# Department of Veterans Affairs Pharmacy Benefits Management and Medical Advisory Panel Recommendation for Initial Choice of Selective Serotonin Reuptake Inhibitor (SSRI) in Treatment Naïve Veterans with Major Depression in the Primary Care Setting

*Selection of therapy for individual patients is ultimately based upon the provider's assessment of clinical circumstances and patient needs. These guidelines are not intended to interfere with clinical judgment, but rather to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.*
*This algorithm is NOT intended to be used for any other indication of the SSRIs including, but not limited to, Obsessive-Compulsive Disorder, Panic disorder, Posttraumatic Stress Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder, and/or Bulimia Nervosa.*
*This algorithm focuses on the pharmacotherapy for major depressive disorder in primary care patients. This does not imply that other non-pharmacological treatment including psychotherapy and rehabilitation are not indicated.*
*It is expected that significant, new clinical trials as well as new pharmacological agents will be forthcoming in this class of medications. Therefore, the following recommendations will be revised as new data become available.*

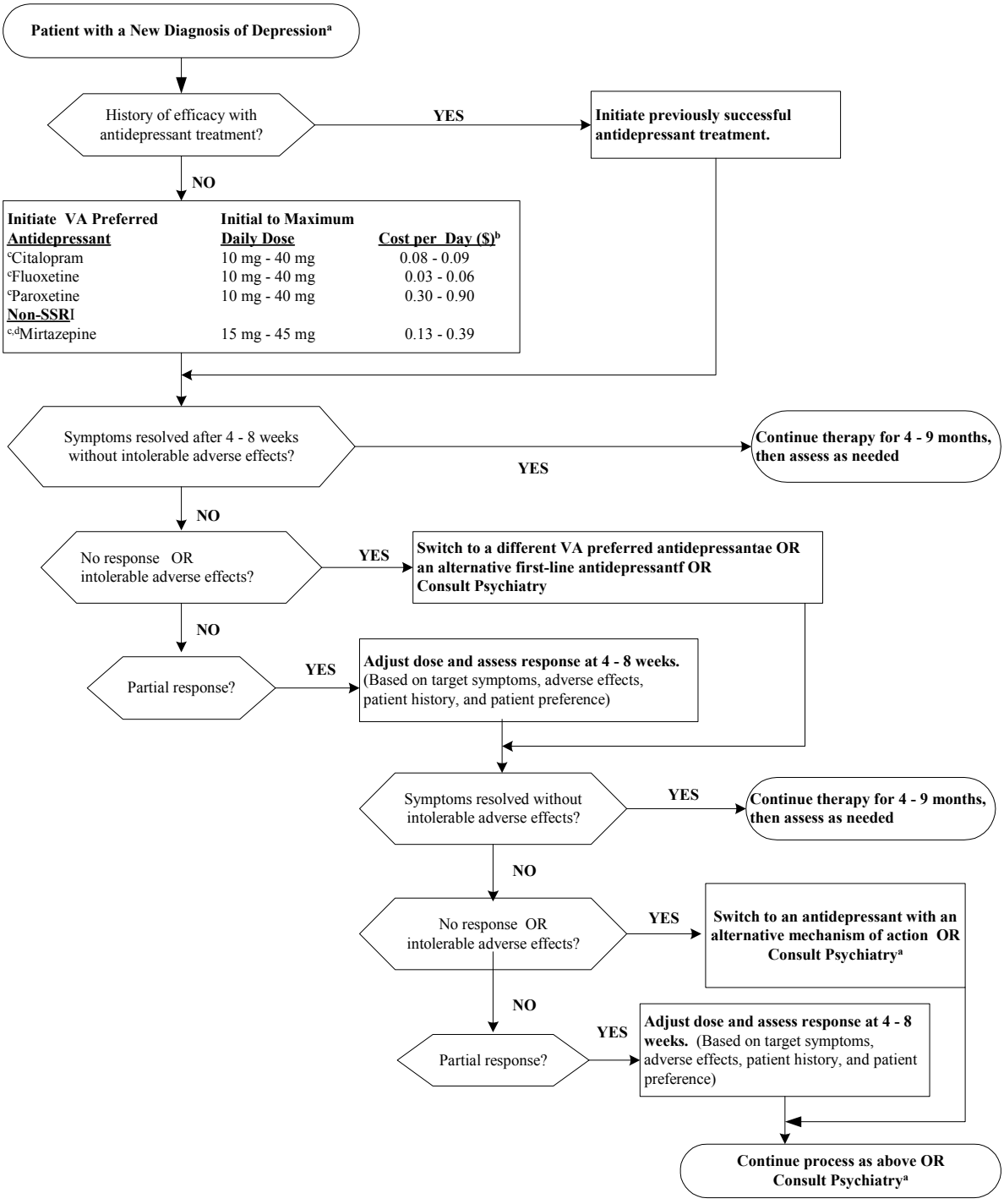
Consensus Goal:

1. To prioritize the selection of SSRI antidepressant medication for treatment naïve patients with the diagnosis of major depressive disorder in the primary care setting in accordance with the national guideline for The Pharmacologic Management of Major Depression in the Primary Care Setting, May 2000.

Consensus Summary:

1. SSRIs should be considered first-line antidepressants for most patients in the primary care setting because of their low toxicity relative to other available antidepressants. There is no consensus in the literature to support one SSRI to be superior in efficacy or safety to another; therefore, if a provider determines an SSRI is indicated, the least expensive agent should be initiated. At this time, the least costly SSRI medications are fluoxetine and citalopram.
2. Consideration of differences in pharmacodynamics, co-morbid medical conditions, and complexity of medication regimens should occur when initiating therapy with a specific SSRI. Fluoxetine and paroxetine exhibit non-linear pharmacokinetics, meaning dose escalation leads to disproportionate increases in blood concentrations, which may be critical for evaluating dose-related side effects such as anticholinergic effects and cardiovascular effects. For this reason, the dosage of fluoxetine and paroxetine in elderly patients should be reduced, as they are more susceptible to such side effects.
3. The VA currently has four SSRIs available as formulary items. These are citalopram, fluoxetine, paroxetine, and sertraline. Non-formulary SSRI antidepressants will not be discussed in these guidelines.
4. Patients newly diagnosed with depression should receive at least three clinical follow-up encounters in the twelve weeks following diagnosis. Of the three clinical follow-up encounters, at least one must be with a prescribing clinician, and no more than one may be by telephone.
5. Initial treatment with fluoxetine or paroxetine may not be preferred for patients in whom a potential for a clinically significant drug-drug interaction exists.

**Department of Veterans Affairs Antidepressant Algorithm for the Treatment of Patients with a New Diagnosis of Depression in the Primary Care Setting**




[a]Refer to Psychiatry at any point during the algorithm and should be considered if any of the following is present: psychotic features, assaultive behavior, suicidal or homicidal thoughts, worsening of symptoms despite treatment, treatment failure after 2 trials of medications in different drug classes, failure to respond to monotherapy or when higher than recommended doses are needed, clinically significant seasonal pattern depression, other comorbid psychiatric conditions, pregnancy, breastfeeding.

[b]Cost per day is based on the lowest VA price and reflects the cost of initial to maximum dose used to treat depression.

[c]Indicates available as a generic.

[d]Mirtazepine is not a SSRI, it increases central noradrenergic and serotonergic activity by antagonizing pre-synaptic alpha-1 receptors.

[e]Fluoxetine is recommended for patients with a history of inadequate response to other antidepressants who have not received a trial of fluoxetine.

[f]Alternative 1st line antidepressants include sertraline, generic bupropion imediate-release or SA, and venlafaxine immediate-release or XR. See Table 3.

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**Comparative Efficacy Trials:**
All antidepressants are considered equally effective for the treatment of uncomplicated unipolar depression and dysthymia. The efficacy of SSRIs has been shown in several clinical trials, meta-analyses, and systematic reviews to be similar to that of tricyclic antidepressants (TCAs).[1-7]

**Comparative Tolerability Trials:**
The improved tolerability of SSRIs, safety in overdose[8], and similar efficacy to TCAs has led these agents to become first-line treatment for uncomplicated unipolar depression and dysthymia. Several suggestions from open-label trials, anecdotal evidence, and trials funded through industry have been made regarding differences in tolerability profiles between specific SSRI agents; however, the incidence of these side effects are reportedly low and few studies have provided quantitative data to support these claims. Currently, there is no consensus that any specific SSRI is more or less tolerated than another, and the clinical significance of such subtle differences has been questioned.

***Fluoxetine and Agitation***
Caution should be taken when interpreting the results of trials due to small sample sizes and potential biases from selective reporting of this adverse effect. In a meta-analysis by Edwards and Anderson[3], the comparative tolerability of SSRIs was evaluated using 20 short-term comparative studies. None of the fluoxetine studies (17) reported an overall difference in treatment dropouts between fluoxetine and its active comparator (8 sertraline; 6 paroxetine; 2 citalopram; 1 fluvoxamine). Fluoxetine was documented to cause more agitation in three studies, however it only reached statistical significance in one study. There was an increased risk of agitation found for fluoxetine in six studies (N=1001) compared to other SSRIs (RR=1.57, 95% CI 1.04-2.37, p=0.031), however the overall rate of agitation was low (7.4%). When the authors examined other stimulatory adverse effects such as anxiety and nervousness (10 studies, N=1971), no statistical difference was found between fluoxetine and its comparators. The authors concluded only 3% more patients on fluoxetine experienced anxiety or agitation compared to other SSRIs, a difference likely to be of minor importance clinically.

***Paroxetine and Anticholinergic Adverse Effects***
Unique to paroxetine, this agent blocks muscarinic acetylcholine receptors to the same degree as the TCA imipramine.[9] Despite this characteristic, anticholinergic side effects most frequently occur with much higher doses than recommended for therapeutic efficacy.[10]

***Sexual Adverse Effects***
Several sexual adverse effects have been described with all SSRIs including orgasm dysfunction, decreased libido, and decreased erectile ability. The precise incidence of these effects are unknown, and higher incidences of sexual dysfunction have been reported in settings where patients were specifically questioned about sexual problems.[7,11,12] Currently, there is no conclusive evidence that the incidence of sexual dysfunction would influence the decision between individual SSRI agents.

**Comparative Pharmacokinetics:**
Differences exist in individual SSRIs with respect to pharmacokinetic parameters, however these differences may not be clinically significant. Each agent's half-life, linearity, age dependencies, and specific considerations in elimination should be considered.

***Half-Life***
Citalopram has a half-life of approximately 36hr at steady-state and is not affected by gender.[13]
Paroxetine's half-life is prolonged in the elderly ranging from 36 to 90 hours with a mean of 53 hours.[14]
Fluoxetine has a long half-life of approximately 1-4 days.[10,15,16] Its pharmacologically active metabolite (norfluoxetine), also exhibits a long half-life ranging between 7 and 15 days.[10,15,16] This long half-life can either be advantageous or disadvantageous. It is advantageous for those patients with poor adherence, since drug concentrations only decrease slightly with a missed dose, resulting in a decreased risk of withdrawal symptoms. Conversely, in the event of non-response or a drug-drug interaction, a much longer washout period would be necessary. For these reasons, the dosage of fluoxetine in elderly patients should be reduced.
Serum concentrations and the elimination half-life of paroxetine are prolonged in elderly patients.[17,18] Therefore reduced dosages should be used in the elderly population.

Sertraline exhibits a sex- and age-dependent half-life. In men, the half-life is approximately 30% shorter (22.4hr) than in females or the elderly (32.1-36.7hr).[19]

***Linearity of Pharmacokinetics***

Citalopram and sertraline exhibit linear pharmackinetics.[10]

Fluoxetine and paroxetine exhibit non-linear pharmacokinetics, meaning dose escalation leads to disproportionate increases in blood concentrations, which may be critical for evaluating dose-related side effects such as anticholinergic effects and cardiovascular effects.[10] For this reason, the dosage of fluoxetine in elderly patients should be reduced, as they are more susceptible to such side effects. This characteristic may be of less importance in determining therapeutic efficacy, as there is currently no conclusive evidence in the literature that plasma concentrations of SSRIs relate to clinical outcome.

***Elimination Characteristics***

Clearance and metabolism of citalopram in the elderly is significantly reduced, therefore lower doses are recommended in geriatric patients.[13,20] No dosage adjustment is necessary for hepatic cirrhosis.

Renal insufficiency does not significantly affect the elimination of fluoxetine, however hepatic cirrhosis significantly reduces its plasma clearance.[15]

Renal insufficiency does not significantly affect the elimination of paroxetine, however hepatic cirrhosis may reduce its plasma clearance.[21,22]

Renal insufficiency does not significantly affect the elimination of sertraline, however hepatic cirrhosis significantly reduces its plasma clearance.[23,24]

Table 1 compares various pharmacokinetic parameters of the SSRIs.

| SSRI | Half-life | Volume of Distribution (L/kg) | Linear Kinetics |
|---|---|---|---|
| Citalopram | 36 hr | 14-16 | Yes |
| Fluoxetine<br>Norfluoxetine | 1-4 days<br>7-15 days | 20-45 | No |
| Paroxetine | 20 hr | 3-12 | No |
| Sertraline | 26 hr | 20 | Yes |

Adapted from Hiemke C, Hartter S. Pharmacol Ther 2000;85:11-28.

**Drug-Drug Interaction Comparison:**

The most clinically significant difference between individual SSRIs is their potential for drug-drug interactions.[25-28] CYP450 drug-drug interactions as well as interactions due to protein binding with citalopram fail to show clinical significance.[29] Fluoxetine, norfluoxetine, and paroxetine are potent inhibitors of CYP2D6. Unless recognized and properly managed, combining these two SSRIs with potentially toxic medications that are substrates of CYP2D6, such as TCAs, antipsychotics, and Type 1C antiarrythmics could result in harm. Fluoxetine is also a moderate inhibitor of CYP 2C9 which explains the possibility of supratherapeutic phenytoin levels with concomitant administration.[30,31] Norfloxetine is a moderate inhibitor of CYP3A4 which explains reported interactions with carbamazepine resulting in carbamazepine toxicities[32], as well as the benzodiazepines. CYP450 drug-drug interactions with sertraline are of minor clinical importance.

Table 2 below compares SSRI drug interaction profiles.

| | Citalopram | Fluoxetine | Paroxetine | Sertraline |
|---|---|---|---|---|
| **P450 Inhibition*** | 2D6 (W)<br>3A4 (W)<br>1A2 (W) | **2D6 (P)**<br>2C9 (M)<br>2C19 (M)<br>3A4 (M)<br>1A2 (W) | **2D6 (P)**<br>2C9 (W)<br>2C19 (W)<br>3A4 (W)<br>1A2 (W) | 2C19 (M)<br>2C9 (W)<br>2D6 (W)<br>3A4 (W)<br>1A2 (W) |
| **Protein Binding** | 80% | 95% | 95% | 98% |

*Refer to Appendix 1 for specific drug-drug interactions, which was adapted from the VHA/DoD Clinical Practice Guideline for the Management of Major Depressive disorder in Adults

**P** = Potent inhibition, clinically significant

M = Moderate inhibition, may be clinically significant
W = Weak inhibition, not likely to be clinically significant

**Table 3. Direct Cost Comparison of First-line Antidepressants:**
**VA Preferred First-Line Antidepressants**

| | Citalopram | Fluoxetine | Paroxetine | Mirtazapine |
|---|---|---|---|---|
| **Daily Dosage Range** | 10 - 40 mg | 10 - 40 mg | 10 - 40 mg | 15 - 45 mg |
| **Cost per tab/cap/day*** | $0.08 – 0.09 | $0.03 - 0.06 | $0.30 - 0.90 | $0.13 - 0.39 |

*Costs estimated using tablet-splitting whenever possible; fluoxetine, paroxetine, and mirtazapine costs based on generic pricing

**Alternative First-Line Antidepressants**

| | Sertraline | Bupropion (generic) | Bupropion SA (generic) | Venlafaxine XR |
|---|---|---|---|---|
| **Daily Dosage Range** | 50 - 200 mg | 100 – 400 mg | 100 – 400 mg | 75 – 300 mg |
| **Cost per tab/cap/day*** | $1.20 - 2.48 | $0.14 – 0.64 | $0.69 – 2.18 | $1.73 – 3.78 |

**Appendix 1. SSRI Drug Interactions**

| PRECIPITANT DRUG | OBJECT DRUG | EFFECT | DESCRIPTION |
|---|---|---|---|
| Azole antifungals | *Citalopram* | increase | May increase plasma levels of citalopram |
| Fluoxetine<br>Sertraline | **Benzodiazepines** | increase | Clearance of BZDs is decreased. BZD levels and drug effects may increase |
| Fluoxetine | Buspirone | decrease & increase | Effects of buspirone may be decreased. Paradoxical worsening of OCD has occurred although combination has been used to potentiate antidepressant action of fluoxetine |
| Fluoxetine | *Carbamazepine* | increase | Serum CBZ levels may be increased which may result in toxicity |
| Carbamazepine | Citalopram | decrease | Carbamazepine may increase the clearance of citalopram |
| Cimetidine | Paroxetine<br>Citalopram | increase | Cimetidine increases concentration of paroxetine and citalopram |
| *Macrolides*<br>*Clarithromycin*<br>Erythromycin | Fluoxetine<br>Citalopram | increase | Clarithromycin added to fluoxetine has been reported to result in delirium. Erythromycin may increase citalopram plasma levels. Use caution when using SSRIs with macrolide antibiotics |
| Fluoxetine<br>Sertraline | Clozapine | increase | Elevated clozapine levels have occurred; closely monitor |
| Cyproheptadine | Fluoxetine<br>Paroxetine | decrease | Effect of fluoxetine may be decreased or reversed; combination has been used to treat fluoxetine induced sexual dysfunction |
| *Dextromethorphan* | Fluoxetine | increase | Hallucinations have occurred during concurrent use |
| Fluoxetine<br>Sertraline | Phenytoin | increase | Fluoxetine and sertraline may increase hydantoin levels |
| Omeprazole | Citalopram | increase | Omeprazole inhibits CYP2C19, therefore possibly reducing the clearance of citalopram |
| Fluoxetine | Haloperidol | increase | May increase serum concentrations; may impair memory and attention |
| All SSRIs | *Lithium* | increase | Although a case report suggests that lithium levels may be increased by fluoxetine, neurotoxicity is probably caused by a pharmacodynamic interaction. Lithium is often used to potentiate antidepressant response to SSRIs |
| Fluoxetine<br>Sertraline | Loratadine | increase | Plasma levels of the non-sedating antihistamine loratadine may be increased; effects on cardiac conduction are unknown. Terfenadine and astemizole have been withdrawn from the market |
| **MAOIs** | *All SSRIs* | increase | Serious sometimes fatal, reactions have occurred (e.g., rigidity, hyperthermia, myoclonus, autonomic instability, rapid vital sign fluctuations) as well as mental status changes (e.g., agitation, delirium, coma). |
| Citalopram | Metoprolol | increase | No clinically significant effects on blood pressure or heart rate. May lose cardioselectivity of metoprolol |
| Paroxetine | *Phenytoin* | decrease | Paroxetine decreases phenytoin levels |

| PRECIPITANT DRUG | OBJECT DRUG | EFFECT | DESCRIPTION |
|---|---|---|---|
| Phenytoin | Paroxetine | decrease | Phenytoin decreases half-life of paroxetine |
| *L-tryptophan* | SSRIs | increase | Concurrent use may result in CNS toxicity (e.g., headache; dizziness; agitation; aggressiveness; worsening OCD) and peripheral toxicity (e.g., nausea and vomiting) |
| *ALL SSRIs* | **TCAs** | increase | Plasma TCA levels may be increased which may result in toxicity. The combination may potentiate antidepressant response for SSRIs due to a pharmacodynamic interaction, but drug combination may warrant a psychiatry consult |
| Fluoxetine | *Valproate* | increase | Serum valproate levels may be increased which may result in toxicity |
| All SSRIs | *Warfarin* | increase | A pharmacodynamic interaction (increased bleeding diathesis in the face of unaltered PT) may occur with paroxetine. Concurrent use of sertraline and warfarin result in a relatively small increase in PT and delayed normalization of PT. Fluoxetine alone may increase bleeding time |
| All SSRIs | *Tramadol* | Seizures | A pharmcodynamic interaction increases the risk of seizures with the concurrent use of tramadol and SSRIs . |

SSRIs = selective serotonin reuptake inhibitors; BZDs = benzodiazepines; OCD= obsessive compulsive disorder; CBZ = carbamazepine; PT= prothrombin time; MAOIs = monoamine oxidase inhibitors; **Bold** = serious drug interaction; *Italics* = moderate; Regular = minor

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