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DEPRESSION IN THE ELDERLY: DRUG INTERACTIONS AND TOLERABILITY FOR FIRST-LINE PHARMACOTHERAPY

Erica M. Fernandez, Pharm.D. Candidate

The estimated rate of depression among elderly is 11% with virtually no difference between men and women.[1] With a growing number of pharmacotherapeutic options, choosing the right medication for the right person is increasingly complicated. In a survey by Kaufman et. al., 12% of the study's elderly population took 10 or more medications, while close to 50% were on at least five medications.[2] Additionally, careful selection of antidepressant therapy is needed as age-related physiological changes are responsible for many variations in the pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs.[3] The vulnerability of elderly patients to the side effects of centrally acting medications adds another challenge to therapy selection. The purpose of this review is to provide information on potential drug interactions and differences in tolerability with first line agents in the treatment of the depressed elderly patient.

AGING EFFECTS ON PK & PD PARAMETERS

Aging limits the ability of the body to continue peak functioning. The absorption, distribution, metabolism, and excretion of medications are dependent upon the function of these regulatory processes within the body. Changes such as decreased blood flow to the liver reduces first pass metabolism, thus affecting the conversion of pro-drugs (e.g. ACE inhibitors) or the metabolism of active ones (e.g. propranolol).[3] Changes in body composition affect the distribution of polar and nonpolar medications due to changes in fat content.[3] Glomerular filtration rate (GFR) is inversely proportional to age, which may necessitate a change in dose or frequency or substituting an alternative first-line treatment.[3]

Although less understood, PD implications of aging have been studied with several drugs. The results of these studies vary from drug to drug. With respect to psychotropic drugs occasionally used as adjuvant therapy in depression, elderly patients are often more vulnerable to experiencing delirium, arrhythmias, extrapyramidal side effects and orthostatic hypotension.[4] Increasing age is also associated with increased sensitivity to the CNS side effects of benzodiazepines.[5]

FIRST-LINE TREATMENT OPTIONS

Several classes of medications are currently available for treating elderly patients with depression. These classes include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs), nefazodone, mirtazapine, and buproprion. These drugs differ in tolerability profiles as well as degree of possible drug interactions.

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SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs are common first-line agents for depression in elderly patients.[5] In 2003, the majority of antidepressants (78%) prescribed to treat depression in elderly were SSRIs.[6] The mechanism by which SSRIs relieve depression remains unknown; serotonin levels increase upon first administration, but depression response takes several weeks.[7] Key differences between SSRIs include the drug's affinity for certain CYP enzymes and their side effect profiles.

Cytochrome P450 (CYP) Metabolism of SSRIs

Drugs with high affinity for cytochrome P450 isoenzymes have a higher potential for interactions with other drugs that are substrates for the same isoenzyme (Table 1). This interaction is more concerning for drugs that have a narrow therapeutic index, since a slight displacement in metabolism may cause subtherapeutic or toxic drug levels. Paroxetine has a high affinity for CYP2D6 and low affinity for CYP3A4.[8, 9] Paroxetine and fluoxetine are both potent inhibitors of CYP2D6 and mild inhibitors of CYP3A4.[10] Fluoxetine is also a moderate inhibitor CYP2C9, and a mild to moderate inhibitor of CYP2C19. In vitro and in vivo studies demonstrated fluoxetine's inhibition at CYP2D6 and CYP2C9 is partially due to its active metabolite (norfluoxetine), which is also responsible for its increased half life compared to other SSRIs.[11] Fluvoxamine potently inhibits CYP1A2 and 2C19, moderately inhibits CYP2C9 and 3A4, but only mildly inhibits 2D6.[10] Sertraline, citalopram, and escitalopram are often considered the SSRIs with the least interaction potential. None are potent inhibitors of any cytochrome P450 isoenzymes, however sertraline is a modestly more potent inhibitor at CYP2D6 than citalopram or escitalopram.[10] The effects of sertraline on CYP2D6 is likely dependent on dose and is smaller than paroxetine.[12] Citalopram is a racemic mixture of R and S enantiomers.[13] The inactive R-enantiomer of citalopram is metabolized by CYP2D6, and believed to be the contributing factor for mild CYP2D6 inhibition.[13] However, two studies have found significantly higher serum concentrations of drugs that are known substrates of CYP2D6 with administration of escitalopram (S-enantiomer).[13, 14]

Studied Drug-Drug Interactions with SSRIs

In vitro studies of isoenzyme potency do not always predict clinically significant interactions. However, isoenzyme potency is directly related to the severity of the drug-drug interaction in many cases. In the case of benzodiazepines, fluoxetine and fluvoxamine have both been found to impair the biotransformation of diazepam, alprazolam and bromazepam.[15-18] Although benzodiazepines have wide therapeutic indices, the combination of benzodiazepines with other centrally acting drugs, such as barbiturates, may lead to severe interactions. Studies show the potent inhibition of CYP2D6 by fluoxetine and paroxetine increase plasma concentrations of many first generation antipsychotics (e.g. haloperidol).[19] The adverse effect profiles include extrapyramidal symptoms, which develop more frequently at higher serum concentrations. The potent inhibition of CYP1A2 by fluvoxamine can lead to 3-fold higher clozapine plasma concentrations.[20] Tricyclic antidepressant (TCA) toxicity has been seen in patients soon after concomitant SSRI administration. Fluoxetine, paroxetine, and sertraline may increase TCA plasma concentrations by 40 to 300 percent.[10, 19]

Fluvoxamine can increase the INR of stable warfarin therapies by up to 65%.[21] This interaction is likely attributable to the potent inhibition of CYP2C19. Due to the ability of SSRIs to inhibit the metabolizing enzymes of β-blockers, coadministration of these agents may lead to elevated serum concentrations of β-blockers, resulting in decreased heart rate and blood pressure. For example, paroxetine inhibits CYP2D6 the major metabolizing enzyme of metoprolol. Likewise, fluvoxamine inhibits CYP1A2 which metabolizes propranolol.[22-23] Cases of increased edema, nausea, and flushing have been reported with verapamil and nifedipine when either was administrated with fluoxetine.[5] Several case reports document possible drug-drug interactions with fluvoxamine and theophylline or tacrine.[19] Multiple case reports associate paroxetine administration temporally with phenytoin intoxication.[19] SSRIs increase the risk of serotonin syndrome, thus monitoring of concomitant drug therapy affecting serotonin levels is vital. Drugs known to alter serotonin include MAOIs, meperidine, dextromethorphan, tramadol and possibly lithium.[19]

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs are newer than SSRI antidepressants, but current available data suggests there are no differences in efficacy between the classes.[24] Venlafaxine, desvenlafaxine, and duloxetine are SNRIs but have different CYP enzyme affinity. Venlafaxine is a weaker inhibitor of CYP2D6 than fluoxetine, fluvoxamine, and sertraline.[10] Studies show minimal effects of venlafaxine on CYP1A2, 2C9, and 3A4.[25] Duloxetine has been studied less frequently in the general population; however, it is a moderate inhibitor of 2D6.[26] In vitro studies show an insignificant inhibitory effect on CYP1A2, and no effects on 2C9, 2C19, and 3A4.[27] Patroneva et.

Table 1. CYP Inhibition and Common Isoenzyme Substrates

	CYTOCHROME P450 ISOENZYME				
Drug	**3A4**	**2D6**	**2C19**	**2C9**	**1A2**
Fluoxetine (Prozac®)	+/++	+++	+/++	++	+
Paroxetine (Paxil®)	+	+++	+	+	+
Fluvoxamine (Luvox®)	++	+	+++	++	+++
Sertraline (Zoloft®)	+	+/++	+	+	+
Citalopram (Celexa®)	0	+	0	0	0
Escitalopram (Lexapro®)	0	0/+	0	0	0
Venlafaxine (Effexor®)	0	0/+	0	0	0
Desvenlafaxine (Pristiq®)	0	0	0	0	0
Duloxetine (Cymbalta®)	0	++	0	0	0
Nefazodone (Serzone®)	++	0/+	-	-	-
Mirtazapine (Remeron®)	0	0	0	0	0
Buproprion (Wellbutrin®)	-	+++	-	-	-
Common Substrates*	alprazolam amlodipine atorvastatin clarithromycin dextromethorphan diazepam diltiazem lovastatin salmeterol simvastatin tacrolimus verapamil zolpidem	amitriptyline carvedilol codeine dextromethorphan flecainide haloperidol lidocaine metoprolol nebivolol ondansetron oxycodone propranolol tamoxifen tramadol	Carisoprodol clopidogrel indomethacin nelfinavir PPIs phenytoin propranolol warfarin	celecoxib glipizide glyburide ibuprofen losartan S-warfarin tolbutamide	amitriptyline naproxen ondansetron propranolol theophylline verapamil zileuton zolmitriptan

* = not a complete list; 0 = none-to-minimal inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = potent inhibition.
PPIs = Proton Pump Inhibitors.
Adapted from various sources.[13,19,35]

al. found duloxetine significantly elevated serum plasma levels of desipramine, a CYP2D6 substrate, while desvenlafaxine (Pristiq®), the active metabolite of venlafaxine, did not.[28] This finding suggests that the ability of venlafaxine to cause significant drug interactions with substrates of CYP2D6 is lower than duloxetine.

Studies evaluating the significant drug interactions with SNRIs in elderly are scarce in comparison with SSRIs. Despite the lack of evidence in elderly, many conclusions from interactions studied in healthy individuals have been extrapolated to this population. Venlafaxine interacts with CYP2D6 substrates, imipramine and risperidone, by decreasing their clearance and increasing serum drug concentrations.[29,30] Preskorn et. al. found duloxetine, but not escitalopram or sertraline, significantly increased the AUC of metoprolol, likely due to its inhibition of CYP2D6.[14]

Other Antidepressants

Other medications often used for depression in elderly include nefazodone, mirtazapine, and buproprion. Nefazodone is a 5HT-2 antagonist that inhibits serotonin and norepinephrine reuptake with weak α_1-adrenergic agonism.[31] Nefazodone is a potent inhibitor of CYP3A4,[31] and can increase the risk of QTc interval with terfenadine, nephrotoxicity with tacrolimus and cyclosporine, and incidents of rhabdomyolysis with simvastatin.[10] Other documented interactions include serum increases in benzodiazepines (alprazolam, triazolam, and midazolam), haloperidol, and clozapine.[10] Nefazodone also weakly inhibits CYP2D6.

Mirtazapine potently antagonizes the 5HT-2 receptors and histamine-1 (H_1) receptors.[31] Mirtazapine is a substrate of CYP3A4 with minimal effects on the CYP enzyme system.[31]

Buproprion produces its actions independent of serotonin; it blocks the reuptake of dopamine and norepinephrine, yet like all other antidepressants its specific mechanism of action is unknown.[32] In vitro studies and in vivo studies differ in conclusions of CYP2D6 inhibition by the active metabolite, hydroxybupropion. In vitro studies suggest the inhibition is minimal,[33] however an in vivo study showed buproprion as a potent CYP2D6 inhibitor when probed with dextramethorphan.[34] Strengthening the evidence of buproprion as a CYP2D6 inhibitor are case reports linking buproprion administration to nortriptyline and metoprolol toxicity.[10] Cytochrome P450 involvement is an important aspect to consider when choosing a first-line treatment option for depression in the elderly.

Side Effect Profiles

An additional characteristic of antidepressants factoring into the decision of first-line therapy is adverse effects. Sedation, fatigue, and drowsiness are some of the most common reasons of discontinuation of antidepressants (Table 2). Preskorn et. al. found the highest reported frequencies of drowsiness among SSRIs with paroxetine and fluvoxamine (14.3% and 17.2% incidence respectively) and fatigue most frequent with paroxetine (10.3% incidence).[36] The affinity of mirtazapine for H_1 receptors produces sedative effects, which may be more pronounced in the elderly. Conversely, reports of insomnia among SSRIs are highest with fluoxetine, citalopram and stertraline.[5] Specifically with SSRIs, a common cause of discontinuation is

Table 2. Comparison of Adverse Effects of Antidepressant Agents.

Adverse Event	# of randomized controlled trials	Comparisons	Mean Increase
Weight gain	7	Mirtazapine vs. fluoxetine, paroxetine, trazodone, venlafaxine	0.8-3.0 kg (mirtazapine)
			Mean Incidence
Sexual dysfunction	5	Paroxetine vs. fluoxetine, fluvoxamine, nefazodone, sertraline	21% vs. 5%
Diarrhea	15	Sertraline vs. buproprion, fluoxetine, mirtazapine, paroxetine, venlafaxine	42% vs. 25%
Nausea and vomiting	15	Venlafaxine vs. SSRIs as a class	33% vs. 22%

Adapted from Simon, G.[37]

nausea with a 15-40% occurrence in patients starting therapy.[5] This adverse effect may be due to the anticholinergic properties of some SSRIs, and can potentially dissipate as the sensitization of 5-HT receptors builds.[5] Both citalopram and escitalopram are associated with less nausea.[5] Alpha 1-adronergic blockade by nefazodone may lead to orthostatic hypotension, thus increasing the risk for falls among elderly patients.[10] Commonly prescribed BPH medications may potentiate this adverse effect. With respect to SSRIs, dizziness in patients with late-life depression is reported very often with paroxetine and sertraline.[5] Not all side effects are created equal; some may be therapeutic for a side effect of another medication. For example, a patient with insomnia caused by levothyroxine may be prescribed mirtazapine in place of a traditional SSRI to aid in sleep. Additionally, patients suffering from constipation regularly may benefit from an agent commonly associated with diarrhea (i.e. sertraline).

SUMMARY

The number of medications available for first-line treatment of depression in elderly patients is considerable. Because of the chronic nature of the disease and the delay in treatment response, starting doses should be lower and titration schedules less aggressive in this population regardless of the choice of antidepressant. The key is choosing medications on a case by case basis. Carefully examine the depressed patient's current medication regimen for possible drug-drug interactions. Consider past medical history and progression of current disease states as predictors of future medications which may interact with the antidepressant. When antidepressant treatment is necessary the common adverse effects of the selected antidepressant should be opposite of side effects that are idiopathically present and/or the result of other medications the depressed patient is taking in an attempt to neutralize patient discomfort.

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