Effects of age and gender on the serum levels of clozapine, olanzapine, risperidone and quetiapine

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Running title: Serum levels of antipsychotics

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Abstract

Objective: To investigate serum concentrations of second generation antipsychotics in relation to age and gender in a population ranging from 18 to 100 years.

Method: Results from a routine therapeutic drug monitoring database were retrieved and 43079 samples from 11968 patients were included (17249 samples for clozapine, 16171 samples for olanzapine, 5343 samples for risperidone and 4316 samples for quetiapine). The dose-adjusted concentration was used as the primary target variable. A linear mixed model was used to allow the inclusion of multiple samples from each patient.

Results: Age had a significant impact on the concentrations of all four drugs. At the age of 80, the dose-adjusted concentrations were up to twice those of the age of 40. At the age of 90, dose-adjusted concentrations were 2-3-fold higher. Age-related increases were largest for clozapine (+108% at 80 years; +197% at 90 years) and smallest for olanzapine (+28% at 80 years; +106% at 90 years). Females generally had dose-adjusted concentrations 20-30% higher than males.

Conclusion: The effect of age on the serum concentrations of the antipsychotics studied becomes pronounced with advanced age. The patient population aged above 70 should be subdivided according to exact age, and considerable dose reductions are recommended.

Keywords: antipsychotics, drug monitoring, aged, sex

Significant outcomes

- When prescribing clozapine, olanzapine, risperidone or quetiapine to older patients, no more than half the dose usually administered to younger patients should be used, and in many cases, particularly to the oldest individuals, even lower doses should be used.
- Females at advanced age are particularly prone to increased concentrations of antipsychotics.
- Given the interindividual variability in the dose-adjusted concentrations observed, we suggest using therapeutic drug monitoring in addition to a thorough clinical follow-up among the oldest age groups.

Limitations

- We did not have data on ethnic background, diagnosis, smoking habits and genotype of the patients.
- Due to the naturalistic design of the study we were unable to verify whether the information stated on the requisition forms was correct.
- The extent of non-compliance among the subjects included was unknown.

Introduction

Second generation antipsychotics are widely used in elderly with psychiatric disorders (1) and particularly among those living in nursing homes (2, 3). However, patients above the age of 65 are rarely included in clinical trials with these drugs (4, 5). Although the core indications for second generation antipsychotics are schizophrenia and bipolar disorder, in the elderly these drugs are more frequently used in other situations such as for behavioral symptoms in dementia (1-3).

There is also a lack of information related to the disposition of second generation antipsychotics in the elderly. Numerous physiological changes take place in older subjects, some of which may cause changes in drug pharmacokinetics (e.g. hepatic metabolic capacity and renal function) and pharmacodynamics (6). In addition, the geriatric population spans over more than 30 years of age, adding to the heterogeneity and unpredictability in terms of drug disposition. It is therefore of importance to have data on drug metabolism not only for the population between 70 and 80 years of age, but also in even older subjects.

In a few previous studies, the impact of advanced age on the metabolism of second generation antipsychotics has been described. In a study in Chinese patients using clozapine, an increment of approximately 10% in the dose-adjusted drug concentrations was found for every decade above the age of 20 (7). In contrast, another study, also from China, found no such effect, but the oldest patient was relatively young, 74 years (8). An American study found a reduction in oral clearance of clozapine of about 6% per decade from the age of 40 (9). Also here, very few patients were above the age of 80.

For olanzapine, one study found that every 5-year change in age above 40 years increased dose-adjusted concentrations by 1.7% in males and 1.3% in females (10). This study included more than 3000 patients, and the oldest patient was 86 years. Another study (11) found an increase of about 27% in the dose-adjusted concentration in patients above 60 years compared to younger subjects.

For risperidone, no discernible influence of age on the dose-adjusted plasma concentrations of risperidone plus its active metabolite 9-hydroxyrisperidone was found in 95 samples from a therapeutic drug monitoring (TDM) service (12) or in a

study in 20 geriatric inpatients (13). In contrast, another study found that the dose-adjusted concentration of risperidone plus active metabolite was almost threefold higher in the age group above 60 than in those below 45 (14). In a study in healthy volunteers given a single dose of risperidone, clearance was reduced by about 30% in the elderly (15), Finally, in a recent study (16), the dose-adjusted concentrations of risperidone as such were not significantly higher in patients above 65 years of age, but the concentrations of the active metabolite was 2.6-fold higher, leading to a 2.0-fold higher concentration of the active moiety in the elderly.

For quetiapine, one study found a mean increase in dose-adjusted concentrations of 13 % per decade from the age of 20 (17), whereas another study found that the concentrations on average were 67% higher in patients above 70 compared to those aged 18-69 (18). Yet another study found that patients aged 65 and above had 50% higher plasma concentrations than younger patients (19).

For gender, differences in dose-adjusted plasma concentrations have been found to a varying degree in small studies for clozapine (7, 8, 20), with females having about 30% higher concentrations than males. For olanzapine the dose-adjusted concentration in one study was 26% higher in females than in males (10). For risperidone, data are inconsistent (14) whereas for quetiapine (17-19), gender has not been found to be a significant predictor of drug plasma concentrations.

In general, the studies cited above have included a relatively low number of patients; with a few exceptions (9, 10, 18, 19) less than 500 patients for all age groups combined. Moreover, the proportion of subjects of advanced age has generally been low, with inclusion of very few patients above the age of 85 and almost none above the age of 90. Thus, the partial conflicting evidence on age influence in the studies presented above might be related to design issues such as the total number of patients included and in particular the number of very old patients.

TDM is a valuable tool for tailoring the dosage of a prescribed medication to the individual pharmacokinetic characteristics in a patient. Although definite concentration-effect relationships have not been established for second generation antipsychotics, serum concentration measurements can be helpful in situations where patients do not respond as anticipated to the drug, such as in cases with a lack of therapeutic effect or with pronounced adverse drug reactions (21-24). TDM

can also be advantageous in patients with other conditions affecting the pharmacokinetics of the drug, such as in cases of concomitant somatic illness, impaired hepatic or renal function, during pregnancy and during co-treatment with potentially interacting drugs (21-24). Reducing phases of suffering by accelerating improvement and diminishing adverse drug reactions will not only have medical benefits for the patients but also decrease costs for the health care system.

The aim of the present study was to investigate the effects of advanced age and gender on the serum concentrations of clozapine, olanzapine, risperidone and quetiapine in a naturalistic setting, based on data from a large routine TDM database.

Method

Study design

TDM has been regarded as a useful tool in the optimization of treatment with psychotropic drugs (25), and Norway has a strong tradition for the use of routine TDM of antipsychotics (26). After obtaining approval from the Regional Committee for Medical and Health Research Ethics, we were able to retrieve results from the analyses of 94 403 serum samples of the four second generation antipsychotics clozapine, olanzapine, risperidone and quetiapine included from the routine TDM database at the Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway, during the years 2000 to 2014. The distribution of samples was 32 416 for clozapine, 36 705 for olanzapine, 17 654 for risperidone and 7 628 for quetiapine. In addition to the specific drug analyzed and the measured drug concentration, the database contained detailed patient information and date of blood sampling (from which patient age and gender were derived) as well as data about prescribed dose, time of last drug intake and blood sampling, and types and doses of concomitant drugs.

Samples from patients below the age of 18 were excluded, as were samples from patients using intramuscular depot formulations of the drugs. For quetiapine, only samples obtained before 2007 were included, in order to avoid inclusion of both immediate release and sustained release formulations of the drug (the latter entered the market in 2007). Moreover, samples where the requisition forms lacked

information about dose and/or time interval between last intake of medication and blood sampling, samples obtained less than 10 hours or more than 24 hours after the last dose, samples obtained in relation to acute intoxications, and samples with non-traceable levels of the medication were excluded. Finally, we excluded samples where the requisition forms described concomitant use of medications that could affect the concentrations of the drug analyzed. After this procedure, 43 079 samples from 11 968 patients were found eligible for inclusion in the study, 17 249 for clozapine, 16 171 for olanzapine, 5 343 for risperidone and 4 316 for quetiapine.

Drug assays

Serum concentrations of the antipsychotics were analyzed with liquid chromatography-mass spectrometry (LC-MS) methods developed in our laboratory. The LC-MS system used was an Agilent MSD 1100 (Agilent, Palo Alto, CA, USA). For clozapine, olanzapine and quetiapine, the methods have been described in detail previously (18, 27, 28). For these three drugs the serum concentration measurements included the parent compound only, without any metabolites.

Risperidone and its active metabolite 9-hydroxyrisperidone were extracted from 1 ml serum with 4 ml hexane:butanol:acetonitrile (93:5:2) after addition of internal standard methylrisperidone. After mixing and centrifugation the organic extract was evaporated to dryness with air and the residue was reconstituted in 50 µL methanol. Separation was performed on a Zobrax SB-C18 (30 x 4.6mm) column with a mobile phase consisting of methanol:ammonium acetate (65:35). Risperidone was monitored at m/z 411.0, 9-hydroxyrisperidone at m/z 427.0 and the internal standard methylrisperidone at m/z 421.0, using positive electrospray ionization. The calibrated range was 2.5 to 1000 nmol/L for both analytes, and linearity was shown throughout this interval. The between-day coefficients of variation at 500 nmol/L were 3.4% for risperidone and 4.6% for 9-hydroxyrisperidone. The limit of quantification was 2.5 nmol/L for both analytes. For risperidone, all concentrations presented and discussed represent the active moiety of the drug, i.e. risperidone plus its active metabolite 9-hydroxyrisperidone, if not otherwise explicitly stated.

The serum concentration of a drug (in nmol/L) was divided by the daily dose (in mg/d) used at the time of sampling, providing a dose-adjusted serum concentration. This variable was used as the primary target variable. The dose-adjusted serum concentration thus corresponds to the concentration per mg medication administered daily. To facilitate the interpretation of these numbers, in the figure presentations the dose-adjusted concentrations are multiplied by the Defined Daily Dose (DDD) of the drug (29) which is the assumed average maintenance dose per day when used for its main indication. The DDD is 300 mg for clozapine, 10 mg for olanzapine, 5 mg for risperidone and 400 mg for quetiapine. To convert from nmol/L to ng/mL, the concentrations and dose-adjusted concentrations should be divided by 3.06 for clozapine, 3.20 for olanzapine, approx. 2.4 for risperidone and active metabolite, and 2.61 for quetiapine.

Statistical analyses

In order to normalize the antipsychotic concentration for variations in time from the last dose to sampling, a non-compartmental exponential model for the elimination phase of the antipsychotics was assumed. The observed concentration at *t* hours since intake (C_t) was then converted to a standardized 12-hour concentration (C_{12}) according to the following equation:

$$C_{12} = C_t e^{-k(12-t)}$$

The rate constant *k* was set according to the equation $k = \log_e 2/t_{½}$, using half-lives of 14 hours for clozapine, 45 hours for olanzapine, 24 hours for risperidone and 9-hydroxyrisperidone and 7 hours for quetiapine (30). As the distributions of the dose-adjusted concentrations were found to be heavily right-skewed, the natural logarithm ($\log_e$) of the dose-adjusted concentrations was employed as the outcome variable in the statistical model to achieve near normality of the residuals.

As multiple samples from the same patient were available, a linear mixed model, allowing correlation between repeated observations, was used. This model assumes that each individual patient possesses a random intercept (i.e. an individual “offset”) in addition to being affected by fixed factors. The factors included in the model for each of the four analytes were gender and age. Model parameters, including

variance components, were estimated by the method of restricted maximum likelihood using the *nlme* package of the software R version 3.3.2, and R and GraphPad PRISM version 6.0 were used for graphical illustrations. Data are presented as means with 95% confidence intervals, or as medians with corresponding minimum and maximum values, as appropriate. P values less than 0.05 were considered statistically significant.

Results

In total, 43 079 samples from 11 968 patients were included in the study, 17 249 samples for clozapine, 16 171 samples for olanzapine, 5 343 samples for risperidone and 4 316 samples for quetiapine. The distribution of samples and patients in various age groups and in males and females is presented in Table 1.

Model parameter estimates of the explanatory factors on the log-transformed dose-adjusted concentrations are shown in Table 2. Age significantly affected the dose-adjusted concentrations, as shown in Table 2 and illustrated in Figure 1. As can be seen from Table 3, the mean dose-adjusted concentrations for the various drugs were about 30-60% higher in patients aged 70 compared to the age of 40. At the age of 80, dose-adjusted concentrations were up to twice those at 40, and at the age of 90, dose-adjusted concentrations were 2-3 times higher than at 40. The increases were most pronounced for clozapine and smallest for olanzapine (Table 3). The distributions of concentrations in subjects of the same age and gender given a dose of one DDD per day, are displayed in Figure 2.

For risperidone, we investigated the effect of age on the dose-adjusted concentration of the parent compound and the metabolite 9-hydroxyrisperidone separately. Compared to a person aged 40, the increases for the parent compound were 40.1% at the age of 70, 69.8% at the age of 80 and 114% at the age of 90. The corresponding increases for the metabolite 9-hydroxyrisperidone were 50.3%, 97.2% and 177%, respectively. The mean parent compound:metabolite ratios in the age groups 18-59 years, 60-69 years, 70-79 years, 80-89 years and above 90 years were 0.59, 0.66, 0.37, 0.39 and 0.26, respectively. The corresponding median ratios were 0.15, 0.17, 0.11, 0.11 and 0.13, respectively. Applying the linear mixed model

previously described to the risperidone parent compound:metabolite ratio did not reveal any significant change with age ($p = 0.38$).

Also gender influenced the dose-adjusted concentrations for the drugs, with females generally having higher dose-adjusted concentrations than males (Table 2, Figure 1). Specifically the dose-adjusted concentrations in females were 28.2% higher for clozapine ($p<0.0001$), 26.1% higher for olanzapine ($p<0.0001$) and 18.7% higher for risperidone ($p<0.0001$). For quetiapine, there was an age by gender interaction, where the differences between genders were virtually non-existing in younger age groups, but increased with age. Thus, according to the model, a woman aged 80 would on average have a dose-adjusted quetiapine concentration 33% higher than a man of the same age (Figure 1). Correspondingly, an 80-year old male would on average have a serum concentration 54.8% higher than a 40-year old male, whereas in females, the corresponding increase was found to be 98.4% (Table 3).

The daily doses used in the various age groups decreased with increasing age. For clozapine, the median dose in those aged 18-59 was 350 mg/d, in those aged 60-69 it was 312 mg/d, in those aged 70-79 it was 300 mg/d, in those aged 80-89 it was 62.2 mg/d and in those aged 90 and above it was 12.5 mg/d. For olanzapine, the corresponding doses were 15, 10, 10, 7.5 and 7.5 mg/d. For risperidone the doses were 4, 3, 2, 1 and 1 mg/d, respectively, whereas the quetiapine doses were 600, 500, 300, 125 and 87.5 mg/d.

Discussion

The principal finding of the present study is that the dose-adjusted concentrations of the antipsychotic drugs studied increased with increasing age; an effect that became particularly prominent at advanced age, i.e. in those above 80-90 years of age. This effect was general and irrespective of the specific pharmacokinetic properties of the drug, although there were some differences in the extent of the effect between the drugs studied.

Our findings are largely in line with what could be expected based upon previous studies (7, 9-11, 14, 16-20) and knowledge on alterations in drug disposition in the elderly (6). However, our results extend previous findings both related to the age

spectrum studied and the fact that we have been able to directly compare four different drugs, which are found to behave somewhat differently with regard to the age effects. Also, we have been able to elucidate more deeply the extent of gender effects on the disposition of the antipsychotics studied.

The most likely mechanism underlying the higher dose-adjusted concentrations in the elderly is a lowered hepatic clearance of the drugs caused by a decreased intrinsic hepatic metabolic function, a lower liver volume and/or a reduced hepatic blood flow, e.g. due to impaired cardiac output (6). The drugs studies are principally metabolized by cytochrome P-450 (CYP) enzymes, but as various isoenzymes are involved (predominantly CYP1A2 for clozapine and olanzapine, CYP2D6 for risperidone and CYP3A4 for quetiapine) (30), the decrease in metabolic function is not caused by reduced metabolic capacity in just one of these.

For risperidone, there was a trend towards a higher increase in dose-adjusted concentrations with age for the metabolite 9-hydroxyrisperidone than for the parent compound risperidone. However, there was no significant age effect on the parent compound:metabolite ratio. It could have been expected that this ratio should decrease with age because the metabolite 9-hydroxyrisperidone is mainly excreted in the urine, and the decline in renal function with age is even more pronounced than the decline in hepatic function (6). However, our results indicate that there is a significant decrease in hepatic CYP2D6 metabolism as well in subjects at advanced age.

In most previous studies (7, 9-11, 13-17) an increase in dose-adjusted concentrations has been found in the elderly, most often defined as those above 65 of 70 years of age, but the extent of this increase has varied considerably and there are also studies where no age-related increases were found (8,12,(13). In almost none of these studies attempts have been made to divide the elderly into separate age groups. In contrast, in the present study we have been able to include a total of more than 1100 individuals above the age of 70, and about 100 individuals aged 90 or more. Finally, in our model we have used the exact age of each subject at the time of sampling, thereby being able to create continuous variables for the age effects.

The model that best described the data was not a regular linear function but a model including a quadratic part in addition to the more traditional linear part. Thus, we

could reveal that there is also a considerable difference between a subject aged 70 and a subject aged 90 with regard to the concentration achieved when treated with the same dose. In fact, when comparing a subject aged 90 and a subject aged 70, the serum concentrations were 72.1% higher for clozapine, 60.8% higher for olanzapine, 67.2% higher for risperidone and 56.9% higher for quetiapine (in males). This clearly illustrates that “elderly” should not be viewed as one group, but rather be subdivided into several groups based upon exact age. However, saying so, it should also be noted that even between individuals at the same age there are considerable differences in what concentrations could be excepted at a given dose of an antipsychotic (Figure 2). This effect is probably to a large extent caused by genetic differences related to CYP enzyme activities (31), but also somatic diseases and environmental factors such as diet, smoking and infections contribute. As can also be seen from Figure 2, the differences between subjects of the same age increase with increasing age. This effect is as expected, as the diversity in general health status (frailty) and in disease-related changes in hepatic and renal function as well as cardiac output is more pronounced as age increases.

We also found that the dose-adjusted concentrations were generally higher in females than in males, although this was not the case for quetiapine in young subjects. CYP1A2, which is the main enzyme involved the metabolism of clozapine and olanzapine, has a lower activity in females than in males (32). CYP2D6 is responsible for the metabolism of risperidone to 9-OH-risperidone, but as the active moiety is used in the calculations in the present study, possible gender effects with this respect would not be expected to influence the dose-adjusted serum concentration. However, the generally smaller size of the liver and the kidneys in females could possibly explain the difference, but this might be of less significance than the CYP1A2 difference, as indicated from the lower gender effect for risperidone than for clozapine/olanzapine. Interestingly, the gender effect for quetiapine was not apparent before menopause but increased in postmenopausal women. One could speculate that this effect is related to the influence of estrogen on CYP3A4 activity, although limited data exist to support such a hypothesis (33).

Due to its naturalistic design, the present study has several limitations. On the basis of the requisition forms, samples from patients with comedication known to cause pharmacokinetic interactions were excluded. We did not, however, have the

possibility to double-check whether the information on co-prescribed drugs (or the lack of such information) was correct or not. Nor did we have the possibility to verify the information given with regard to dose, time of last medication intake and time of sampling. We do, however, believe that the possibly inaccurate nature of this information is counterbalanced by the large number of observations, and we cannot see any reason why age-related systematic differences should exist with this respect. Moreover, to refine the data used in the final model, we used 12-hour-adjusted concentrations instead of the actual concentration measured if the time interval from the last dose intake to sampling was not exactly 12 hours.

We do not have data on the genotype, diagnosis, smoking habits and ethnic background of the patients included. Given that the study is conducted in Norway it is reasonable to assume that the majority of the included patients are of Caucasian ethnicity. It is unknown whether the subjects included are representative for the whole population of patients using the four antipsychotic drugs included. It is also unknown to what degree the patients were adherent to the treatment. Studies on the possible effects of age as such on adherence are inconclusive, although the elderly more often have diseases and conditions that are related to reduced adherence (34). It should also be noted that if adherence were lower in the elderly than in younger subjects in the present study, the real age effect is in fact underestimated. In a few studies, females have been found to have higher adherence than males (35, 36), but in most studies, no gender effects have been revealed (37). In a previous study from our group, that female outpatients using olanzapine were less adherent to their medication than male outpatients, whereas for clozapine no such difference was found (27).

The doses used in the elderly were found to be lower than in younger subjects. The corresponding measured serum concentrations in the elderly were clearly lower than in younger subjects for clozapine and quetiapine and somewhat lower for risperidone, but not for olanzapine (Table 4). These results contrasts a previous study on the use of antidepressants (38), but is basically the same as found in a former study on risperidone (16). It is unknown whether the lower doses used in the older age groups are a result of administration to patients with less severe symptoms and other diagnoses than the younger patients, or whether the clinicians may have taken the increased susceptibility of adverse effects in the elderly into consideration.

The dosing recommendations for risperidone, e.g. when used in dementia, clearly advocate low doses. A recent study from Norway showed that there is an increasing off-label use of low doses of quetiapine, most likely used as a sedative/hypnotic agent in insomnia (39), and this use might be more common in the elderly. It should also be emphasized that as many of the older patients in the present study had undergone repeated TDM, this could be one explanatory factor for the obviously appropriate dose reductions observed. Therefore, the dose reductions and relatively low measured serum concentrations seen in the current study do not necessarily reflect the situation in elderly patients not undergoing TDM.

In conclusion, this study indicates that when prescribing clozapine, olanzapine, risperidone and quetiapine to elderly patients, no more than half the dose usually administered to younger patients should be used, and in many cases, particularly to the oldest individuals, even lower doses should be used. Given the interindividual variability in dose-adjusted concentrations observed, particularly among the oldest age groups, we also suggest using TDM to monitor the serum levels of the drugs in addition to a thorough clinical follow-up.

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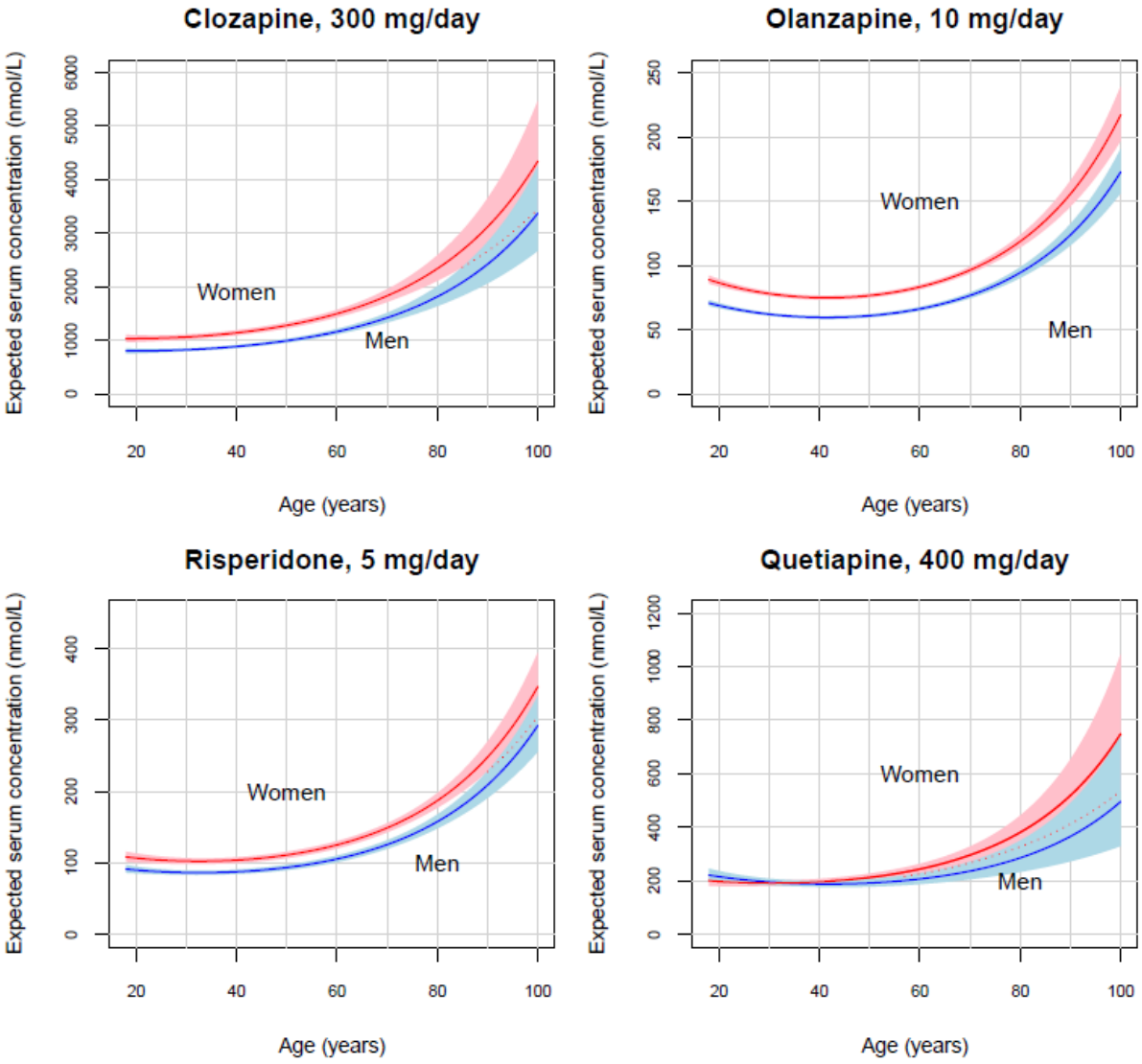
Figure legends

Figure 1

Expected serum concentrations of clozapine (top left), olanzapine (top right), risperidone plus active metabolite (bottom left) and quetiapine (bottom right) in women and men related to age, applying the model presented in Table 2. The shaded areas represent 95% confidence intervals. The daily doses used in the model are 300 mg for clozapine, 10 mg for olanzapine, 5 mg for risperidone and 400 mg for quetiapine. For clozapine, a concentration of 1000 nmol/L corresponds to 327 ng/mL. For olanzapine, a concentration of 100 nmol/L corresponds to 31 ng/mL. For risperidone plus active metabolite, a concentration of 100 nmol/L corresponds to 42 ng/mL. For quetiapine, a concentration of 200 nmol/L corresponds to 77 ng/mL.

Figure 2

Plots of age-related expected serum concentrations in males (left panel) and females (right panel) for clozapine, olanzapine, risperidone plus active metabolite, and quetiapine. The daily doses used in the model are 300 mg for clozapine, 10 mg for olanzapine, 5 mg for risperidone and 400 mg for quetiapine. The solid line is identical to the overall expected values shown in Figure 1. The dashed lines show the degree of deviation from the overall value in the individual patient, according to deciles (from the bottom and upwards in each figure, the dashed lines represent the 10, 20, 30, 40, 60, 70, 80 and 90 percentiles of the distribution of concentrations in the population of that age). For clozapine, a concentration of 1000 nmol/L corresponds to 327 ng/mL. For olanzapine, a concentration of 100 nmol/L corresponds to 31 ng/mL. For risperidone plus active metabolite, a concentration of 100 nmol/L corresponds to 42 ng/mL. For quetiapine, a concentration of 500 nmol/L corresponds to 192 ng/mL.


Clozapine, 300 mg/day
Expected serum concentration (nmol/L)
0
1000
2000
3000
4000
5000
6000
Women
Men
20
40
60
80
100
Age (years)
Olanzapine, 10 mg/day
Expected serum concentration (nmol/L)
0
50
100
150
200
250
Women
Men
20
40
60
80
100
Age (years)
Risperidone, 5 mg/day
Expected serum concentration (nmol/L)
0
100
200
300
400
Women
Men
20
40
60
80
100
Age (years)
Quetiapine, 400 mg/day
Expected serum concentration (nmol/L)
0
200
400
600
800
1000
1200
Women
Men
20
40
60
80
100
Age (years)

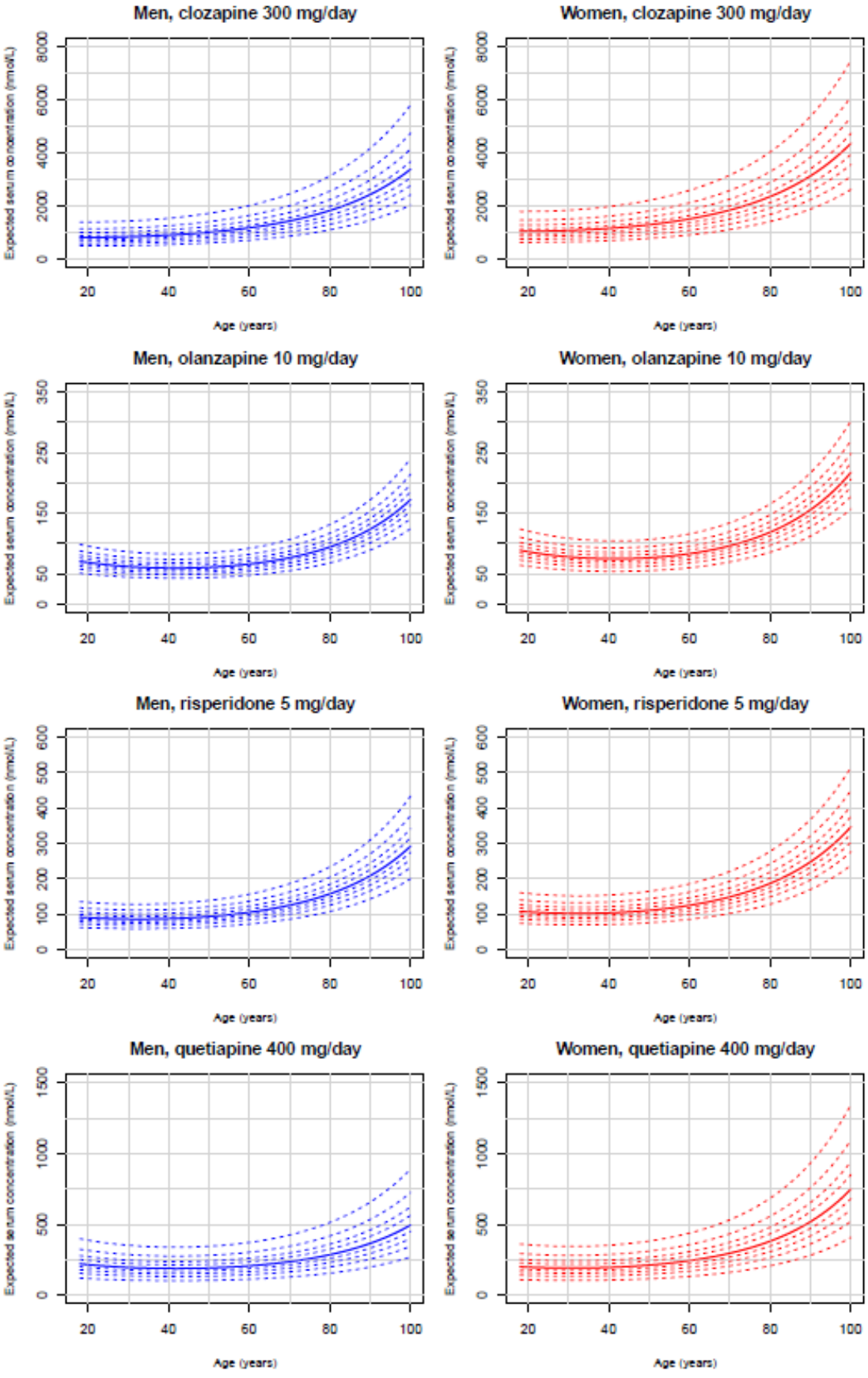

Men, clozapine 300 mg/day
Women, clozapine 300 mg/day
Men, olanzapine 10 mg/day
Women, olanzapine 10 mg/day
Men, risperidone 5 mg/day
Women, risperidone 5 mg/day
Men, quetiapine 400 mg/day
Women, quetiapine 400 mg/day
Age (years)

Table 1. Number of samples for clozapine, olanzapine, risperidone and quetiapine for males and females in each age group and in total. The numbers in parentheses are the numbers of patients. The numbers of the patients in each age group exceed the total number of patients because a patient can be represented with samples in more than one age group.

Age group	Gender	Clozapine	Olanzapine	Risperidone	Quetiapine
18-59 years	Males	9499 (1131)	8283 (2872)	2544 (1153)	1861 (781)
	Females	6056 (680)	5254 (2098)	1822 (854)	2052 (926)
60-69 years	Males	692 (115)	649 (295)	173 (87)	100 (55)
	Females	462 (87)	904 (381)	241 (130)	129 (82)
70-79 years	Males	274 (38)	222 (118)	85 (58)	32 (21)
	Females	185 (36)	515 (243)	157 (105)	66 (36)
80-89 years	Males	28 (11)	86 (52)	62 (43)	17 (9)
	Females	46 (21)	203 (143)	178 (116)	46 (31)
≥90 years	Males	0 (0)	4 (4)	22 (15)	0 (0)
	Females	7 (3)	51 (33)	59 (38)	13 (8)
Total	Males	10493 (1255)	9244 (3163)	2886 (847)	2010 (967)
	Females	6756 (767)	6927 (2663)	2457 (1063)	2306 (1243)

Table 2. Model parameter estimates of the explanatory factors on the $\log_e$-transformed dose-adjusted concentrations for the various antipsychotics. For details, see Methods section.

	Estimate	P value	95 % CI Lower bound	95 % CI Upper bound
Clozapine				
Intercept	1.060	<0.001	0.904	1.217
Female	0.253	<0.001	0.201	0.305
Age	-0.00807	0.024	-0.01509	-0.00104
Age × age	0.000220	<0.001	0.000141	0.000292
Olanzapine				
Intercept	2.321	<0.001	2.240	2.401
Female	0.229	<0.001	0.202	0.256
Age	-0.0258	<0.001	-0.0294	-0.0223
Age × age	0.000311	<0.001	0.000275	0.000347
Risperidone[1]				
Intercept	3.134	<0.001	2.993	3.275
Female	0.171	<0.001	0.123	0.219
Age	-0.0175	<0.001	-0.0235	-0.0115
Age × age	0.000268	<0.001	0.000212	0.000325
Quetiapine				
Intercept	-0.254	0.044	-0.501	-0.007
Female	-0.209	0.041	-0.408	-0.009
Age	-0.0238	<0.001	-0.0347	-0.0130
Age × age	0.000286	<0.001	0.000170	0.000401
Age × female	0.00620	0.0109	0.00143	0.01098

[1] For the sum of the concentration of risperidone and the active metabolite 9-hydroxyrisperidone

Table 3. Dose-adjusted serum concentrations in (nmol/l)/(mg/d) according to the ages 40, 70, 80 and 90 years and according to gender for clozapine, olanzapine, risperidone and quetiapine, applying the model presented in Table 2. Numbers in parentheses represent percent increase from the concentration at the age 40 years in the same gender.

Group	**Gender**	**Dose-adjusted serum concentrations**			
		Age 40 years	**Age 70 years (percent change from age 40)**	**Age 80 years (percent change from age 40)**	**Age 90 years (percent change from age 40)**
Clozapine	Males	2.97	4.82 (+62.3 %)	6.19 (+108 %)	8.30 (+179 %)
	Females	3.83	6.21 (+62.3 %)	7.97 (+108 %)	10.7 (+179 %)
Olanzapine	Males	5.94	7.62 (+28.1 %)	9.37 (+57.5 %)	12.3 (+106 %)
	Females	7.50	9.61 (+28.1 %)	11.8 (+57.5 %)	15.4 (+106 %)
Risperidone[1]	Males	17.6	25.3 (+44.2 %)	31.9 (+81.4 %)	42.3 (+141 %)
	Females	20.9	30.1 (+44.2 %)	37.8 (+81.4 %)	50.3 (+141 %)
Quetiapine	Males	0.475	0.603 (+27.2 %)	0.735 (+54.8 %)	0.947 (+ 99.6 %)
	Females	0.493	0.756 (+53.2%)	0.979 (+98.4 %)	1.343 (+172 %)

[1] For the sum of the concentration of risperidone and the active metabolite 9-hydroxyrisperidone

Table 4. Median doses with interquartile ranges in parentheses, and median measured concentrations with interquartile ranges in parentheses, in various age groups for clozapine, olanzapine, risperidone and quetiapine. Recommended reference ranges at our laboratory are: 300-2500 nmol/L for clozapine, 30-200 nmol/L for olanzapine, 20-120 nmol/L for risperidone (including the active metabolite 9-hydroxyrisperidone) and 50-700 nmol/L for quetiapine.

Age group	**Clozapine dose (mg/d)**	**Olanzapine dose (mg/d)**	**Risperidone dose (mg/d)**	**Quetiapine dose (mg/d)**
18-59 years	350 (250-500)	15 (10-20)	4 (2-5)	600 (400 -800)
60-69 years	312 (200-462)	10 (10-20)	3 (2-4)	500 (300-700)
70-79 years	300 (100-350)	10 (7.5-15)	2 (1-3)	300 (106-575)
80-89 years	62.2 (25-100)	7.5 (5-10)	1 (1-2)	125 (62.5-200)
≥90 years	12.5 (12.5-16.6)	7.5 (5-10)	1 (1-1.5)	87.5 (50-119)
Age group	**Clozapine concentration (nmol/L)**	**Olanzapine concentration (nmol/L)**	**Risperidone concentration[1] (nmol/L)**	**Quetiapine concentration (nmol/L)**
18-59 years	1123 (588-1678)	95 (59-146)	66 (40-104)	252 (127-458)
60-69 years	1294 (794-1940)	114 (69-176)	79 (46-118)	228 (121-393)
70-79 years	1107 (317-1721)	105 (63-162)	56 (33-91)	149 (78-317)
80-89 years	279 (186-849)	83 (49-130)	49 (31-85)	116 (60-195)
≥90 years	95 (74-115)	84 (61-131)	40 (26-68)	101 (40-151)

[1] Sum of the concentration of risperidone and the active metabolite 9-hydroxyrisperidone