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Treatment of depression: Are psychotropic drugs appropriately dosed in women and in the elderly? Dosages of psychotropic drugs by sex and age in routine clinical practice

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Abstract

Background: Several researchers have shown higher concentration-dose ratios of psychotropic drugs in women and the elderly. Therefore, lower dosages of psychotropic drugs may be recommended in women and the elderly. This study describes sex- and age-related dosage of psychotropic drugs prescribed to patients with major depressive disorder (MDD) in routine clinical practice.

Method: Influence of sex and age on dosages are analysed for the 10 most commonly prescribed drugs in our dataset consisting of 32,082 inpatients with MDD. Data stems from the European drug safety program "Arzneimittelsicherheit in der Psychiatrie". The observed sex and age differences in prescriptions are compared to differences described in literature on age- and gender-related pharmacokinetics.

Results: Among patients over 65 years, a statistically significant decrease in dosages with increasing age (between 0.65% and 2.83% for each increasing year of age) was observed, except for zopiclone. However, only slight or no influence of sex-related adjustment of dosage in prescriptions was found.

Conclusion: Age appears to influence adjustment of dosage in most psychotropic drugs, but to a lower extent than data on age-related pharmacokinetics suggests. Although literature also suggests that lower dosages of psychotropic drugs may be appropriate for females, this study found women are usually prescribed the same dosage as men.

KEYWORDS
age, AMSP, dosage, drug safety, gender, major depressive disorder, overdose, psychotropic drugs, sex, TDM

Waldemar Greil and Mateo de Bardeci equally contributed for this article.

1 | BACKGROUND

When treated with the same dosage, women show higher drug plasma levels than men for numerous drugs (Reis et al., 2009; Weiss et al., 2005; Zucker & Prendergast, 2020). This is due to sex differences in height, body weight, fat proportion, kidney function, activity of cytochrome P (CYP) 450 enzymes and smoking habits (Aichhorn, Marksteiner et al., 2006; Aichhorn, Whitworth et al., 2006; Meibohm et al., 2002; Oliveira et al., 2007; Schwartz, 2003; Soldin & Mattison, 2009). Sex differences in pharmacokinetics with a significantly higher concentration-dose ratio in women have been demonstrated for a number of psychotropic substances, for example, mirtazapine (Reis et al., 2009; Unterecker et al., 2013), olanzapine (Castberg et al., 2017; Weiss et al., 2005), venlafaxine (Hansen et al., 2017; Reis et al., 2009; Sigurdsson et al., 2015; Unterecker et al., 2012), escitalopram (Reis et al., 2009; Scherf-Clavel et al., 2019) and duloxetine (Lobo et al., 2009). While various authors have reported sex differences in the pharmacodynamic properties of psychotropic drugs, these have only been poorly studied with regard to therapeutic application. The differences in sex-dependent drug tolerability appear to be mostly due to differences in pharmacokinetic properties. Female sex hormones in particular seem to have a considerable influence on the desired and undesired effects of psychotropic drugs (Kokras et al., 2019; Soldin & Mattison, 2009; Spoletini et al., 2012).

Though reported inconsistently in current literature (D'Incau et al., 2014; Greenblatt et al., 2019), women appear to report a higher rate of adverse drug reactions (ADRs; Greil et al., 2019; Zucker & Prendergast, 2020; Zopf et al., 2008), perhaps due to higher plasma concentrations (Zucker & Prendergast, 2020), while in general, elderly patients appear more likely to suffer from ADRs (Beijer & de Blaey, 2002). However, in regards to psychotropic drugs, a number of studies have shown similar incidence rates of severe ADRs in elderly as in young patients (Greil et al., 2019; Gray et al., 2019; Singh et al., 2017). On the other hand, an increase of concentration-dose ratios with age is described for various psychotropic drugs, for example, mirtazapine (Reis et al., 2009; Unterecker et al., 2013), venlafaxine (Hansen et al., 2017; Reis et al., 2009; Sigurdsson et al., 2015; Unterecker et al., 2012), quetiapine (Aichhorn et al., 2006; Bakken et al., 2011; Castberg et al., 2017), citalopram (De Mendonça Lima et al., 2005; Reis et al., 2009; Unterecker et al. 2013), escitalopram (Reis et al., 2009), olanzapine (Castberg et al., 2017; Weiss et al., 2005), zopiclone (Gaillot et al., 1987) and sertraline (Reis et al., 2009; Unterecker et al., 2013). Since age-related changes in body composition and polypharmacy lead to different pharmacokinetics and pharmacodynamics, lower doses of psychotropic drugs in the elderly are often recommended (Hiemke et al., 2018; Katzman et al., 2014; Thürmann, 2020; Tveit et al., 2020).

In the past, women have been under-represented in clinical trials (Liu & Mager, 2016), therefore leading to a weaker understanding of sex differences in pharmacological treatment. According to Sørup et al. (2020), the influence of patient's sex on ADRs is an understudied factor. This may be especially problematic in the treatment of psychiatric conditions because women are more likely to be treated with psychotropic drugs than men (Glaeske et al., 2012).

In 2013, the U.S. Food and Drug Administration (FDA) approved label changes specifying new maximum dosing recommendations for zolpidem, being 5 mg/day for females and 10 mg/day for males (U.S. Food and Drug Administration [FDA], 2013a, 2013b). According to the FDA, higher dosages may lead to next-morning impairments, especially driving impairment (U.S. FDA, 2013a, 2013b). However, this recommendation is controversial. It has been argued that disturbed sleep in under-dosed females treated with zolpidem may impair driving even more than the intake of 10 mg/day (Greenblatt et al., 2019).

In this study, a large data set from a pharmacovigilance project is used to examine the dosage of psychotropic drugs in the treatment of major depressive disorder (MDD) in relation to sex and age in clinical routine. We selected the 10 most prescribed drugs in our dataset and additionally zolpidem due to the sex-specific recommendation made by the FDA stated above.

2 | METHOD

2.1 | Data source

The analysed prescription data of the present study was gathered by the project "Arzneimittelsicherheit in der Psychiatrie" (AMSP; drug safety in psychiatry). Established in 1993, AMSP is an ongoing European multi-center drug safety program which collects data on psychopharmacotherapy and severe ADRs occurring in psychiatric inpatients in a naturalistic setting. AMSP´s pharmacovigilance methods have been described in detail previously (Engel et al., 2004; Grohmann et al., 2004, 2014). In brief, AMSP consists of two principal data collections (i.e., prescription data and severe ADRs) from a total of 116 hospitals in Germany, Switzerland and Austria, as well as temporarily from Belgium and Hungary. The number of participating hospitals increased from nine in 1994 to 63 in 2015. In a cross-sectional approach, all participating hospitals record drug prescriptions for all inpatients under surveillance on two reference days per year. All drugs administered on these days are assessed along with the patients' age, sex and psychiatric diagnosis. Evaluations of the AMSP database have been approved by the Ethics Committee of the University of Munich and the Ethics Committee of the Hannover Medical School (Nr. 8100 BO S 2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP program is a continuous observational post-marketing drug surveillance program and does not interfere with the ongoing clinical treatment of patients under surveillance.

2.2 | Sample description

A total of 32,082 patients aged 18 to 89 years hospitalized between 2001 and 2015, with a primary diagnosis of MDD are

investigated. The dosages of the 10 most prescribed drugs and zolpidem are analysed (descending in the frequency of prescription): mirtazapine (n = 10,431), venlafaxine (n = 8072), lorazepam (n = 7757), quetiapine (n = 6993), citalopram (n = 3909), escitalopram (n = 3842), olanzapine (n = 3441), duloxetine (n = 3070), zopiclone (n = 2936), sertraline (n = 2909) and zolpidem (n = 1873). Tricyclic antidepressants were not among the 10 most frequently prescribed drugs during the period studied. The frequency distribution according to sex and age differed only slightly; among patients over 65 years, two additional antipsychotic drugs were among the most frequently prescribed drugs: risperidone and pipamperone (see: Table S4). The sample consists of 11,887 (37.1%) males and 20,195 (62.9%) females. Note that a patient may have had more than one psychotropic drug prescribed. Table 1 shows a summary of the sample composition.

In order to identify potential confounding variables that could account for distortions in the analysis, the following variables were considered: severity of MDD, psychiatric comorbidity, differences in calendar year and differences in age distribution.

In Figure 1, the number of male and female patients per calendar year are depicted. Substantial discrepancies in the male to female ratio over time were not observed.

No substantial differences in the severity of MDD among male and female patients were found (Table 2). Table 3 shows the severity of MDD for young and elderly patients. Elderly patients were more likely to suffer from severe MDD with psychosis than younger patients (18.0% vs. 12.2%). Psychiatric comorbidity documented in 20.5% of patients did not differ essentially between women and men (see additional files for data). Further analysis is based on the assumption that differences in severity of MDD and small differences in male to female ratio over years did not lead to a significant distortion. Distribution of age (depicted in Figure 2), on the other hand, differs substantially. In particular, there were proportionally more elderly women than elderly men. Therefore, analysis was adjusted in order to consider differences in distribution of age.

2.3 | Statistical analysis

Statistical analysis was performed using R version 3.6.2. To assess the influence of age in dose of psychotropic drugs, the slope of a linear fit among patients older than 65 and younger than 90 years of age was computed. Significance was estimated using a t-test on the coefficient of the slope under the hypothesis to be zero. Along with the slope, the percentage of change in relation to the previous year was computed, which was calculated from the coefficient of an exponential fit. In analogy to literature on differences in age-related pharmacokinetics, the age groups of up to 65 years old and over 65 years old were selected. The elderly group served as reference. p-values were computed using a Wilcoxon test.

In order to account for sex differences in dosage, we adjusted for age by comparing prescriptions in patients with similar age. Patients were first categorized by sex and then assigned to different age groups. Mean dosage of each group for both sexes was calculated separately. The sex difference within each age group was calculated with female patients serving as reference. Finally, the total sex difference was calculated as the weighted mean of all percentage differences, by weighting with the number of patients (male and female) of each age group. Significance was determined using a paired Wilcoxon signed-rank test.

TABLE 1 Sample composition

Sample composition	
Total number of patients	32,082
Number of males	11,887 (37.1%)
Number of females	20,195 (62.9%)
Age of males in years (mean ± SD)	49.5 ± 15.3
Age of females in years (mean ± SD)	51.9 ± 16.5
Number of psychotropic drugs prescribed per patient (mean ± SD)	2.6 ± 1.3

Abbreviation: SD, standard deviation.

3 | RESULTS

3.1 | Age

Dosage in relation to age for antidepressant drugs, antipsychotic drugs and hypnotic and tranquilizing drugs are shown in Figures 3–5. Table 4 shows the mean differences of dosages in patients up to 65 years and older than 65 years.

3.1.1 | Age: antidepressants drugs

Among the six analysed antidepressant drugs (Figure 3), a slight increase of daily dose for each additional year of age in young patients and a decrease in elderly patients was detected. Dosage remained relatively unchanged among patients between 35 and 65 years of age. Among patients older than 65 years, a decrease between 0.65% for the noradrenergic and specific serotonergic antidepressant drug (NaSSA) mirtazapine and 1.32% for the selective serotonin reuptake inhibitor (SSRI) sertraline for every increasing year of age was observed. Dose of the SSRIs citalopram and escitalopram decreased by 0.68% and 1.13%, respectively, and 1.00% and 0.76% for the selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) venlafaxine and duloxetine. All of these findings are statistically significant ($p < 0.01$). When comparing mean prescribed dosages between patients up to 65 years old and older than 65 years old, statistically significant differences were found for all antidepressant drugs with the exception of mirtazapine, varying from 7% for citalopram to 14% for venlafaxine (Table 4). When the

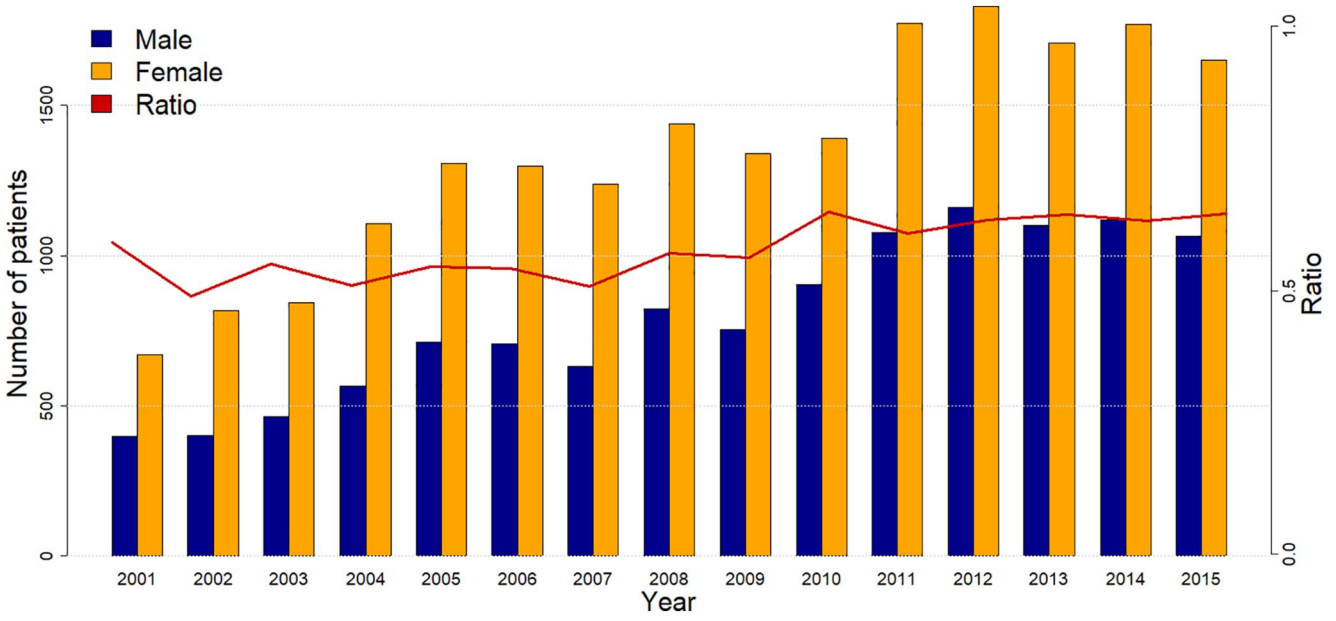


FIGURE 1 Number of patients with MDD by calendar year. Number of male and female patients per calendar year between 2001 and 2015. Blue: Males. Orange: Females. Red: Male to female ratio. MDD, major depressive disorder

TABLE 2 Severity of MDD according to sex

Severity of MDD according to sex	
Mild MDD ("F32.0","F33.0")	368 (1.2%)
Male	151 (1.3%)
Female	217 (1.1%)
Moderate MDD ("F32.1","F33.1")	8237 (25.7%)
Male	3033 (25.5%)
Female	5204 (25.8%)
Severe MDD ("F32.2", "F33.2")	18,257 (56.9%)
Male	6720 (56.5%)
Female	11,537 (57.1%)
Severe MDD with psychosis ("F32.3", "F33.3")	4308 (13.4%)
Male	1645 (13.8%)
Female	2663 (13.2%)
No info or other MDD ("F32.8","F32.9","F33.4","F33.8,"F33.9")	912 (2.8%)
Male	338 (2.8%)
Female	574 (2.8%)

Note: Diagnoses according to 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Severity of MDD is similar between male and female patients.

Abbreviation: MDD, major depressive disorder.

TABLE 3 Severity of MDD according to age

Severity of MDD according to age	
Mild MDD ("F32.0","F33.0")	368 (1.1%)
Up to 65 ys	287 (1.3%)
Over 65 ys	81 (1.2%)
Moderate MDD ("F32.1","F33.1")	8237 (25.7%)
Up to 65 ys	6803 (26.8%)
Over 65 ys	1434 (21.4%)
Severe MDD ("F32.2", "F33.2")	18,257 (56.9%)
Up to 65 ys	14,501 (57.1%)
Over 65 ys	3756 (56.1%)
Severe MDD with psychosis ("F32.3", "F33.3")	4308 (13.4%)
Up to 65 ys	3104 (12.2%)
Over 65 ys	1204 (18.0%)
No info or other MDD ("F33.4","F32.9","F32.8","F33.9","F33.8")	912 (2.8%)
Up to 65 ys	693 (2.7%)
Over 65 ys	219 (3.3%)

Note: Diagnoses according to ICD-10. Overall, severity of MDD is similar between young and elderly patients (despite differences for moderate MDD and severe MDD with psychosis).

Abbreviations: MDD, major depressive disorder; ys, years of age.

comparison of dosages starts at age 30 (i.e., comparison of age groups 30-65 and 66-89), the differences between the two age groups are only slightly greater and the lack of difference in dosage for mirtazapine remains unchanged. This also applies to the hypnotic drug zoplicone; see below.

3.1.2 | Age: antipsychotics drugs

Dosage of the two antipsychotic drugs olanzapine and quetiapine shows a plateau among young and middle-aged patients (Figure 4). However, a more pronounced slope than in

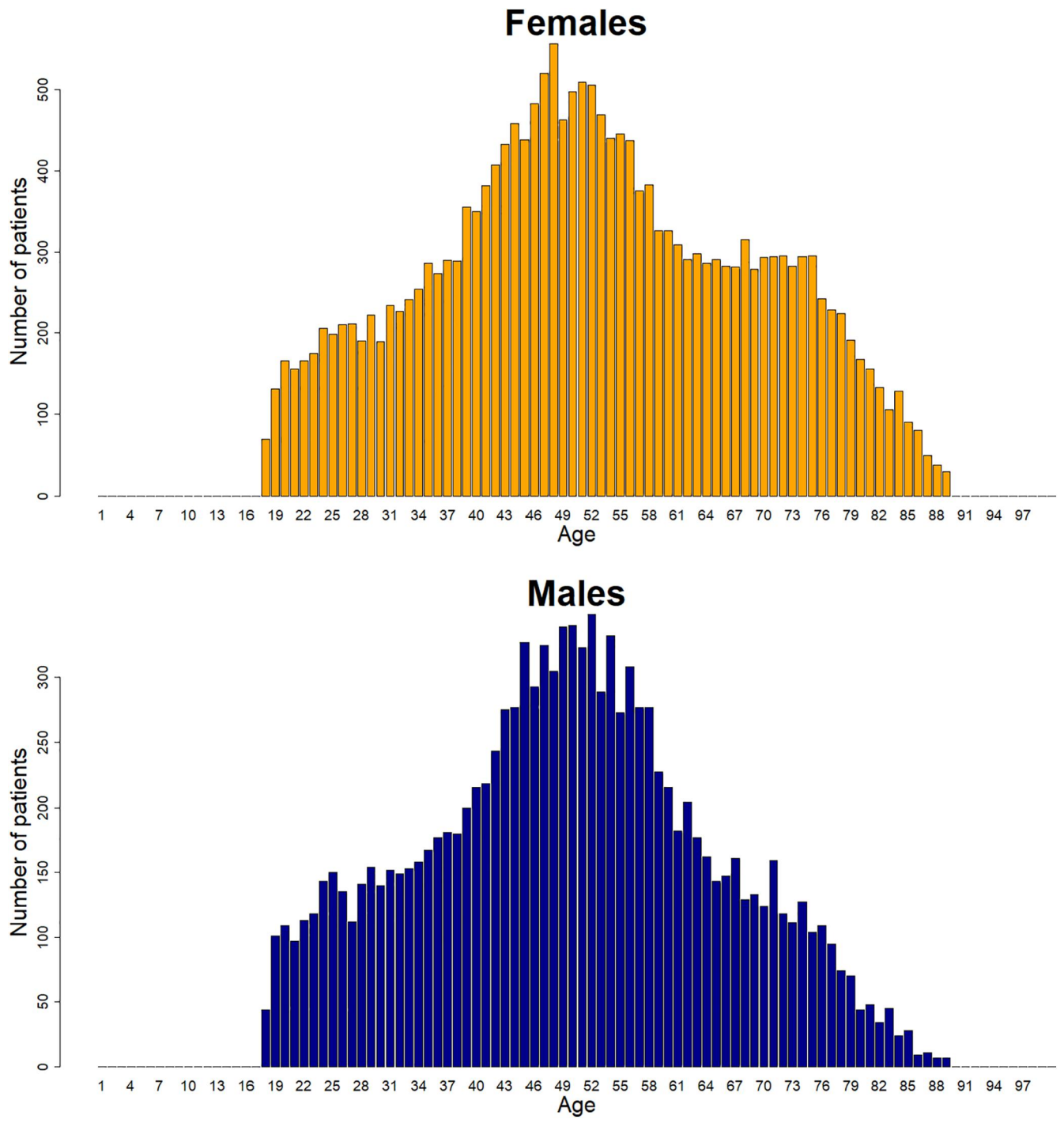


FIGURE 2 Distribution of age

antidepressant drugs was observed in elderly patients. Among patients over 65 years old, a decrease of 2.48% (olanzapine) and 2.83% (quetiapine) in daily prescribed dosages for each increasing year of age ($p < 0.0001$) was found. When comparing the mean prescribed dosages between patients up to 65 years old and older than 65 years old, statistically significant differences of 24.4% for olanzapine and 21% for quetiapine were detected (Table 4).

3.1.3 | Age: hypnotic and tranquilizing drugs

Distribution of prescribed daily dosage differs substantially between the two hypnotic drugs zopiclone and zolpidem and the tranquilizing drug lorazepam (Figure 5). Dosage of zolpidem showed a slight increase in young patients, a plateau in middle-aged patients and a decrease in elderly patients (Figure 5a). This distribution is similar to the distribution of antidepressant drugs. A consistent dosage of

TABLE 4 Mean dosage differences in patients up to 65 and older than 65 years

	18ys to 65 ys			66ys to 89 ys				
Drug	N	Mean dose [mg/d]	SE	N	Mean dose [mg/d]	SE	Difference [%](means)	p-value (means)
Citalopram	3130	29.2	0.2	779	27.3	0.5	+7.0	<0.001
Escitalopram	3143	16.3	0.1	699	14.4	0.3	+13.4	<0.001
Sertraline	2357	102.8	1.0	552	93.6	2.0	+9.7	<0.001
Mirtazapine	7419	33.2	0.2	3012	33.6	0.3	NS	NS
Venlafaxine	6587	200.5	1.1	1485	175.9	2.2	+14.0	<0.001
Duloxetine	2462	79.9	0.6	608	73.0	1.2	+9.4	<0.001
Olanzapine	2601	10.2	0.1	840	8.2	0.2	+24.4	<0.001
Quetiapine	5673	215.1	2.6	1320	177.8	4.4	+21.0	<0.001
Zolpidem	1379	10.5	0.1	494	9.5	0.1	+10.4	<0.001
Zopiclone	2162	7.2	0.1	774	7.2	0.1	NS	NS
Lorazepam	5624	1.9	0.0	2133	1.5	0.0	+29.7	<0.001

Note: Number of patients (*N*), prescribed mean dosages and standard error (SE) for antidepressant, antipsychotic and hypnotic drugs in inpatients up to 65 and over 65 years old. On the right hand the difference between means as percentage change is shown, in which the elderly patient group serves as reference. *p*-values are calculated using a Wilcoxon test.

Abbreviation: ys: years of age.

approximately 7.2 mg zopiclone per day was seen for all age groups (Figure 5b). Dose of lorazepam showed a steady decline among all age groups (Figure 5c).

Among patients over 65 years old, daily prescribed dose decreased for each increasing year of age for zolpidem by 1.17% and lorazepam by 1.26% ($p < 0.001$). Zopiclone did not show any significant age-related adjustments in dosage. When comparing the mean difference in prescribed dosages between patients up to 65 years old and older than 65 years old, statistically significant differences were found for zolpidem (10.4%) and lorazepam (29.7%) but not for zopiclone (Table 4).

3.2 | Sex

The influence of sex on prescribed dosages of antidepressant, antipsychotic and hypnotic and tranquilizing drugs are shown in Figures 6–8. The analysis of the dosages of the 11 drugs studied showed statistically significant interactions between age and sex for escitalopram, quetiapine and olanzapine with more prominent sex differences for dosages in the elderly compared to younger adults ($p < 0.001$).

3.2.1 | Sex: antidepressants drugs

Statistically significant differences in daily dose prescriptions between sexes were detected for both escitalopram and venlafaxine of which males received 5.13% and 4.59%, respectively, more than females (Figure 6). Dosage of citalopram, sertraline, mirtazapine and duloxetine did not reveal statistically significant sex differences.

3.2.2 | Sex: antipsychotic drugs

Among antipsychotic drugs, statistically significant differences were detected for olanzapine of which males received 4.94% more than females (Figure 7). Dosage of quetiapine was unrelated to sex.

3.2.3 | Sex: hypnotic and tranquilizing drugs

Dosage of the hypnotic drugs zolpidem and zopiclone and the tranquilizing drug lorazepam did not show any significant association to sex (Figure 8).

4 | DISCUSSION

4.1 | Age

The findings of the present study are discussed in context of the currently available literature regarding the influence of age and sex on plasma levels of patients taking psychotropic drugs. A comprehensive table describing primary findings of the studies referred to can be found in the supplementary material (Table S1).

4.1.1 | Age: antidepressant drugs

In 2009, Reis et al. (2009) analysed plasma levels for citalopram and escitalopram at steady state, finding that elderly patients over 64 years old had 84% and 91% higher plasma levels than younger

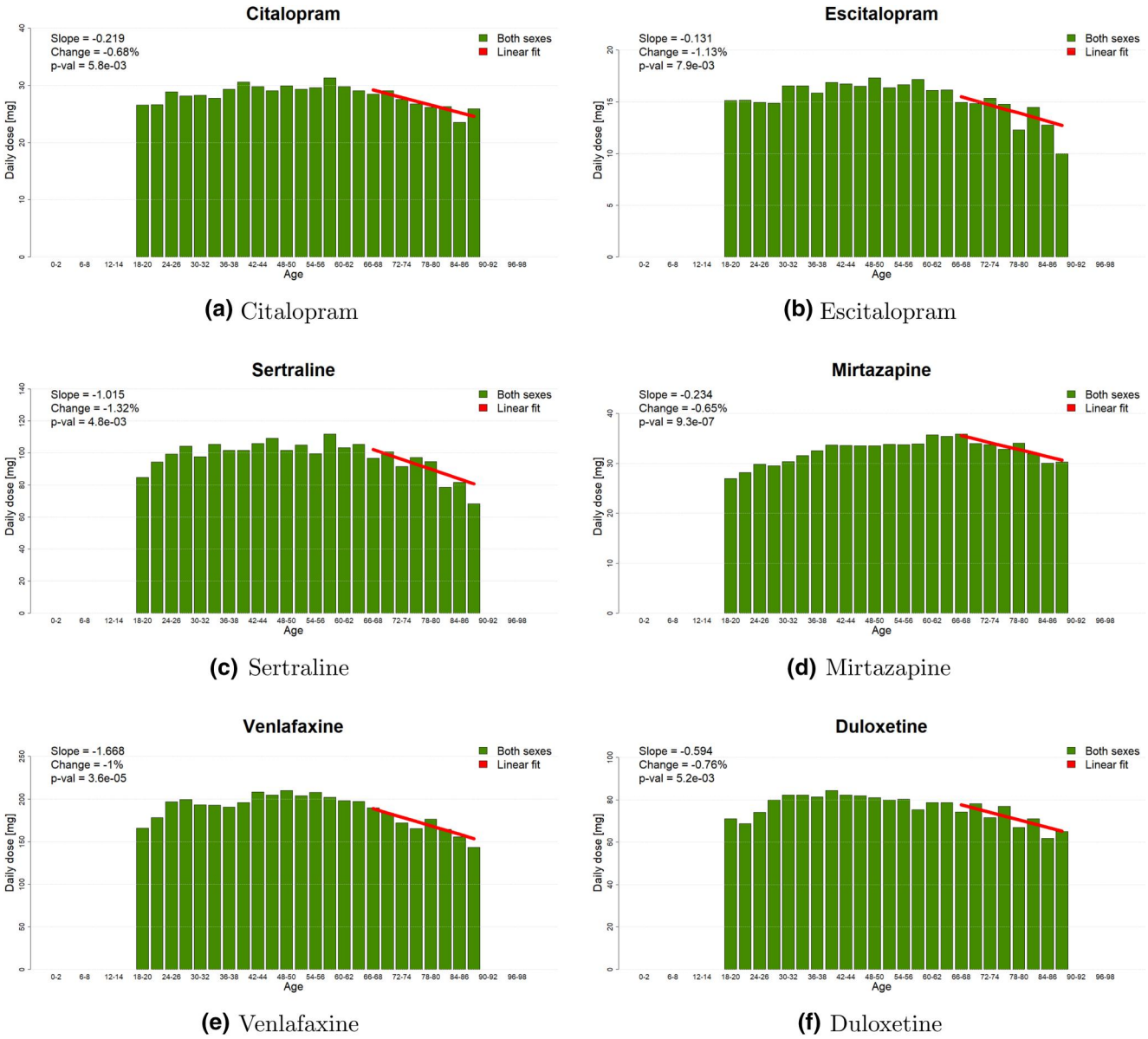
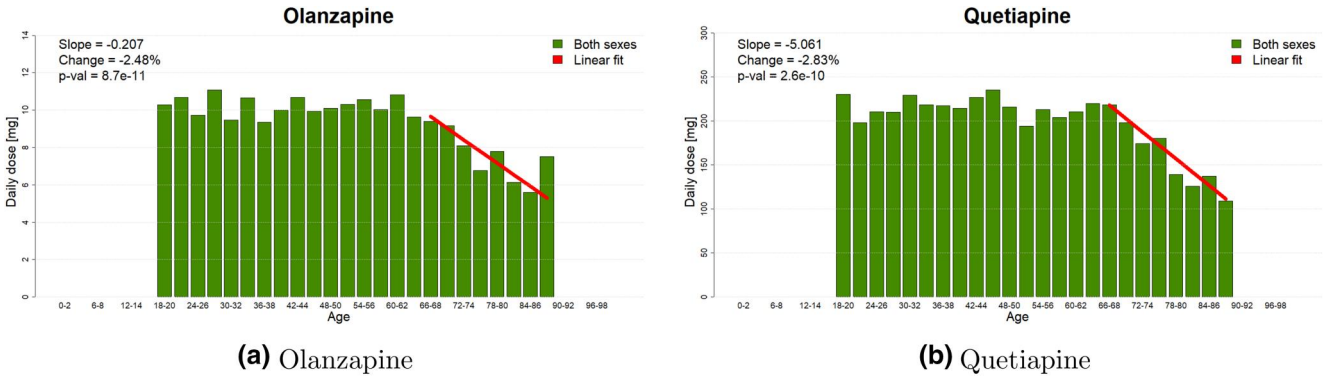


FIGURE 3 Daily dose according to age: Antidepressant drugs. Daily prescribed doses (mg) of antidepressant drugs according to age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups consisting of three consecutive years. In red, a linear model fitted to patients between 66 and 89 years old is shown. Slope: Thes lope of the linear model, describing the average absolute difference of daily dose in relation to the previous year in elderly patients. Change: Average percentage change in relation to the previous year in elderly patients. p-val: *p*-value under the hypothesis that the slope is zero, $p < 0.001$ for all drugs

patients at the same dosage. The present study detected much smaller differences in dosage of only 7.0% (citalopram) and 13.4% (escitalopram). Reis et al. (2009) found 31% higher plasma levels of sertraline in older patients, while we observed a difference of only 9.7% in prescribed dosage of sertraline. Among elderly venlafaxine-users, Reis et al. (2009) detected a 38% difference in plasma levels between elderly and young patients, whereas this study found only 14% lower dosages used in the treatment of older patients.

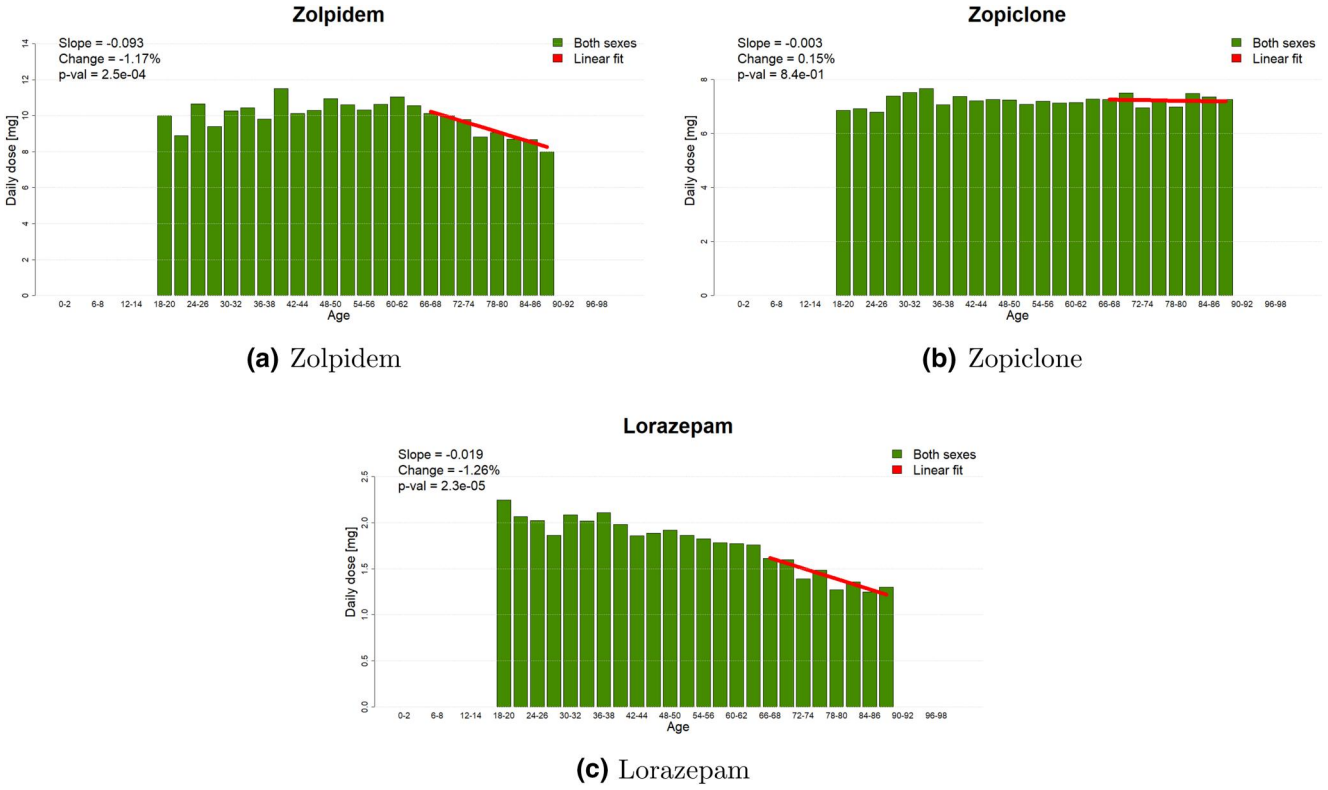
A significant decrease in dosage prescription of duloxetine among the elderly and significant differences between young and elderly was found in the present study. In comparison, a study by Lobo et al. (2009) computed a fit over all ages and found a slope of −0.33 for apparent total clearance. Using the same method for the description of dosages in the present data, the analogue slope shows −0.146 (Figure S1). This consideration indicates the influence of age on prescription of duloxetine is substantially smaller than the influence on plasma levels according to literature.

This study was unable to detect any age-related dose reduction of mirtazapine. In contrast, an increase of plasma levels in elderly of over 40% was seen (Reis et al., 2009). Although we found statistically



(a) Olanzapine **(b)** Quetiapine

FIGURE 4 Daily dose according to age: Antipsychotic drugs. Daily prescribed doses (mg) of antipsychotic drugs according toage including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups consisting of three consecutive years. In red, a linear model fitted to patients between 66 and 89 years old. Slope: The slope of the linear model, describing the average absolute difference of daily dose in relation to the previous year in elderly patients. Change: Average percentage change in relation to the previous year in elderly patients. p-val.: *p*-value under the hypothesis that the slope is zero, $p < 0.001$ for both antipsychotic drugs



(a) Zolpidem **(b)** Zopiclone **(c)** Lorazepam

FIGURE 5 Daily dose according to age: Hypnotic and Tranquilizing drugs. Daily prescribed doses (mg) of hypnotic and tranquilizing drugs according to age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients with in age groups consisting of three consecutive years. In red, a linear model fitted to patients between 66 and 89 years old. Slope: The slope of the linear model, describing the average absolute difference of daily dose in relation to the previous year in elderly patients. Change: Average percentage change inrelation to the previous year in elderly patients. p-val.: *p*-value under the hypothesis that the slope iszero, n.s. (not significant) for zopiclone; $p < 0.001$ for lorazepam and zolpidem

significant differences in prescribed dosages of young patients in comparison to elderly patients for the above mentioned antidepressant drugs, the differences in literature on age-related pharmacokinetics appear to be more pronounced than reflected in actual clinical drug utilization.

4.1.2 | Age: antipsychotic drugs

Patients over 65 years of age were treated with significantly lower mean dosages of olanzapine and quetiapine (24.4% and 21%, respectively) than patients under 65 years of age. As observed among

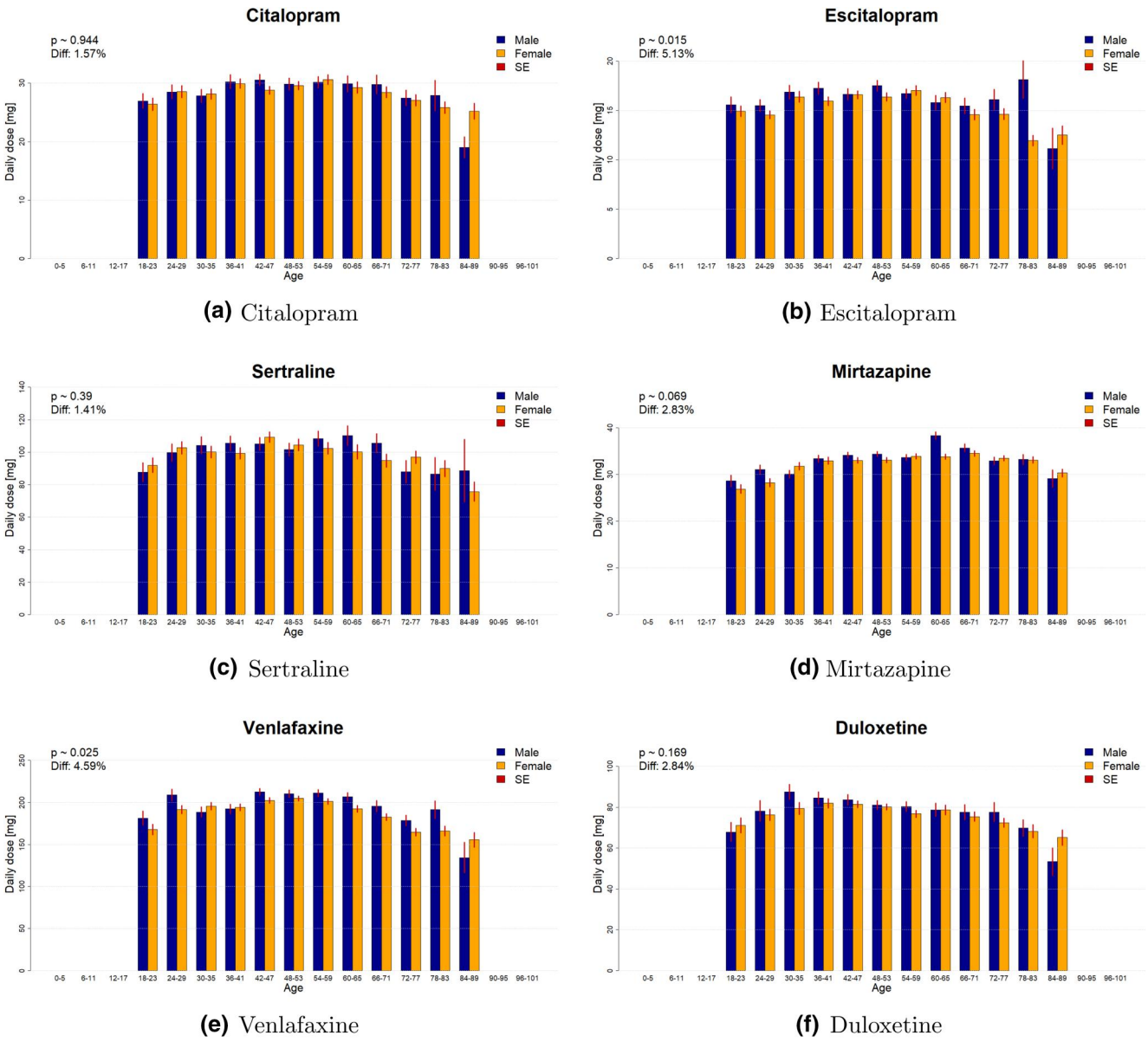


FIGURE 6 Daily dose according to age and sex: Antidepressant drugs. Daily prescribed doses (mg) of antidepressant drugs according toage: males in blue and females in orange. The standard error is depicted in red. The height of the bars corresponds to the mean daily dosage for inpatients within age groups consisting of six consecutive years. p: The *p*-value is computed from a (paired) Wilcoxon signed-rank test under the hypothesis that there are no differences between sexes. Diff: The percentage difference between sexes. Female patients serve as reference. Prescribed dosage differences between men and females were small. $p < 0.05$ for escitalopram and venlafaxine; n.s. for all other antidepressant drugs

antidepressant drugs, differences in pharmacokinetics seem to be greater than reflected in the smaller doses observed in this study: Castberg et al. (2017) found 75% higher plasma levels of olanzapine in elderly and 35% for quetiapine, whereas Bakken et al. (2011) found 50% higher levels of quetiapine (see also: Figures S2 and S3).

4.1.3 | Age: hypnotic and tranquilizing drugs

Data on pharmacokinetics for the hypnotic and tranquilizing drugs analysed in this study does not pertain to steady state but for a single dose of the respective drug. Dosage prescriptions of zolpidem in the present study are only 10.4% higher in young patients, whereas Olubodun et al. (2003) found more pronounced age differences. Compared to younger men, elderly males had a 133% higher maximum concentration (C_{max}), a 80% longer half-life and a 264% increased Area Under the Curve (AUC). In female patients, elderly women had 80% higher C_{max} and 60% increased AUC, while half-life did not significantly differ (Olubodun et al., 2003).

Gaillot et al. (1987) found increasing differences of zopiclone with increasing age. Patients between 60 and 68 years old had 31% higher AUC and patients between 74 and 85 years old had 105%

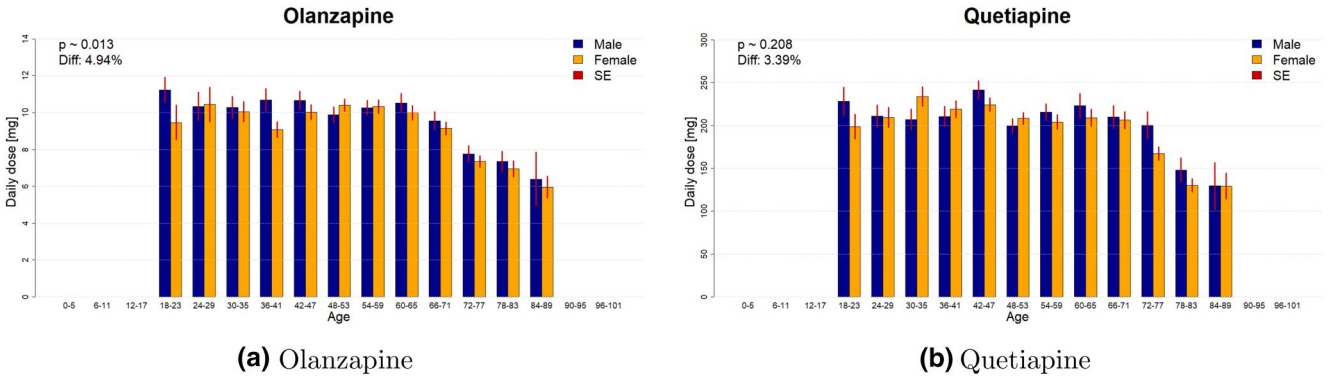


FIGURE 7 Daily dose according to age and sex: Antipsychotic drugs. Daily prescribed doses (mg) of antipsychotic drugs according to age: males in blue and females in orange. The standard error isdepicted in red. The height of the bars corresponds to the mean daily dosage for inpatients within age groups consisting of six consecutive years. p: The *p*-value is computed from a (paired) Wilcoxon signed-rank test under the hypothesis that there are no differences between sexes. Diff: The percentage difference between sexes. Female patients serve as reference. The prescribed dosage differences between men and females are either small or statistically insignificant: $p < 0.05$ for olanzapine, n.s. for quetiapine

higher AUC than younger people. This study was unable to find any age-related dose adjustment of zopiclone. Instead, dosage was the same among all age groups of around 7.2 mg/day.

Elimination half-life of lorazepam has been considered unrelated to age, while clearance of lorazepam has been shown to be 22% lower in elderly patients (Greenblatt et al., 1979). This study found a 30% difference in dosage between young and elderly patients.

While it seems that age-related pharmacokinetics are—to a limited extent—considered for zolpidem and zopiclone, data for lorazepam is too lacking to draw conclusions.

4.2 | Sex

A comprehensive table summarizing the primary findings on sex differences in plasma levels of psychotropic drugs is provided in the supplementary material (Table S2).

4.2.1 | Sex: antidepressant drugs

In general, data on sex-related pharmacokinetic differences of antidepressant drugs are limited. The sex-related differences in drug plasma levels described in literature appear to be greater than the sex-related dosage adjustments detected in this study. Treated with the same dose, female patients have been reported to have 25% and 9% higher drug plasma levels of citalopram and escitalopram, respectively, at steady state than men (Reis et al., 2009). Scherf-Clavel et al. (2019) were able to detect an even greater sex difference in dose-corrected serum concentration of escitalopram of 39.6% in patients up to 65 years and of 45.9% in patients over 65 years old. In comparison, the prescribed dosages of citalopram and escitalopram in this study were only 1.6% and 5.1% lower in females.

Similarly, sex-related plasma levels of venlafaxine and mirtazapine differed by 16% for mirtazapine and 42% for venlafaxine (Reis et al., 2009), whereas this study only found a difference of 2.8% and 4.6% in prescribed dosages of the respective antidepressant drugs. Sigurdsson et al. (2015) detected 18.8% higher dose-adjusted serum concentrations of venlafaxine at steady state in women.

A dosage difference of 1.4% was detected for sertraline. This finding is consistent with the results of Reis et al. (2009) in which they did not find statistically significant differences in plasma levels of sertraline. Lobo et al. (2009) estimated the pharmacokinetic sex difference of duloxetine to be 64% for the same dosage, which is in part explained by differences in smoking habits. In contrast, this study only found a 2.8% dose difference. Steady-state plasma levels of duloxetine are 43% higher in non-smokers than in smokers and plasma levels of duloxetine in non-smoking women are 2.3 times higher than in smoking men (according to a pharmacokinetic model, Lobo et al. 2009).

With the exception of sertraline for which no sex-related differences were found, the difference in dosage prescriptions between sexes for the other five most prescribed antidepressant drugs do not reflect data on sex-related pharmacokinetics.

4.2.2 | Sex: antipsychotic drugs

Castberg et al. (2017) found a 26.1% higher dose adjusted plasma concentration of olanzapine in women than in men. In contrast, this study found a difference in prescribed dosage of only 4.9%.

Both Bakken et al. (2011) and Castberg et al. (2017) were unable to find evidence of sex-related changes in pharmacokinetics of quetiapine. Similarly, this study was also unable to detect sex-related dosage adjustments.

Similar to antidepressant drugs, several authors have provided evidence of much higher pharmacokinetic sex differences

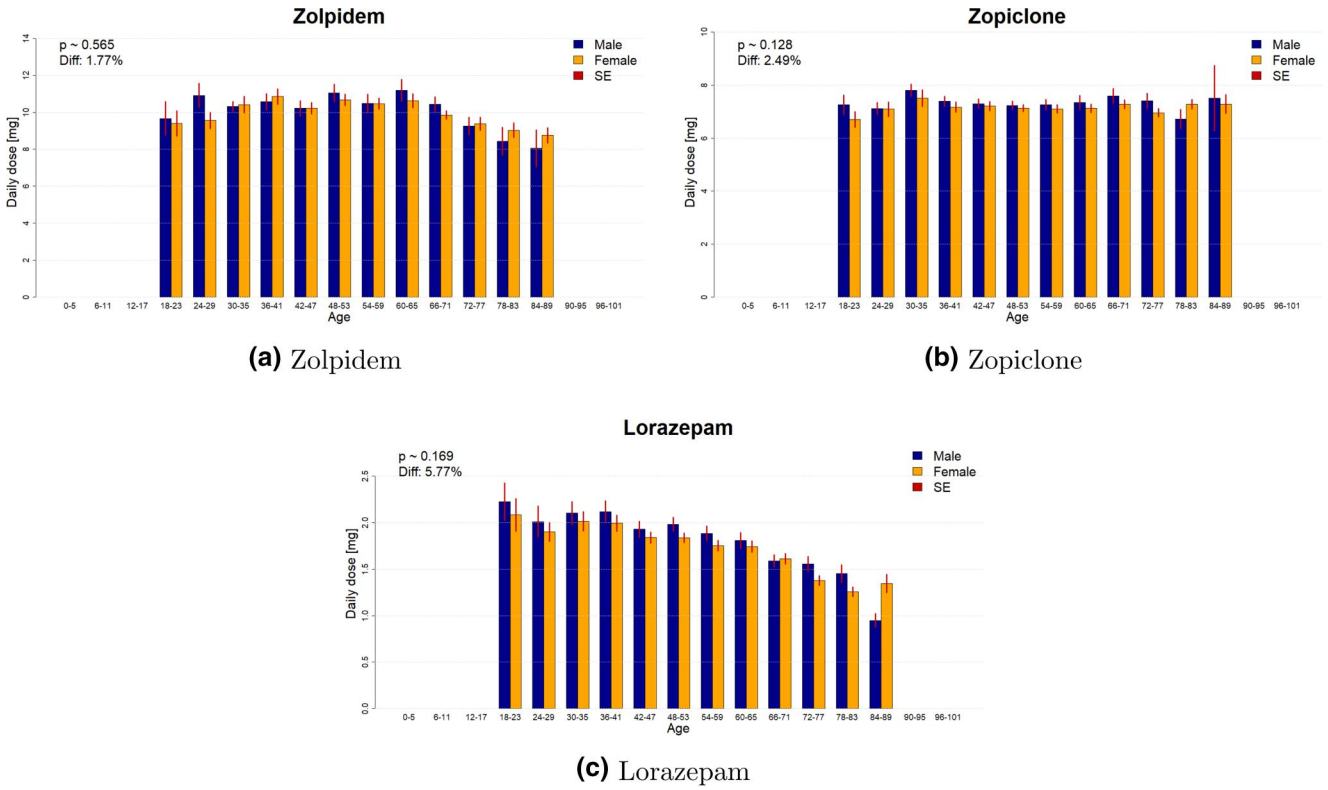


FIGURE 8 Daily dose according to age and sex: Hypnotic and Tranquilizing drugs. Daily prescribed doses (mg) of hypnotic and tranquilizing drugs by age: males in blue and female in orange. The standard error is depicted in red. The height of the bars corresponds to the mean daily dosage for inpatients within age groups consisting of six consecutive years. p: The *p*-value is computed from a (paired) Wilcoxon signed-rank test under the hypothesis that there are no differences between sexes. Diff: percentage difference between sexes. Female patients served as reference

(Castberg et al., 2017; Weiss et al., 2005) than the dosage reductions applied in clinical practice.

4.2.3 | Sex: hypnotic and tranquilizing drugs

Very limited literature is presently available about the pharmacokinetics of lorazepam. Greenblatt et al. (1979) were unable to detect an apparent relation between sex and pharmacokinetics after application of a single intravenous dose of lorazepam. Similarly, we did not find evidence of sex affecting dosage prescriptions of lorazepam.

Greenblatt et al. (1979) conducted a study in which the clearance of zolpidem was analysed. Although significant differences between sexes in terms of pharmacokinetics were found, no evidence of sex-related effectiveness or ADRs was found. The present study was also unable to detect sex-related prescription differences. It is not clear whether sex should be considered when dosing zolpidem. The results of the present study show that physicians in Germany, Switzerland and Austria tend to prescribe zolpidem without considering the FDA recommendations of a maximum dose of 5 mg for women (mean dose for both sexes of about 10 mg per day).

According to Gaillot et al. (1983), C_{max} of zopiclone is 14% to 24% higher and AUC is 16% to 20% higher in women than men. In contrast, the present study found no evidence of sex-related dosage adjustment.

Literature concerning the pharmacokinetics of zolpidem, zopiclone and lorazepam is not only limited, but also rather outdated.

4.2.4 | Sex: influence of smoking and of co-medication

Since smoking, which is more prevalent among males, induces CYP1A, the blood levels of drugs metabolised via this enzyme, especially duloxetine, mirtazapine and olanzapine, are greatly reduced. Hence, the dose differences between the sexes should be even greater than the sex-related pharmacokinetic differences for these drugs. Currently available data generally refers to blood levels of smokers and non-smokers together. Therefore, and in line with literature, the present study compares real world data for both plasma levels and dosages (smokers and non-smokers combined). An exception is duloxetine, for which exact data are known. Bioavailability differed by 30% between smokers and non-smokers and by 40% between men and women due to the higher activity of CYP1A2 in men (Lobo et al. 2009). Carbamazepine, an inducer of CYP1A2 and CYP3A, reduces the plasma levels of several

psychotropic drugs investigated in our study: citalopram, duloxetine, escitalopram, mirtazapine, olanzapine, quetiapine, sertraline, venlafaxine and zolpidem (interaction check via www.mediq.ch). However, the influence of such combinations on the results of our study is estimated to be very low, as only 1.7% of all patients were treated with carbamazepine. The effect of contraceptives on the plasma levels of the drugs studied is judged to be small and not clinically relevant (www.mediq.ch). Thus, the co-medication is not expected to have influenced the principal conclusions of the study regarding age and sex.

4.3 | Limitations and strengths

Several limitations of the study must be noted. First of all, the diagnosis of MDD was established in clinical routine and not necessarily based on standardised diagnostic procedures. Secondly, only the data presented here (i.e., age, diagnosis, gender, year of treatment) was available for analysis. In turn, other clinically relevant aspects expected to significantly influence psychotropic drug use such as non-psychiatric comorbidity, duration of treatment, concomitant drug use, smoking status, pharmacogenomics of drug-metabolizing enzymes (e.g., CYP isoenzymes), renal clearance, body weight, BMI and clinical course of treatment were not considered. Accordingly, an adjustment of results for any of these potentially confounding factors could not be made. Thirdly, the plasma drug levels of the patients were not available, instead mean values were taken from literature. We were also unable to compare the dosages in the subgroups with a predetermined „optimal dosage" because such has not been determined. Therefore, comparisons of dosages are made within the study population, that is, females versus males and young versus old. Furthermore, the study is based on the assumption that plasma levels are valid parameters for determining appropriate dosage. Only a specific (i.e., hospitalized) cohort of patients with MDD was examined. Psychiatric inpatients may be more affected than outpatients therefore necessitating different drug treatment strategies. Several of the psychotropic drugs (i.e., hypnotics and tranquilizers) discussed in the present study are generally used under acute circumstances and are not intended to be used as a long-term treatment option. This may lead physicians to less extensively consider age- or sex-dependent dosage reduction. Furthermore, this study was unable to evaluate the diagnosis indicating the use of a certain psychotropic drug. Several of the presented psychotropic drugs are used in the treatment of other psychiatric conditions and symptoms, such as anxiety disorder (especially SSRIs and SSNRIs) and psychotic symptoms in patients with dementia (e.g., quetiapine), as well as non-psychiatric conditions such as overactive bladder (duloxetine) or neuropathic pain (e.g., duloxetine). Depending on the alternative diagnosis indicating the use of a psychotropic drug, dosage may be higher or lower than when used in the treatment of MDD. However, the calculations of sex differences in doses in patients without any psychiatric comorbidities confirm the results in principle (for all drugs studied).

Strengths of this study include the large collective of patients with MDD and the clinical setting of this study therefore presenting data on drug dosage under real-life circumstances. Data stems from different a large number of German-speaking hospitals which varied over the years of data collection and therefore data does not only reflect prescription patterns of a small geographical region.

5 | CONCLUSION

We found that patients´ age influences a physicians' decision regarding dosage of many of the most commonly prescribed psychotropic drugs examined in this study, but to a lesser extent than what studies examining drug plasma concentrations in elderly patients suggest. Sex, on the other hand, appears not to relevantly influence physician decision-making. Plasma level differences found in literature on pharmacokinetic differences between sexes are overall much larger than the prescribed dosage differences we were able to observe. As mentioned in limitations, patients' body weight was not available, therefore, the results were not adjusted for weight, which is a clinically relevant consideration. According to the Federal Statistical Office of Germany, males have an average body weight of 85 kg and women of 68.7 kg (Federal Statistical Office of Germany, 2018). Accordingly, men in average have a 23.7% higher body mass than women (Federal Statistical Office of Germany, 2018). The present data suggests that not only the sex differences in pharmacokinetics are not considered, but also sex differences in body mass do not seem to influence clinical decision-making. Overall, the results of our study imply two possibilities: either plasma levels do not correlate with drug efficacy and ADRs as generally believed or physicians greatly underestimate biological sex differences. The latter interpretation may also explain the partially disproportionate number of ADRs in women. Although there is a large overlap in biological parameters between sexes, mean plasma levels appear to differ substantially. However, these sex differences were not reflected in the mean dosages used in this patient collective. One reason for the lack of or only small differences in sex- and age-related doses might be that clear dosing instructions for women or for older people are not available for many drugs (see Summary of Product Characteristics [SPC] in the Additional File 1; Tables S1 and S2). There is an urgent need for studies examining whether adjusting the dosage in women on the basis of plasma levels leads to better efficacy and lower frequency of ADRs than "treatment as usual" with similar dosages for both sexes.

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CONFLICT OF INTERESTS

Sermin Toto is a member of the advisory board for Otsuka and Janssen-Cilag and has received speaker honoraria from Janssen-Cilag, Lundbeck/Otsuka and Servier. Johanna Seifert has taken part in an educational event sponsored by Lundbeck/Otsuka. All other authors state they have no conflicts of interest to declare.

ETHICS STATEMENT

Evaluations of the AMSP database have been approved by the Ethics Committee of the University of Munich and the Ethics Committee of the Hannover Medical School (Nr. 8100 BO S 2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP program is a continuous observational post-marketing drug surveillance program and does not interfere with the ongoing clinical treatment of patients under surveillance. All methods (statistical analyses) were carried out in accordance with relevant guidelines and regulations.

AUTHORS CONTRIBUTIONS

Waldemar Greil and Sermin Toto initiated the study. Waldemar Greil and Mateo de Bardeci wrote the main manuscript text. Mateo de Bardeci. conducted the final statistical analyses and prepared figures and tables. Xueqiong Bernegger carried out the preliminary statistical analyses. Hans Stassen designed the database for the evaluation and supervised the statistics. Anita L. Wagner undertook the literature research. Anita L. Wagner, Katja Cattapan, Marcel Sieberer, Hans Stassen, Renate Grohmann and Sermin Toto gave suggestions for improvement of the various versions of the manuscript. Johanna Seifert proofread and created the final version. All authors reviewed and accepted the final version.

DATA AVAILABILITY STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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