Effect of age on the pharmacokinetics of duloxetine in women

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Aims

The effect of age on duloxetine pharmacokinetics was evaluated in healthy volunteers and in patients with urinary incontinence.

Methods

Twenty-four healthy subjects (12 women 65–77 years, and 12 women 32–50 years) were given a single 40-mg oral dose of duloxetine in Study 1. Plasma concentration-time data were analysed by noncompartmental pharmacokinetic methods. Sparse plasma samples were obtained from patients with urinary incontinence treated in two phase II studies: 70 women (24–77 years) who received duloxetine 20 mg day⁻¹, 30 mg day⁻¹, or 40 mg day⁻¹ in Study 2A and 128 women (28–64 years) who received duloxetine 20 mg day⁻¹, 40 mg day⁻¹, or 80 mg day⁻¹ in Study 2B. Based upon the combined data, a model was developed to characterize population pharmacokinetics of duloxetine using the nonlinear mixed-effects modelling program (NONMEM).

Results

In Study 1, the elderly (≥ 65 years) exhibited a statistically significant slower elimination rate constant λ_z compared with younger subjects {elderly-younger difference = -0.022 h^{-1} [95% confidence interval (CI) $-0.036, -0.008$]}. However, no statistically significant differences in either CL/F [elderly-younger difference = -17.4 l h^{-1} (95% CI $-41.1, 6.23$)] or V/F [elderly-younger difference = 115.9 l (95% CI $-168.6, 400.4$)] were observed. The population pharmacokinetic analysis of Studies 2A and 2B revealed that the CL/F of duloxetine decreased with increasing age. Despite statistical significance, the age effect only accounted for 3% of the interindividual variability in CL/F and unexplained sources of the variation in clearance were still substantial ($> 50\%$). Adverse events were generally mild to moderate, and the incidence of adverse events was generally similar in elderly and non-elderly participants in these studies.

Conclusions

Whereas the results suggest that age has an effect on duloxetine pharmacokinetics, primarily reflected as a slower λ_z in the elderly, the magnitude of mean changes in CL/F, or V/F was small relative to the large interindividual variation in pharmacokinetics. Elderly participants had a safety profile of duloxetine comparable to their younger counterparts. Specific dose recommendations for duloxetine in the elderly are not warranted.

Introduction

Duloxetine hydrochloride–[LY248686 (+)-N-methyl-5-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride] – is a potent and balanced dual inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake. Preclinical studies demonstrate that it potently blocks the uptake of 5-HT and NE, weakly inhibits dopamine reuptake and has low or no affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors [1]. In animal models, duloxetine has been shown to be effective in urinary incontinence and depression [2, 3]. The safety and pharmacokinetics of duloxetine have been evaluated extensively in humans. Previously published results show that duloxetine pharmacokinetics are proportional across a range of doses of 20 mg to 40 mg given twice daily to 12 healthy male subjects [4]. Steady-state conditions are attained after 5 days of dosing, as predicted by an elimination half-life of approximately 12 h [4].

The elderly (≥ 65 years) often have a higher prevalence of adverse drug reactions than younger patients [5]. Differences in tolerability or efficacy may be attributable to age-related physiological changes causing alterations in the pharmacokinetics of drugs [6–8]. Thus, it is of clinical interest to examine the effect of age on the pharmacokinetics of a drug that is likely to be prescribed to elderly patients. Diseases such as urinary incontinence or depression are particularly prevalent in the elderly. Therefore, we assessed the effect of age on the pharmacokinetics of duloxetine both in healthy volunteers (Study 1) and in patients with urinary incontinence (Studies 2A and 2B).

Methods

Subjects and treatments

Study 1 Healthy women as determined by medical history and physical examination were enrolled in this open-label, single-dose phase I study after obtaining a written informed consent. Subjects were classified by age (between 18 and 50 years old or ≥ 0.565 years old). Subjects in both age groups were given a single oral dose of 40 mg duloxetine in the morning (2 h before breakfast). All prescription or nonprescription medications were discontinued on enrolment in the study. Subjects stayed at the study site for approximately 3 days, from the evening before dosing until discharge, and were required to fast from midnight until 2 h after dosing. The dosage formulation for duloxetine was a 20-mg capsule containing enteric-coated pellets (10% w/w duloxetine hydrochloride). Subjects were given two cap-

sules for a 40-mg dose. The study protocol and the informed consent form were reviewed and approved by an independent investigational review board.

Studies 2A and 2B Female patients with mixed type or stress urinary incontinence were enrolled in two multicentre double-blind placebo-controlled randomized phase II trials after giving their written informed consent. Patients in Study 2A were randomly assigned to receive duloxetine 20 mg once daily (qd), 30 mg qd, 40 mg qd (30 mg qd escalating to 40 mg qd) or placebo during a 6-week active treatment period. Patients in Study 2B were assigned randomly to receive duloxetine 20 mg qd, 20 mg bid, 40 mg bid or placebo during a 12-week period of active treatment. In both studies, participants did not change treatment groups and a maximum of seven visits were scheduled for each participant. Duloxetine was supplied as 10- or 20-mg capsules containing enteric-coated pellets (10% w/w duloxetine hydrochloride). The placebo capsules were indistinguishable from duloxetine capsules. The study protocol and the informed consent form were reviewed and approved by a local institutional review board for each investigational site.

Blood sampling and bioanalytical analysis Serial blood samples were collected from the healthy subjects enrolled in Study 1 at 0 (predose), 1, 2, 4, 6, 8, 10, 13, 16, 22, 30, 38, 48, and 72 h after oral administration of duloxetine. Plasma was assayed for duloxetine using a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method over the linear concentration range of 0.5 ng ml⁻¹ to 100 ng ml⁻¹ (Lilly Research Centre, Windlesham, UK). Duloxetine and the stable label internal standard were extracted from plasma using C8 solid-phase extraction plates. The analytes were chromatographed on an HPLC analytical column (Hichrom Ltd, Theale, UK) attached to a Perkin-Elmer Sciex API III⁺ mass spectrometer (Foster City, CA) set in the multiple reaction monitoring mode. During the validation, the overall accuracy expressed as the absolute relative error ranged from 2.7% to 7.4% and the precision expressed as the relative standard deviation ranged from 3.7% to 8.0%.

Sparse plasma samples were obtained from patients with urinary incontinence who participated in the pharmacokinetic evaluation. In Study 2A, sample collection was scheduled within prespecified time intervals at visits that occurred before and approximately 0, 2, 4 and 6 weeks after the start of duloxetine treatment. In Study 2B, sample collection was scheduled within prespecified time intervals at visits that occurred approximately 0, 4, 8 and 12 weeks after the start of duloxetine treatment.

For both studies, a sample was obtained at the discontinuation visit if any patient discontinued early. Plasma was assayed for duloxetine using a validated HPLC with fluorescence detection method over the linear concentration range of 1 ng ml⁻¹ to 100 ng ml⁻¹ (Covance Labs, Madison, WI, USA) in Study 2A] and using the previously described HPLC/MS/MS method in Study 2B. The HPLC/fluorescence assay is a modification of the HPLC/fluorescence assay published by Johnson *et al.* [9]. Duloxetine and the internal standard (analogue of duloxetine) were extracted from alkaline plasma with methylene chloride and the extracted analytes were derivatized with dansyl chloride prior to injection onto a C18 HPLC column. During the validation of the HPLC/fluorescence assay, the overall accuracy expressed as the absolute relative error ranged from 2.3% to 5.6% and the overall precision expressed as the relative standard deviation ranged from 4.0% to 6.3%. For both HPLC/fluorescence and HPLC/MS/MS assays, quality control samples were analysed with each batch to ensure the validity of the data in a batch.

Pharmacokinetic analysis

Noncompartmental analysis methods were used to determine pharmacokinetic parameters using WinNonlin (Professional version 1.5] Pharsight Corp., Mountain View, CA, USA) in Study 1. The maximum observed concentration and the corresponding sampling time were denoted as $C_{\max}$ and $T_{\max}$, respectively. The elimination rate constant (λ_z) was determined as the slope of a regression line going through data points in the terminal log-linear phase of a plasma concentration-time curve. The elimination half-life value ($t_{1/2,z}$) was calculated as $\ln(2)/\lambda_z$. The area under the concentration-time curve from time zero to the last sampling time with quantifiable concentration ($AUC_{0-t_{\text{last}}}$) was calculated using the linear trapezoidal method and extrapolated to infinite time as $AUC_{0-\infty} = AUC_{0-t_{\text{last}}} + C_{\text{last}}/\lambda_z$, where C_{last} is the concentration at the last measurable time calculated from the regression equation. The apparent plasma clearance (CL/F) was estimated as dose divided by $AUC_{0-\infty}$ and the apparent volume of distribution (V/F) was estimated as CL/F divided by λ_z . Statistical hypothesis testing was performed on selected pharmacokinetic parameters using the SAS® System for Windows (SAS Institute, Cary, NC, USA). Mean parameter estimates (except for $T_{\max}$) were compared using the *t*-test for two samples. The power to detect a 50% change in the parameter means was estimated based on the *t*-distribution and the observed standard deviation for $C_{\max}$ and $AUC_{0-\infty}$. Median $T_{\max}$ values were compared nonparametrically using the SAS procedure NPAR1WAY.

Population pharmacokinetic analysis was performed on the data pooled from Studies 2A and 2B using the nonlinear mixed-effects modelling program (NONMEM, Version V] University of California at San Francisco, CA, USA) with the PREDPP package [10]. Both one- and two-compartment open models were evaluated as the structural pharmacokinetic model. The interindividual variability (η) was assumed to be log-normally distributed and evaluated on model parameters as $P = \theta \cdot \text{Exp}(\eta)$, where P and θ are the individual's estimate and typical value for a pharmacokinetic parameter, respectively. The residual error (e) was parameterized as $Y = F + e$ (additive term), $Y = F \cdot (1 + e)$ (proportional term) or a combined additive/proportional term, where Y and F are the observed and model predicted concentrations, respectively. An indicator variable (1 for Study 2A and 0 for Study 2B) was used to differentiate residual variances associated with the two studies. The first order conditional with interaction estimation method was used in model fitting procedures. The comparison of two models was made based upon changes in the objective function, diagnostic graphs (e.g. agreement between predicted and observed concentrations, the magnitude and randomness of residual values) and the precision of parameter estimates.

Covariates identified *a priori* (Table 1) were tested statistically on the CL/F and V/F of duloxetine. For a continuous covariate, its relationship with a pharmaco-

Table 1

Patient factors tested in the population pharmacokinetic analyses

Continuous covariate	Categorical covariate
Age	Alcohol use
Alkaline phosphatase	Dose group
Body weight	Ethnic origin
Body surface area	Project code
Creatinine	Smoking status
Creatine phosphokinase	
Estimated creatinine clearance*	
Hepatic enzymes (alanine transaminase, aspartate transaminase, gamma glutamyl transferase)	
Total bilirubin	

*Creatinine clearance was estimated for women by the Cockcroft-Gault formula as $0.85 \cdot [(140 - \text{age (years)}) \cdot \text{weight (kg)}] / [72 \cdot \text{serum creatinine concentration (mg/dl)}]$.

kinetic parameter was evaluated using a linear model ($\theta_1 + \theta_2 \cdot \text{COV}$), an exponential model [$\theta_1 \cdot \text{Exp}(\theta_2 \cdot \text{COV})$], and a power model ($\theta_1 \cdot \text{COV}^{\theta_2}$), where θ_1 was the typical value of the parameter, θ_2 was the effect of the covariate, and COV was the value of the covariate. For a categorical covariate, its relationship with a pharmacokinetic parameter was evaluated as $P = \theta_1 \cdot (1 + \theta_2 \cdot \text{IND})$, where IND was an indicator variable. A covariate was considered to be of potential significance if its addition to the model caused a decrease in the objective function at least 6.6 points (χ^2 distribution, 1 degree of freedom, $P < 0.01$). Potentially significant covariates were added in combination to form a full model. Subsequently, covariates in the full model were removed individually so that only those reaching statistical significance (the removal caused an increase in the objective function at least 10.8 points for 1 degree of freedom, $P < 0.001$) were retained in a final model. The robustness of the final model was evaluated using parameter sensitivity and leverage analyses [11, 12].

Safety assessment

Clinical evaluation, clinical laboratory tests (chemistry, haematology and urinalysis), vital signs, physical examinations and electrocardiograms (ECGs) before and after the start of duloxetine dosing provided the basis for the assessment of safety and tolerance of duloxetine in the elderly, compared with that in the younger group.

Results

Pharmacokinetics

Healthy volunteers Twelve elderly women, 65–77 years old (mean 69 years), and 12 younger women, 32–

50 years old (mean 42 years), were included in the pharmacokinetic evaluation. Six of the 12 elderly subjects were Hispanic, five were Caucasian, and one was Asian. Eleven of the younger subjects were Hispanic and one was Caucasian. Figure 1 illustrates the individual and mean plasma concentration-time profiles obtained in elderly and younger subjects administered a single oral 40-mg dose of duloxetine. Table 2 summarizes the principal pharmacokinetic parameters and presents a statistical assessment of these parameters. There was no statistically significant difference in C_{max} , $\text{AUC}_{0-\infty}$, or CL/F value between the elderly and the younger groups, although the mean elimination rate constant, λ_z , was significantly smaller (31% on average) in the elderly compared with that of younger subjects. Although the mean CL/F in the elderly group appeared numerically lower than that in the younger group, it did not reach statistical significance. We speculate that the lack of statistical significance was due to the relatively small sample size of 24 (12 in each age group), which rendered only 67% power to detect a 50% change in $\text{AUC}_{0-\infty}$. It appears that the higher mean CL/F value in the younger group may have been driven by two subjects with high parameter estimates relative to other study participants. The impact can be clearly observed in Figure 2 that compares individual and mean CL/F values between these two age groups.

Patients with urinary incontinence Seventy patients (266 plasma samples) from Study 2A and 128 patients (555 plasma samples) from Study 2B were included in the pharmacokinetic evaluation. The combined analysis dataset consisted of 198 patients and 821 plasma samples (1–6 per individual). In this study population, patients were 24–77 years old (mean 52 years), of whom 24 participants were elderly, and were overwhelmingly Caucasian. A one-compartment base

Figure 1

Individual (—) and mean (●) plasma concentration-time profiles of duloxetine obtained from elderly and younger subjects administered a single oral 40-mg dose of duloxetine

Table 2

Noncompartmental pharmacokinetic parameters of 40 mg duloxetine in elderly and younger women (Study 1)

Parameter	Arithmetic mean (CV%)		Difference, with 95% confidence interval (elderly-younger)	P-value
	Younger (n = 12)	Elderly (n = 12)		
Age (years)	42 (32–50)	69 (65–77)	nc	nc
AUC _{0–t} (ng h ^{−1} ml ^{−1})	677.7 (49)	824.5 (37)	146.8 (−123.6, 417.3)	0.272
AUC _{0–∞} (ng h ^{−1} ml ^{−1})	699.3 (49)	866.9 (39)	167.6 (−119.1, 454.2)	0.238
C _{max} (ng ml ^{−1})	49.8 (38)	49.4 (32)	−0.4 (−15.1, 14.4)	0.958
T _{max} ^a (h)	4.0 (2.0–4.0)	5.0 (1.0–6.0)	1 (−1, 2) ^b	0.139
CL/F (l h ^{−1})	70.3 (48)	52.9 (38)	−17.4 (−41.1, 6.23)	0.141
V/F (l)	962.0 (34)	1077.9 (32)	115.9 (−168.6, 400.4)	0.407
λ _z (h ^{−1})	0.072 (27)	0.049 (26)	−0.022 (−0.036, −0.008)	0.003
t _{1/2,z} ^c (h)	9.7 (6.9–14.7)	14.0 (9.8–26.7)	nc	nc

AUC_{0–t}, Area under the plasma concentration-time curve from time zero to last measurable time point; AUC_{0–∞}, AUC from time zero to infinite time; C_{max}, maximum plasma concentration; CL/F, apparent plasma clearance; n, number of subjects included in means; nc, not calculated; V/F, apparent volume of distribution; T_{max}, time to reach C_{max}; λ_z, elimination half-life; t_{1/2,z}, elimination half-life. ^aMedian (range). ^bConfidence interval not applicable in nonparametric analysis; median and range in difference reported. ^cHarmonic mean (range).

Figure 2

Individual and mean (—) apparent plasma clearances of duloxetine in elderly (65 to 77 years (○)) and younger (32 to 50 years (●)) subjects. (The error bar represents 1 SD, mean ± SD.)

model with η evaluated on both CL/F and V/F, and e parameterized as a proportional term was found adequately to describe duloxetine pharmacokinetics (Figure 3). Two-compartment models offered no improvement in data fitting. In addition, the covariance between CL/F and V/F (omega block) was included in the model. Table 3 presents the population estimates and

standard errors of the estimate (SEE) for the base and final model parameters. These pharmacokinetic, covariate and variability parameters were estimated with reasonable precision (SEE < 26%). Among the covariates screened (Table 1), age was the only one identified to be statistically significant and its relationship with CL/F might be best described by a power function. The inclusion of age decreased the interindividual variability in CL/F by around 3%. Figure 4 illustrates individual empirical Bayesian estimates of duloxetine CL/F in relation to age. The residual errors associated with Studies 2A and 2B differed by only 10%, suggesting that the precision of the two assay methods was not substantially different.

Safety

Healthy volunteers There were no serious adverse events. The most common adverse events were nausea (12 of 24 subjects) and headache (10 of 24 subjects). Other adverse events reported for two or more subjects were dizziness (four of 24 subjects), diarrhoea (three of 24 subjects), hypertension (three of 24 subjects), and dysmenorrhea (two of 24 subjects). Adverse events were similarly distributed in both age groups. There were no clinically significant abnormal laboratory values, or electrocardiogram changes detected during screening or during study. Three subjects (two younger and one elderly) were discontinued from the study due to adverse events.

Figure 3

Scatter plots of individual predicted vs. observed concentrations and individual weighted residuals vs. individual predicted concentrations

Table 3

Duloxetine population pharmacokinetics in female patients with urinary incontinence

Parameter description	Population estimate (% SEE)	
	Base model	Final model
<i>Pharmacokinetic parameters</i>		
CL/F (l h ⁻¹)	53.5 (4.6)	52.6 ^a (4.5)
V/F (l)	994 (7.8)	954 (7.9)
Ka (h ⁻¹)	0.268 (13.5)	0.257 (13.8)
<i>Covariate parameters</i>		
Effect of age on CL/F ^b	—	-0.945 (23.5)
<i>Variability</i>		
Inter-patient variability in CL/F	57.4% (16.5)	54.2% (15.5)
Inter-patient variability in V/F	55.2% (25.1)	53.9% (24.0)
Covariance between CL/F and V/F	45.2% (23.5)	44.3% (22.1)
Proportional residual error associated with Study 2A	36.9% (12.7)	36.5% (12.6)
Proportional residual error associated with Study 2B	46.4% (9.4)	46.8% (9.2)

SEE, Standard error of the estimate; CL/F, apparent clearance; V/F, apparent volume of distribution; Ka, absorption rate constant. ^aTypical CL/F value at an age of 51.8 years (covariate model centering age at its population mean). ^bCL/F = $52.6 \times (\text{age}/51.8)^{-0.945}$.

erly) exhibited mild elevations of blood pressure. One younger subject had a supine blood pressure of 110/80 mmHg prior to dosing. After receiving duloxetine, her supine pressure ranged from 100/62 to 150/90. A second younger subject had a normal supine blood pressure prior to duloxetine administration (120/80) and a single elevated supine reading of 150/90 approximately 12 h after administration. One elderly subject had an elevated supine pressure of 160/80 prior to dosing and a maximum supine pressure of 170/90 12 h after dosing. All blood pressure elevations were transient.

Patients with urinary incontinence Among patients who received duloxetine in Study 2A, the most frequently reported adverse events were nausea (14%),

headache (9%) and diarrhoea (7.7%). Patients at 65 years of age and older were compared with patients younger than 65 years with regard to adverse events reported by two or more subjects receiving duloxetine. The incidence of adverse events was similar (within 5%) in both the elderly and the young group with the following exceptions: dry mouth and somnolence were more common in the elderly group (11.7% vs. 5% and 8.3% vs. 1.9%, respectively). Headache and flu-like syndrome were more common in the younger group (10.6% vs. 5% and 5% vs. 0%, respectively). There were no significant changes in laboratory tests related to duloxetine administration. For patients in Study 2B, clinical laboratory assessments, vital signs, ECGs, and physical findings were stable relative to baseline, and no clinically mean-

Figure 4

The relationship of apparent plasma clearance with age in patients with urinary incontinence. Individual estimates (O); and predicted values (—)

ingful differences were detected among treatment groups.

Discussion

These studies demonstrated a measurable effect of age on duloxetine pharmacokinetics following single- or multiple-dose administration. In patients with urinary incontinence, the population pharmacokinetic analysis revealed a statistically significant correlation between CL/F and age [$CL/F = 52.6 \cdot (age/51.8)^{-0.945}$]. The power function with a negative exponent indicates that duloxetine CL/F decreases in a curvilinear fashion with increasing age and the typical value changes in greater magnitude before than after the population mean of 51.8 years (Figure 4). The influence of age on CL/F might be attributed more to a decrease in systemic clearance than to an increase in oral bioavailability. This is supported by the larger magnitude of the change in mean λ_z (31%, $P < 0.01$) compared with the change in mean CL/F in the elderly. However, the slightly longer half-life in elderly subjects (14 h on average) implied that plasma concentration of duloxetine should not have accumulated substantially following qd or bid dosing.

Duloxetine is well absorbed and cleared primarily by extensive metabolism to numerous metabolites that include oxidation, methylation and conjugation pathways. Enzyme kinetic and *in vitro* studies suggest a role for multiple enzymes in the initial oxidative metabolism, including CYP2D6, and CYP1A2 (data on file). The major circulating metabolites found in humans include the glucuronide conjugate of 4-hydroxy duloxetine and the sulphate conjugate of 5-hydroxy, 6-methoxy dulox-

etine [13]. The elderly may exhibit a decrease in the rate of duloxetine elimination because of an altered hepatic clearance, possibly associated with age-related reduction in liver size, liver blood flow and drug metabolizing enzyme activity [6–8]. In contrast, the oral bioavailability of duloxetine may be influenced by old age in a manner largely determined by age-related changes in gastrointestinal (GI) absorption and first-pass metabolism. In general, drug absorption from the GI tract decreases with increasing age due to alterations in gastric acidity, splanchnic blood flow and GI motility [14–16]. For duloxetine, however, a decrease in GI absorption may be offset by a decrease in first-pass metabolism such that the net effect on duloxetine bioavailability results in less apparent difference between elderly and younger subjects. On the other hand, the magnitude of the plasma clearance after intravenous administration in comparison with liver blood flow suggests that duloxetine is not a high hepatic clearance drug (data on file). Taken altogether, it appears that the most relevant physiological changes in the elderly are those associated with a potential decrease in duloxetine metabolism.

The age-related changes in duloxetine pharmacokinetics are likely to be overshadowed by large inter-individual variation in plasma concentrations. In the population pharmacokinetic analyses, the age effect accounted for only a small proportion (3%) of the inter-individual variability in CL/F. The interindividual coefficient of variation for this parameter in the final model was substantial (> 50%), corresponding to highly variable long-term plasma exposure in any age group and across the investigated age ranges. Likewise, duloxetine CL/F in Study 1 spanned a similar range between elderly and younger healthy volunteers. The exception appears to be two high clearance values in the non-elderly group (Figure 2). As a result, the difference in AUC between the elderly and younger groups was not statistically significant. Therefore, there is relatively little to be gained with respect to plasma concentrations by making dosage adjustments for duloxetine solely on the basis of age.

The inference of no clinically relevant changes in duloxetine pharmacokinetics with increasing age are further supported by comparisons of safety data between the elderly and non-elderly groups of patients and healthy volunteers. The frequency of adverse events was generally similar between the two age groups and no safety concern (intolerability) was noted in these elderly individuals when given duloxetine at the investigated dose levels. However, because these studies involved relatively small numbers of patients and may

not reflect the true incidence of adverse events, this finding should not be over-interpreted. An integrated safety analysis of seven double-blind, placebo-controlled clinical trials suggests that the safety and tolerability of duloxetine does not differ across subgroups of age, gender, or origin (data on file).

In conclusion, the CL/F of duloxetine typically decreased with increasing age, principally reflecting a slower rate of drug elimination. However, the magnitude of the mean change was small relative to the magnitude of interindividual variation in pharmacokinetics. Plasma concentrations produced by the same dose of duloxetine span a similar range between elderly and non-elderly individuals. Importantly, the elderly participants in these studies had a safety profile of duloxetine comparable to their younger counterparts. Therefore, the identified age-related pharmacokinetic changes are not considered clinically significant over the age range of 24–77 years and specific dose recommendations for the elderly are not warranted.

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