450mg	Tremor; dizziness, weight loss, headache, insomnia, agitation	2D6	Drugs metabolized by P450 CYP2D6 - bupropion inhibits CYP2D6 → increased drug concentrations (i.e., TCAs, SSRIs, antipsychotics, antiarrhythmics, beta-blockers); MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); Levodopa and Amantadine – increased incidence of adverse experiences; Drugs that lower seizure threshold (antipsychotics, antidepressants, theophylline, systemic steroids) → increased incidence of seizures; CNS acting drugs (i.e., alcohol) – increased CNS depression.
αSSA **Mirtazapine**	15-45mg	Weight gain, increased appetite, somnolence, dizziness	N/A	MAOIs – serious or fatal reactions → hyperthermia, rigidity, myoclonus, autonomic instability, fluctuation of vital signs, mental status changes (agitation progressing to delirium and coma); Serotonergic drugs (triptans, linezolid, lithium, tramadol, St. John's Wort) → serotonergic syndrome; Drugs that are metabolized by or inhibit CYP450 enzymes – Phenytoin and carbamazepine – increase mirtazepine clearance → reduce mirtazapine concentration; CYP enzyme inhibitors – increased mirtazapine concentration (cimetidine, ketoconazole, HIV protease inhibitors, azole antifungals,, erythromycin, nefazodone); CNS acting drugs (i.e., alcohol) – increased CNS depression; Warfarin – increased bleeding; Diazepam – impairment of motor skills.

IV. REFERENCES

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11. Wellbutrin® (Bupropion) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2010.
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ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who handle these medications (e.g.,* ***primary care providers, mental and behavioral health providers, and clinic staff****, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*