Pharmacokinetic Considerations
of Antidepressant Use in the Elderly

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The elderly can be more difficult to treat with antidepressants than are young adults. Older patients take more medications, which increases the potential for drug interactions. Their altered physiology results in widely variable plasma drug concentrations from standard doses. Pharmacokinetic and pharmacodynamic changes in this population may predispose patients to experience an increased number of adverse events. The newer antidepressants have been studied for pharmacokinetic changes in the elderly compared with younger volunteers. Most antidepressants show some changes, including slower metabolic clearance and an extended elimination half-life, although the changes described are not uniform between drugs. Recommended initial doses are lower for the elderly for all antidepressants, although optimal doses may not differ from those for younger patients once dosing is individualized. *(J Clin Psychiatry 1999;60[suppl 20]:38–44)*

Aging is a major source of variability in drug response. At major transitions in the life span, the efficiency of the processes controlling drug absorption, distribution, metabolism, and elimination undergoes substantial change.[1] Cytochrome P450 enzymes are present in the fetal liver, some unique to this period, and the ability to glucuronidate drugs rapidly matures shortly after birth. Throughout the neonatal and early childhood periods, the activity of major drug metabolizing enzymes increases dramatically.[2,3] From late adolescence through early adulthood, relative stability exists. Roughly from an age of 40 years onward, changes in body composition, renal function, cardiac output, and other physiologic processes begin to accelerate with the result of an age-related increase in the variability of drug disposition and response and an overall gradual diminution in the rate of drug elimination.

Drugs that have been developed as antidepressants are now used commonly throughout the life cycle for a variety of indications. Antidepressants are most frequently developed for young adults, for whom the major components of drug disposition are most constant. Dosage recommendations developed for this population may be suitable for the majority of adults who receive the drug; however, modifications in the frequency of dosing or the total daily dose administered may be required to achieve optimal pharmacotherapy in the elderly patient (aged 60 years and older).

The starting dose of an antidepressant for the elderly patient should be lower compared with the initial dose used to treat a young adult. Part of the reasoning that supports this commonly accepted generalization relates to well-recognized changes in the elderly in the disposition of drugs. In general, the elderly are more difficult to treat safely. Pharmacokinetic changes that accompany aging result in higher and more variable plasma drug concentrations.[4] Elderly patients are more sensitive to a given drug concentration. The elderly frequently take multiple medications. Finally, homeostatic reserve may be compromised in the elderly patient, leading to more fragility in the tolerance to adverse events.

This review will highlight some of the recognized changes associated with advanced age in the ability to eliminate drugs. A summary is provided of the current state of knowledge of antidepressant pharmacokinetics in the elderly. The clinical implications for dosing antidepressants in the elderly are discussed.

PHYSIOLOGIC BASIS FOR
ALTERED ANTIDEPRESSANT DISPOSITION

The fundamental change in elderly patients is a decreased capacity for adaptation, which applies to virtually all organs and systems. Table 1 lists some changes in physiologic characteristics that have consequences for drug disposition. Many changes result in a slowed or impaired drug elimination with the consequence of increased plasma concentration of drugs. In addition, with aging there is a loss of lean body mass (primarily muscle) and a corresponding gain in the proportion of adipose tissue. In women, this

Table 1. Physiologic Changes in the Elderly Associated With Altered Pharmacokinetics

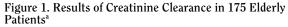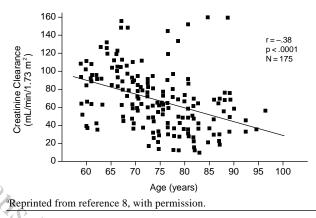| Organ System	Change	Pharmacokinetic Consequences
Gastrointestinal tract	Decreased intestinal and splanchnic blood flow	Decreased rate of drug absorption and possible reduced bioavailability
Circulatory	Decreased concentration of plasma albumin and increased α_1-acid glycoprotein	Increased or decreased free concentration of drugs in plasma
Kidney	Decreased glomerular filtration rate	Decreased renal clearance of drugs and increased plasma concentration
Muscle	Decreased lean body mass and increased adipose tissue	Altered volume of distribution of some drugs leading to increased elimination half-life
Liver	Decreased activity and/or amount of drug-metabolizing enzymes; decreased hepatic blood flow	Decreased hepatic clearance of drugs and increased plasma concentration

average increase in the proportion of body fat is from an average of 33% in 20-year-olds to 48% in those older than 70 years, whereas the corresponding change in men is from 18% to 36%.[5] This change in body composition will result in proportionate increases in the volume of distribution for lipid-soluble drugs (most psychotropics except lithium, lorazepam, and oxazepam). The half-lives for these medications will also increase, since half-life is directly proportionate to volume of distribution. Despite the age-associated increased proportion of body fat, overall body weight begins to decline after age 50, so that drug doses normalized to body weight may be higher in elderly patients who receive the same daily dose as younger adults. Thus, a need for reduced dosage of drugs should be anticipated in the elderly population.

Decreased blood flow to a number of areas, including the gastrointestinal tract, liver, and kidneys, results in altered passage of drugs. Changes that may affect the rate and/or completeness of oral drug absorption include decreased gastric acid output, slowed gastrointestinal motility, and decreased splanchnic blood flow. For nutrients such as vitamins and minerals, which may be absorbed by active transport, absorption may be lessened. For psychoactive drugs with high lipid solubility, absorption depends largely on passive diffusion across a concentration gradient, and total absorption may be less affected. Generalizations about altered bioavailability of drugs in the elderly are difficult to substantiate with experimental data. Observed changes have not shown consistent trends toward impairment.

Drug distribution is likely to be more variable in the elderly because of decreased concentration of plasma albumin. Plasma protein binding of acidic drugs is diminished when albumin concentration drops. This may contribute to the decreased clearance of diazepam in old age.[6] However, the plasma concentration of α_1-acid glycoprotein may be increased in the elderly population and in persons with depression.[7] This effect can lead to a diminished free concentration of basic drugs, including many antidepressants, whose plasma protein binding is largely dependent on α_1-acid glycoprotein concentration.

As mentioned above, body weight may decrease with age, especially in the very elderly (aged 85 years and

Figure 1. Results of Creatinine Clearance in 175 Elderly Patients[a]

[a]Reprinted from reference 8, with permission.

older) and frail elderly. Decreased lean body mass with increased adipose tissue stores is a recognized accompaniment of aging. Loss of muscle mass may lead to increased volume of distribution of lipid-soluble drugs, especially in women. Because elimination half-life is partly a function of the extent of distribution, these effects may lead to slower drug elimination apart from any change in hepatic or renal clearance of administered drugs.

Renal function steadily diminishes with aging. Renal blood flow, diminished glomerular filtration rate, loss of glomeruli in the renal cortex, and diminished tubular secretory capacity lead to impaired renal function in the elderly. Figure 1 shows the result of determining creatinine clearance in 175 elderly patients.[8] There is a progressive decline in creatinine clearance values associated with aging. However, considerable variability exists. For example, some 90-year-old patients appear to have a creatinine clearance as well maintained as patients 60 years of age. However, a decline in renal function may be masked by a decreased production of creatinine in persons with lower muscle mass.

The progressive decline in renal function with age will result in lower elimination of drugs that are partially or completely renally cleared. In this last category of drugs are 2 mood stabilizers, lithium and gabapentin. The results
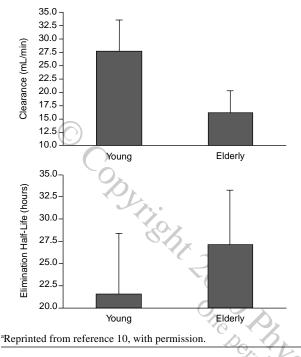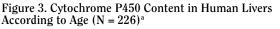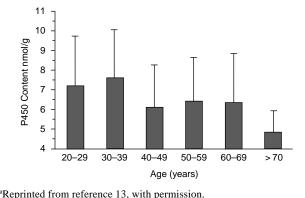
Figure 2. Lithium Clearance and Half-Life in Young and Elderly Populations[a]

[a]Reprinted from reference 10, with permission.

Figure 3. Cytochrome P450 Content in Human Livers According to Age (N = 226)[a]

[a]Reprinted from reference 13, with permission.

of a comparison of the disposition of lithium in the elderly with that in a younger population are shown in Figure 2.[10] The elderly subjects have reduced clearance and a longer elimination half-life. These changes mean that lithium will require a longer time to reach a steady-state concentration in the body upon chronic dosing, and the absolute steady-state concentration will be higher for a given daily dose in the elderly population.

The newer antidepressants, including the selective serotonin reuptake inhibitors, bupropion, nefazodone, mirtazapine, and venlafaxine, are all primarily eliminated by oxidative metabolism via the cytochrome P450 enzymes.[11] The effects of aging on the cytochrome P450 system and other enzymes that metabolize psychoactive drugs are incompletely investigated. It has been assumed that liver drug metabolism decreases with age in humans as it does in animals.[4] When antipyrine is used as a general marker for P450 oxidative capacity, its metabolism declines over time.[12] This is supported by recent in vivo evidence of cytochrome P450 measurements in 226 subjects who underwent liver biopsies.[13] The results are shown in Figure 3. Cytochrome P450 content declined in the fourth decade of life, remained unaltered during the next 2 decades up to 69 years, and then declined again in elderly subjects older than 70 years of age.

Data are available to address age-related changes in some of the cytochrome P450 (CYP) isoenzymes. Current knowledge is summarized in Table 2. CYP2D6 and CYP3A4 are the most important enzymes from the stand-point of the number of currently marketed drugs that are substrates for P450 enzymes. The isoenzyme CYP2D6 constitutes only about 1.5% of the total P450 content of the liver,[21] but is specifically responsible for the metabolism of 25% of all known drugs,[22,23] including the hydroxylation of several antidepressants (paroxetine, nortriptyline, and venlafaxine) and antipsychotics (perphenazine and risperidone). In our study of CYP2D6 phenotyping in healthy, unmedicated, older volunteers, we did not find an age-associated decline in CYP2D6 activity.[8] In contrast to CYP2D6, CYP2C19 is a polymorphic enzyme that may be subject to age-associated metabolic differences. This polymorphic enzyme catalyzes the metabolism of clomipramine and citalopram, antidepressants for which age-related decrements in demethylation have been shown.[16,24] Isoenzyme-specific effects of age and/or illness would be expected to modify the incidence of poor metabolizers, which occurs in 3% of whites, 15% to 25% of Asians, and 6% of some African populations.[25]

Approximately 30% of the P450 content of the liver is composed of CYP3A4 enzyme.[21] Together, CYP3A4 and CYP2D6 participate in the metabolism of an estimated 80% of currently used drugs.[22,23] Data on age-associated changes in CYP3A4 are confounded by gender differences and complicated by substantial presence of intestinal CYP3A4. Thus, using the demethylation of intravenously administered radiolabeled erythromycin as an index of hepatic CYP3A4 activity, Hunt et al. found elderly volunteers to have similar values as those aged 20 to 60 years.[2] Nonetheless, there is evidence that CYP3A4 activity is greater in younger women than men and postmenopausal women. These gender- and age-related pharmacokinetic differences have been demonstrated in studies of the CYP3A4 substrates erythromycin, prednisolone, tirilazad, verapamil, alfentanil,[5] diazepam (partial 3A4 substrate), alprazolam, and nifedipine.[19,20] Nefazodone levels, for example, have been reported to be 50% higher in older women when compared with those in younger subjects and older men.[26]

Table 2. Some Cytochrome P450 (CYP) Enzymes Involved in Drug Metabolism and the Effect of Age[a]

CYP	In Vitro Data	In Vivo Data	References
Total P450	Liver biopsy data show slight fall in content after 40 years and more substantial reduction after 70 years	Antipyrine clearance decreased with age	Vestal et al,[12] Sotaniemi et al[13]
1A2	NA	Caffeine, theophylline clearance decreased	Loi et al[14]
2A6	NA	Probably no reduction in warfarin clearance	Wynne et al[15]
2C9/19	NA	Stereoselective metabolism of citalopram enantiomers differed from younger subjects	Kunik et al,[16] Foglia et al[17]
2D6	No change	Minimal change in debrisoquine metabolic ratio with aging	Pollock et al,[8] May et al[9]
2E1	NA	NA	
3A4	Microsomal activities not altered	Clearance reduced of erythromycin, nifedipine, and alprazolam	Schmucker et al,[3] Robertson et al,[18] Miglioli et al,[19] Hunt et al[20]

[a]Abbreviation: NA = not available, more data are needed.

Nonetheless, for sertraline, which is also a CYP3A4 substrate, younger males appear to have higher clearances than older males and women of any age.[27]

Pollock et al. assessed the CYP2D6 phenotype in 175 healthy patients ranging from age 59 to 95 years, with a mean age of 75 years, using the metabolic ratio of debrisoquine and 4-hydroxy debrisoquine in urine.[8] The findings demonstrated a lack of a relationship between age and the metabolic ratio, implying that debrisoquine oxidative metabolism does not change with aging alone. However, a substantial number of studies with CYP3A4 substrates including diazepam (partial 3A4 substrate), alprazolam, and nifedipine have shown age-related decreases in elimination.[18,19]

Other age-related physiologic changes apart from changes in CYP activity may explain the generally observed decrease in drug clearance with age. A significant reduction occurs in liver blood flow and liver size with age. For drugs whose clearance is partly dependent on hepatic blood flow, this age-related effect will decrease clearance and increase half-life. For drugs whose elimination is also partly dependent on renal clearance, proportionally more of total body clearance will be dependent on hepatic mechanisms. The end result is that a variety of changes in the elderly population lead to a diminished ability to metabolize and eliminate drugs apart from specific demonstrated decreases in hepatic CYP activity.

ANTIDEPRESSANT PHARMACOKINETICS IN THE ELDERLY

The newer antidepressants have been studied in the elderly to estimate their pharmacokinetic parameters, although studies are less frequent in the frail elderly. In general, either no change or a reduction in clearance is found.[28] These findings translate into recommendations for initiating therapy in the elderly at a reduced dosage compared with that used in younger patients. The guidelines are often general, with recommended reductions of one third to half of the usual starting dose. The findings of pharmacokinetic studies in the elderly are summarized in Table 3.

Bupropion

Sweet and colleagues reported the pharmacokinetics of bupropion in 5 elderly women and 1 elderly man, aged 63 to 76 years.[29] Mean bupropion elimination half-life was 34.2 hours (range, 19.4–43.8 hours), which can be compared with a mean half-life in younger patients of 14.0 hours.[41] The half-lives and the area under the plasma concentration versus time curves (AUC) for the major metabolites were all longer and higher compared with those for younger patients. Thus, the elderly are at increased risk for diminished efficacy or frank toxicity due to accumulation of bupropion and its metabolites. The conclusion of this small study was that initial starting doses in the elderly should be reduced by at least 25% to achieve the same steady-state bupropion concentration as in younger patients.

Nefazodone

The single-dose and steady-state pharmacokinetics of nefazodone were reported in healthy elderly subjects (12 men and 12 women > 65 years old) compared with younger men and women.[26,30] A 300-mg dose was first given as a single administration followed by 300 mg twice a day for 8 days. At steady state, exposure to nefazodone and hydroxy-nefazodone was about 50% higher in elderly women compared with the other 3 groups. The exposure to the metabolite m-chlorophenylpiperazine at steady state was similar in elderly and young subjects. If similar exposure to active drug results in equivalent antidepressant response, then the results of this study suggest that the dosing of nefazodone could be 50% less than in younger patients. As considerable variability exists in both young and elderly, then initial doses should be lower, but ultimate treatment doses for optimal effect will need to be titrated to response.

Venlafaxine

Venlafaxine was studied in 18 elderly volunteers aged 60 to 80 years, and the results were compared with those of a group of young adults aged 21 to 44 years.[42] Single- and multiple-dose designs were employed with a single

Table 3. Pharmacokinetics of Newer Antidepressants in the Elderly and Current Recommendations for Dosing[a]

Drug	Study Population	Study Design	Findings	Dosing Recommendations/Reference
Bupropion	6 patients aged 63–76 y	Single dose 100 mg Chronic dosing 100 mg tid	20% reduction in clearance, extended half-life (mean = 32 hours), increased concentration of metabolites	Reduced initial dosing at least by 25% in elderly; Sweet et al[29]
Nefazodone	13 NV aged 65–78 y	Single doses of 50, 100, and 200 mg	AUC, half-life higher in elderly	Use half the initial dose in elderly; Barbhaiya et al[26,30]
Venlafaxine	18 NV aged 60–80 y	Single dose of 50 mg and 50 mg tid × 5 days	24% increase in steady-state half-life in elderly, 14% increase of metabolite in elderly	Dose adjustment based on age is not necessary; Klamerus et al[31]
Mirtazapine		Single dose	Concentration higher and half-life longer in elderly men and women compared with young men	Use cautiously in elderly[32]
Citalopram	11 patients aged 73–90 y	Chronic dosing at 20 mg/d	Steady-state concentration increased, clearance decreased, and half-life prolonged	Fredericson Overo et al,[33] Foglia et al[17]
Fluoxetine	11 NV aged 65–77 y	Single dose, 40 mg	Minimal differences reported	No change recommended by manufacturer[34]; Bergstrom et al[35]
Fluvoxamine	13 patients aged 63–77 y	50 mg bid for 28 days	Similar AUC and half-life as in young	DeVries et al[36]
Paroxetine	14 elderly; 16 NV; therapeutic drug monitoring results	Single and multiple dose, 20–40 mg/d	Increased steady-state variability, average concentration	Use 10-mg dose initially; Hebenstreit et al,[37] Ghose,[38] Bayer et al,[39] Lundmark et al[40]
Sertraline	22 NV > 65 y	50 mg increasing to 200 mg/d for 21 days	Concentration higher in elderly men or women compared with young men but similar to young women	No specific recommendation, dosage adjustment unlikely; Ronfeld et al[27]

[a]Abbreviations: AUC = area under the plasma concentration versus time curve, NV = healthy normal volunteers.

50-mg venlafaxine dose followed by 50-mg doses every 8 hours for 5 days. For venlafaxine, there were no significant differences in single-dose kinetic estimates, but a 24% increase in elderly steady-state half-life (4.2 ± 1.4 hours vs. 4.7 ± 1.4 hours) was reported. For O-desmethylvenlafaxine, a significantly lower apparent clearance was present in the elderly (0.29 vs. 0.38 L/h/kg) as was a longer half-life (13.2 vs. 10.3 hours). The steady-state clearance of venlafaxine was reduced by about 23% in the elderly subjects compared with the single-dose clearance (1.16 ± 0.71 L/h/kg vs. 0.98 ± 0.54 L/h/kg). This slight nonlinear disposition is consistent with a saturable O-demethylation pathway.[31] The main finding of this study was that steady-state plasma concentration in the elderly was only about 16% greater than in the younger subjects. This degree of increase would not appear to be a prominent risk factor for increased adverse events. Thus, venlafaxine dose adjustments for age are probably not necessary based on average pharmacokinetic differences between young and elderly.

Citalopram

Citalopram was studied in subjects older than 60 years of age in 2 studies.[17,33] The citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, in a single-dose study, whereas in a multiple-dose study they were increased by 23% and 30%, respectively. The plasma concentrations obtained in the elderly receiving 20 mg/day were approximately equal to the concentrations in younger patients receiving 40 mg/day. Following discontinuation of dosing, the half-life of citalopram ranged from 36 to 90 hours with a mean of 53 hours. On this basis, citalopram is recommended in a reduced starting dose of 20 mg/day for elderly patients, which is half the dose for younger adults.

Fluvoxamine

DeVries and colleagues found a mean fluvoxamine elimination half-life of 25 hours (range, 16–34 hours) in 13 elderly volunteers compared with a mean of 22 hours (range, 15–29 hours) in 6 young adults.[36] These data suggest only a minimal prolongation of half-life in the elderly. Other data demonstrate that the clearance of fluvoxamine may be reduced by up to 50% in the elderly.[43]

Fluoxetine

The data related to disposition of fluoxetine in the elderly are sparse. Reviews of published data have held that plasma concentrations may be twice as high in the elderly as in young adults.[35] Data from the manufacturer showed no difference between elderly and young patients in a single-dose study. The study consisted of a single 40-mg dose in 11 healthy elderly patients aged 65 to 77 years.[34] On this basis, the manufacturer makes no specific recommendation about dosing differences in the elderly.

Sertraline

In a study of age and gender, elderly men and women showed higher average concentrations of sertraline and its metabolite desmethylsertraline than did young males; however, concentration was similar to that in young females.[27] Normal healthy volunteers took ascending doses of sertraline beginning at 50 mg/day and increasing to 200 mg/day for 21 days. A difference in concentration of 25% separated the elderly men and women along with the young women from the young men. Disposition has previously been shown to be linear across the usual daily dose range of 50 mg to 200 mg with sertraline. It is unlikely that dosage adjustments based on age are necessary for sertraline.

Paroxetine

The disposition of paroxetine has been well defined in elderly patients.[37–40] Elderly patients treated with paroxetine displayed a wider variability in steady-state plasma concentrations compared with younger patients, a statistically higher mean concentration, and longer average half-life.[44] In elderly patients taking 20 mg/day, the minimum mean ± SD steady-state plasma concentration in 14 patients was 78.9 ± 73.3 ng/mL compared with 48.7 ± 25.9 ng/mL in 16 nonelderly patients. Similar findings were available in studies in which patients received either 30 or 40 mg/day. Considering that the average steady-state plasma concentrations were higher in the elderly, it was recommended that paroxetine treatment in elderly depressed patients be initiated at a lower starting dose, 10 mg/day, compared with the 20-mg/day dose recommended for young adult patients.
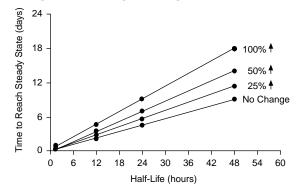
When single- and repeat-dose pharmacokinetic studies have been performed with paroxetine, the elderly have been observed to have higher-than-predicted steady-state concentrations. This is apparently due to nonlinear disposition of paroxetine, either saturation of presystemic elimination with multiple dosing or hepatic elimination through a high-affinity, low-capacity enzyme pathway.[45] In some patients, the elderly more so than younger patients, an increase in dose will result in disproportionately higher plasma concentration than expected from linear kinetics.

Mirtazapine

The mean elimination half-life of mirtazapine in elderly men (31.1 ± 15.1 hours) and elderly women (39.0 ± 10.8 hours) was significantly longer than in younger men (22.1 ± 3.7 hours) but not young women (35.4 ± 13.7 hours).[32] This is a similar gender and age difference in disposition to that reported for sertraline. The result is that young men tend to have lower plasma concentrations of mirtazapine than the other 3 groups after both single and multiple dosing.

ANTIDEPRESSANT DOSING IN THE ELDERLY

It is clear that the ability to metabolize and eliminate drugs does not decline uniformly or in a linear fashion with aging. There is a large variability in the physiologic response to growing old. Some elderly patients are able to eliminate antidepressants as efficiently as the average young adult, whereas other patients have a more pronounced impairment in drug elimination. This impairment is quite likely due to an accelerated rate of decline in many physiologic functions that occurs around age 70 in the elderly and especially in the frail elderly. Dosage requirements will most often be reduced for this population. Although some elderly patients may require dosing similar

Figure 4. Time to Reach Approximate Steady-State Conditions Following Chronic Dosing for a Drug With a Specific Half-Life[a]

[a]The points represent a theoretical half-life of 2, 12, 24, or 48 hours. The lines represent the effect of a prolonged half-life in the elderly of 25%, 50%, or 100% compared with no change in a younger population.

to younger adults, the variability in pharmacokinetics is such that elderly patients are less predictable than younger adults.

Good clinical practice suggests initiating antidepressant dosing at a reduced dose in the elderly. The generally longer half-life and reduced clearance means that steady-state plasma concentrations will not be achieved for a longer period of constant dosing compared with younger patients. Figure 4 shows the time to reach a steady-state drug concentration during chronic daily dosing according to a drug's elimination half-life. This length of time is a multiple of approximately 4 to 5 times the drug's half-life. The figure shows that the longer a drug's half-life, the more pronounced the delay to reach a steady state for a given impairment in the elderly compared with a drug with a shorter half-life. For an antidepressant with a half-life of 48 hours in young adults, a prolonged half-life of 100% in an elderly patient means an increase from 9 to 18 days of continuous dosing to reach steady state. This example can be compared with the selection of an antidepressant with a half-life of 12 hours in young adults, which is prolonged 100% in the elderly. In this situation, the delay to reach steady-state is a change from 4.5 to 9 days.

In practical terms, an antidepressant such as fluoxetine with a relatively long half-life in young patients (2–3 days for fluoxetine, 6–7 days for norfluoxetine) may not reach steady-state conditions for a period of weeks during continuous dosing in the elderly. Although plasma concentration measures of the newer antidepressants have not shown a strong correlation with efficacy or adverse events, the increased sensitivity to drug effects in the elderly makes a prolonged wait to achieve steady-state dosing an undesirable clinical situation.

An extended half-life of an antidepressant in the elderly means that drug will wash out of the body at a slower rate than in the younger patient. Side effects that are related to dose or concentration may take longer to diminish. This

may be especially important for drugs with active metabolites that accumulate in the elderly.

Drug names: alfentanil (Alfenta), alprazolam (Xanax and others), antipyrine (Auralgan and others), bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), nifedipine (Adalat, Procardia), nortriptyline (Pamelor and others), oxazepam (Serax and others), paroxetine (Paxil), perphenazine (Trilafon and others), prednisolone (Prelone and others), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor), verapamil (Calan and others), warfarin (Coumadin).

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