

Treatment of Depression: Are Psychotropic Drugs Overdosed in Women and in the Elderly? Dosages of Psychotropic Drugs by Sex and Age in Clinical Routine

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Abstract

Background:

Psychotropic drugs show higher concentration-dose ratios in women and in the elderly. Furthermore, women partially exhibit more adverse drug reactions than men. Lower dosages in most psychotropic drugs may be recommended in women and in the elderly. This study describes prescribed dosages of psychotropic drugs in depressive patients across sexes and age groups in clinical routine.

Method:

In 32'082 inpatients with depressive disorders (data acquired by the European drug safety program AMSP), the influence of sex and age on prescribed dosages are analysed for the 10 most commonly prescribed drugs in our dataset (descending in the frequency of prescription: mirtazapine, venlafaxine, lorazepam, quetiapine, citalopram, escitalopram, olanzapine, duloxetine, zopiclone and sertraline) and additionally zolpidem. Confounding variables for sex differences, such as severity of depression and age distribution are examined. Dose decline in patients over 65 years is calculated. The observed sex and age differences in prescriptions are compared to differences in pharmacokinetic literature.

Results

Among patients over 65, a statistically significant decrease in dosages for increasing age (between 0.65% and 2.83% every year of age) was observed, except for zopiclone. On the other hand, only slight or no influence of sex in prescribed dosages was found.

Conclusion

Age definitely influences physicians' decisions in most drugs, but to a lower extent than pharmacokinetic data suggests. Although lower dosages of psychotropic drugs are appropriate for females according to pharmacokinetic data, they are usually prescribed the same dosage as males. Thus, various psychotropic drugs may be overdosed in women.

Background

At the same dosage, women show higher plasma levels than men for numerous drugs [1–3]. This is due to sex differences in height, body weight, fat proportion, kidney function, the activity of CYP 450 enzymes and the frequency of smoking [4–9]. Sex differences in pharmacokinetics with a significantly higher concentration-dose ratio in women have been proven for a number of psychotropic substances, e.g. mirtazapine [1, 10], olanzapine [2, 11], venlafaxine [1, 12–14], escitalopram [1, 15] and duloxetine [16].

Furthermore, despite ambiguous results [17, 18] women report a higher rate of adverse drug reactions (ADRs) [3, 19, 20].

Although elderly generally suffer from ADRs more often [21], in the case of psychotropic drugs a number of studies under naturalistic conditions showed similar percentages of severe ADRs in elderly as in young patients [20, 22, 23]. On the other hand, an increase of concentration-dose ratios with age is described for various psychotropic drugs, e.g. mirtazapine [1, 10], venlafaxine [1, 12–14], quetiapine [4, 11, 24], citalopram [1, 10, 25], escitalopram [1], olanzapine [2, 11], zopiclone [26] and sertraline [1, 10]. Since age-related changes in body composition and polypharmacy lead to different pharmacokinetics and pharmacodynamics in the elderly, the recommendation to lower the dosage of psychotropic drugs in the elderly is generally accepted [27–29, 29a].

Although women are the main users of psychotropic drugs [30], they are underrepresented in treatment studies, and therefore treatment guidelines are mainly based on findings in male patients [31]. According to Sørup et al. [32], the influence of patient's sex on ADRs is an understudied factor.

In 2013, the U.S. Food and Drug Administration (FDA) approved label changes specifying new maximal dosing recommendations for zolpidem, being 5 mg/day for females and 10 mg/day for males [33, 34]. According to the FDA, higher dosages could lead to next-morning impairments, especially driving impairment [33, 34]. However, this guidance is controversial. It has been argued that a disturbed sleep by underdosed zolpidem in females may impair driving even more than the intake of the 10 mg/day dose [18]. This controversy motivated our inclusion of zolpidem in our study.

In this study, a large data set from a pharmacovigilance project is used to test whether in clinical routine the dosage of psychotropic drugs in the treatment of depression is lower in females than in males. We selected the 10 most prescribed drugs in our dataset and additionally zolpidem. Furthermore, we also analyse to which extent the dosages of psychotropic drugs are influenced by age in general and within the group of elderly.

Method

Data source

The analysed prescription data of the present study was gathered in the project “Arzneimittelsicherheit in der Psychiatrie” (AMSP; drug safety program in psychiatry). AMSP is an ongoing European multi-center drug safety program which collects data on psychopharmacotherapy and severe adverse drug reactions from psychiatric hospitals in a naturalistic setting since 1993. AMSP's pharmacovigilance methods have been described in detail previously [35-37]. Briefly, AMSP consists of two principal data collections (prescription data and severe adverse drug reactions) from 116 hospitals so far in Germany, Switzerland and Austria, as well as temporarily from one hospital each in 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 leading 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.

Sample description

32'082 patients older than 17 and younger than 90 years of age, hospitalized between 2001 and 2015, with a leading admission diagnosis of major depressive disorder (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=8'072), lorazepam (n=7'757), quetiapine (n=6'993), citalopram (n=3'909), escitalopram (n=3'842), olanzapine (n=3'441), duloxetine (n=3'070), zopiclone (n=2'936), sertraline (n=2'909) and zolpidem (n=1'873). 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.

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 males in years (mean \pm S.D.)	49.5 \pm 15.3
Age females in years (mean \pm S.D.)	51.9 \pm 16.5
Number of psychotropic prescriptions per patient (mean \pm S.D.)	2.6 \pm 1.3
S.D.: standard deviation	

When analysing prescribed dosage differences between sexes, it is important to identify possible confounding variables that could account for distortions in the analysis. In this study, we examined the following possible confounding variables: severity of MDD, differences along calendar years and differences in age distribution.

In figure 1, the number of male and female patients along calendar years are depicted. We do not see any substantial difference in the ratio between male and female patients over time.

Table 2 shows no substantial differences in the severity of cases for male and female patients. Table 3 gives the severity of cases for young and elderly patients. In the small group of psychotic MDD (13.4%),

there is a higher percentage in the elderly than in younger patients (18.0% versus 12.2%). Nevertheless, we assume that severity and differences over years cannot distort our analysis to a significant extent. On the other hand, the age distributions (depicted in figure 2) differ substantially. In particular, there are proportionally more elderly women than elderly men. Therefore, we need to adjust our analysis in order to take into account differences in age distributions.

Table 2
Severity of cases by sex

Severity of cases by sex		
Mild MDD ("F32.0", "F33.0")		368 (1.2%)
Male		151 (1.3%)
Female		217 (1.1%)
Moderate MDD ("F32.1", "F33.1")		8'237 (25.7%)
Male		3'033 (25.5%)
Female		5'204 (25.8%)
Severe MDD ("F32.2", "F33.2")		18'257 (56.9%)
Male		6'720 (56.5%)
Female		11'537 (57.1%)
Psychotic MDD ("F32.3", "F33.3")		4'308 (13.4%)
Male		1'645 (13.8%)
Female		2'663 (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%)
Diagnoses according to ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems). The severity of cases is very similar between male and female patients.		

Table 3
Severity of cases by age

Severity of cases by 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")	8'237 (25.7%)
Up to 65 ys	6'803 (26.8%)
Over 65 ys	1'434 (21.4%)
Severe MDD ("F32.2", "F33.2")	18'257 (56.9%)
Up to 65 ys	14'501 (57.1%)
Over 65 ys	3'756 (56.1%)
Psychotic MDD ("F32.3", "F33.3")	4'308 (13.4%)
Up to 65 ys	3'104 (12.2%)
Over 65 ys	1'204 (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%)
Diagnoses according to ICD-10. The severity of cases is overall similar between young and elderly patients (despite differences for psychotic and moderate MDD). ys: years of age	

Statistical analysis

The statistical analysis was performed using R version 3.6.2. To assess the influence of age in the decision of prescribed dosages, the slope of a linear fit among patients older than 65 and younger than 90 years of age is computed. To estimate its significance, a t-test is performed on the coefficient of the slope under the hypothesis to be zero. Along with the slope, also the percentage change in relation to the previous year is computed, which is calculated from the coefficient of an exponential fit. Since in pharmacokinetic literature the age differences are often compared between age groups of up to 65 years old and over 65 years old, we also compared the mean dosage differences between these age groups in a table, with the elderly group chosen as reference. We compute the p-value from a Wilcoxon test.

In order to account for the sex differences in dosages, we adjust for age by comparing prescriptions in patients with similar age. We divide the patients by sex and assign them to 24 age groups of three consecutive years, and we calculate the mean dosage in each group for both genders separately. Then, we calculate the sex difference within each age group, where female patients are chosen as reference. Finally, the total sex difference is calculated as the weighted mean of all percentage differences, by weighting with the number of patients (male and female) of each age group. We depicted the analysis by plotting the daily prescribed doses in relation to patients' age in bars of six consecutive years. To calculate the significance, we run a paired Wilcoxon signed-rank test, in which the input are the mean values of male and female of the 24 age groups.

Results

Age

The results of the influence of age in dosage prescription are depicted in figure 3 with antidepressants, figure 4 with antipsychotics and figure 5 with hypnotics and tranquilizers. Several bar plots can be seen, in which the height of the green bars gives the mean daily prescribed doses in mg including both sexes, and the x-axis gives the age of the patients. Further, a red line is depicting a linear fit in patients over 65 years old. The slope of the fit is computed in the upper left corner, along with the percentage change. The percentage change is the average percentage increase (or decrease) of daily dosage in relation to the previous year of age. Along with the slope and the percentage change, the p-value under the hypothesis of zero slope is computed. Further, in table 4 the mean differences of dosages between patients up to 65 years and older than 65 years is shown. This description holds for each of the following three sections.

Table 4
Mean dosage differences between patients up to 65 and older than 65 years

Drug	Over 17ys to 65ys			Over 65ys to 89ys			Difference [%](means)	p-value (means)
	N	Mean dose	SE	N	Mean dose	SE		
		[mg/d]			[mg/d]			
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

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 is chosen as reference. The p-value from a Wilcoxon test is calculated. ys: years of age

Age: Antidepressants

In the six analysed antidepressants (Fig. 3), we found for each additional year of age a slight increase of daily dose in young patients, a plateau in middle aged patients and a decrease in elderly patients. 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 can be seen. For the SSRI citalopram and escitalopram, we found a decrease of 0.68% and 1.13%, respectively, and for the serotonin and norepinephrine reuptake inhibitors (SNRI) venlafaxine and duloxetine a decrease of 1% and 0.76%, respectively. The results of all these antidepressants are statistically significant at a level of 0.01. Comparing the mean prescribed dosages between patients up to 65 years old and older than 65 years old, we found statistically significant differences except for mirtazapine, varying from 7% for citalopram to 14% for venlafaxine (Table 4).

Age: Antipsychotics

In figure 4 for both antipsychotics, olanzapine and quetiapine, a plateau can be seen in young and middle age patients. However, a more pronounced slope than in antidepressants can be seen in elderly patients. Within patients over 65 years old, we found a decrease of 2.48% and 2.83% in daily prescribed dosages for each increasing year for olanzapine and quetiapine respectively ($p < 0.0001$). Comparing the mean prescribed dosages between patients up to 65 years old and older than 65 years old, we found statistically significant differences of 24.4% for olanzapine and 21% for quetiapine (Table 4).

Age: Hypnotics and Tranquilizers

Between the two hypnotic drugs (zopiclone and zolpidem) and the tranquilizer drug lorazepam depicted in figure 5, the distribution of the daily prescribed dosages differs substantially. In the case of zolpidem (Figure 5a), a slight increase can be seen in young patients, a plateau in middle aged patients and a decrease in elderly patients. This distribution is similar to the distribution of antidepressants. For zopiclone (Figure 5b), a constant dosage around 7.2 mg per day can be seen for all ages. Therefore, age does not seem to influence prescribed dosages in the case of zopiclone. On the other hand, for lorazepam (Figure 5c), a steady reduction of prescribed dosages can be seen across all ages.

Within patients over 65 years old, we found a decrease of 1.17% and 1.26% in daily prescribed doses for each increasing year of age for zolpidem and lorazepam respectively ($p < 0.001$). In the case of zopiclone, we did not find statistically significant differences with increasing age. 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).

Sex

The results for sex influence in prescribed dosages is given in figure 6 with antidepressants, figure 7 with antipsychotics and figure 8 with hypnotics and tranquilizers. Several plots can be seen, where the y-axis gives the prescribed daily dose and the x-axis the age. Doses of males are depicted in blue and of females in orange, the standard errors are depicted in red. On the upper left corner further statistics can be found: the p-value under the hypothesis, that there is no difference between sexes; furthermore, the difference between sexes computed as percentage change, where females are chosen as reference. This description holds for each of the following three sections.

Sex: Antidepressants

In the case of antidepressants (figure 6), we found statistically significant differences in daily dose prescription between sexes for escitalopram and venlafaxine, in which males received respectively 5.13%

and 4.59% more than females. For citalopram, sertraline, mirtazapine and duloxetine we did not find statistically significant differences between sexes.

Sex: Antipsychotics

Regarding antipsychotics (Figure 7), we found statistically significant differences for olanzapine, in which males receive 4.94% more than females. For quetiapine, we did not find statistically significant differences.

Sex: Hypnotics and Tranquilizers

Among the hypnotic drugs zolpidem and zopiclone, and the tranquilizer lorazepam (Figure 8), we did not find statistically significant differences between males and females.

Discussion

Age

In order to discuss our findings, we present a literature review about age and sex influence on plasma levels of patients taking psychotropic drugs and compare it to the influence of age and sex on prescribed dosages in our findings. A comprehensive table describing bullet points of the different studies in literature can be found in the supplementary material (Additional file 1; Table 1 and 2 supplementary). In the following sections only the key studies in literature are cited and compared to our findings.

Age: Antidepressants

Reis et al. [1] analysed in 2009 the plasma levels for citalopram and escitalopram at steady state of 2330 and 1470 subjects respectively, finding that elderly patients over 64 years old had 84% and 91% higher plasma levels than younger patients at the same dosage. Whereas, in the prescribed dosages we only found a difference of 7.0% and 13.4%. For sertraline, Reis et al. [1] found a difference of 31% in 1071 patients, and 44% for mirtazapine in 660 patients. In contrast, for sertraline we only observed a difference of 9.7% in prescribed dosages, and for mirtazapine we did not find statistically significant results. Reis et al. [1] also analysed the plasma levels of venlafaxine. They found at the same dosage 38% difference in plasma levels between elderly and young patients whereas we only found a difference of 14%.

For duloxetine, we found a significant decrease in dosage prescription within the elderly and significant differences between young and elderly. In comparison, a study of Lobo et al. [16] 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 our data, the analogue slope shows -0.146 (Additional file 2, Fig. 1 supplementary). The slopes need to be normalized in order to be compared, which yields -0.50 for the apparent clearance, and

-0.17 for dosage prescription. Again, the influence of age on prescription of duloxetine is substantially smaller than the influence on the plasma level according to the literature.

The case of mirtazapine is particularly noteworthy, since we found no differences in the prescription between young and elderly patients, and literature shows an increase of plasma levels in elderly above 40%. Although we found statistically significant differences between prescribed dosages in young and elderly patients for the remaining antidepressants, the differences in pharmacokinetic literature are clearly more pronounced than in real clinical decisions.

Age: Antipsychotics

Regarding the antipsychotics olanzapine and quetiapine, we found statistically significant mean differences in prescribed dosages of 24.4% and 21% respectively (between patients up to 65 and over 65 years old). In literature, the differences in pharmacokinetics are more pronounced: Castberg et al. [11] found 75% higher olanzapine plasma levels in elderly analysing 6239 patients and 35% for quetiapine in 1949 patients. Bakken et al. [24] found 50% higher levels analysing 601 patients for quetiapine (see also Additional File 2, Fig.1 and 2, suppl.).

Age: Hypnotics and Tranquilizers

For the analysed hypnotics and tranquilizers, we did not find literature describing pharmacokinetic data at steady state, but for single dose. For zolpidem, dosage prescriptions in our dataset are only 10.4% higher in young patients, whereas Olubodun et al. [38] found more pronounced age differences: in males 133% in the maximum concentration (C_{max}), 80% in half-life and 264% in the Area Under the Curve (AUC); in females 80% in C_{max} and 60% in AUC. No significant differences have been found by Olubodun et al. [38] in half-life between younger and elderly females [38].

In the case of zopiclone, Gaillot et al. [26] found increasing differences with increasing age. Elderly between 60 and 68 years old had 31% higher AUC, and elderly between 74 and 85 years old had 105% higher AUC. We did not find any influence of age in dosage prescriptions of zopiclone. In particular, we found a flat distribution with daily doses around 7.2 mg/day.

For lorazepam, Greenblatt et al. [40] found no significant influence of age in elimination half-life ($n=30$), but a total clearance of 22% less in elderly patients. We found a difference in dosage prescriptions of 30% between young and elderly patients.

In summary, for zolpidem and zopiclone physicians take into account the kinetic data only to a limited extent. In the case of lorazepam, there is not enough pharmacokinetic data to draw conclusions.

Sex

A comprehensive table describing bullet points of the different studies in literature about sex differences in plasma levels of psychotropic drugs is given in the supplementary material (Additional file 1; Table 2 supplementary).

Sex: Antidepressants

Although pharmacokinetic data of several antidepressants is surprisingly limited, we found overall much higher differences in plasma levels between sexes in pharmacokinetic literature than in real clinical decisions. In 2009, Reis et al. [1] analysed the plasma levels for citalopram and escitalopram at steady state of 2330 and 1470 subjects respectively, and reported that female patients have 25% and 9% higher plasma levels than men at the same dosage. In the prescribed dosages we only found a difference of 1.6% and 5.1%. Also Scherf-Clavel et al. [15] examined 114 patients with prescriptions of escitalopram finding a sex difference in dose-corrected serum concentration of 39.6% in patients up to 65 years and of 45.9% in patients over 65 years old.

Reis et al. [1] also investigated the plasma levels of 660 patients with mirtazapine prescriptions and 716 with venlafaxine prescriptions. They found plasma level differences of 16% and 42%, whereas we only found a difference of 2.8% and 4.6% in prescribed dosages. Sigurdsson et al. [13] also studied 1417 patient with venlafaxine prescriptions and found at steady state that women have 18.8% higher dose-adjusted serum concentrations.

For sertraline, we found a dosage difference of 1.4%. This case is consistent with the results of Reis et al. [1] in which they did not find statistically significant differences in plasma levels for sertraline in 1071 patients. For duloxetine, Lobo et al. [16] estimated the pharmacokinetic sex difference to be 64% for the same dosage, which is in part explained by differences in smoking habits. In contrast, we only found a 2.8% dose difference in real clinical decisions.

Overall, the difference in dosage prescriptions between sexes for the six most prescribed antidepressants does not reflect pharmacokinetic data except for sertraline, since there was no difference found in prescribed dosages as well as in plasma levels.

Sex: Antipsychotics

For olanzapine, Castberg et al. [11] found a 26.1% higher dose adjusted plasma concentration in women than in men for 5826 patients on stable dose. In contrast, we found a prescribed dosage difference of only 4.9%.

For quetiapine, Bakken et al. [24] investigated 601 patients and did not find evidence that sex influences pharmacokinetics. Similarly, we did not find evidence that sex influences prescribed dosages. On the other hand, Castberg et al. [11] examined 2210 patients with quetiapine prescriptions and did not find evidence of sex differences in plasma levels for young patients, but with increasing age, the

pharmacokinetic differences become noticeable and significant. In our study, we did not find evidence of increasing dosages differences with increasing age in real clinical conditions.

Similarly to antidepressants, for antipsychotics we found literature with evidence of much higher pharmacokinetic sex differences than naturalistic differences in dosage prescriptions.

Sex: Hypnotics and Tranquilizers

For the benzodiazepine lorazepam, we surprisingly found very limited literature about its pharmacokinetics. There is a study of Greenblatt et al. from 1979 [40], where 30 patients are analysed with a single intravenous dose. No apparent relation between sex and pharmacokinetics was found. Similarly, we did not find evidence of sex affecting dosage prescriptions of lorazepam.

Greenblatt et al. [40] also conducted a study in 2019 in which the clearance of zolpidem in 70 patients was analysed. Although significant differences between sexes in terms of pharmacokinetics was found, according to the study, no evidence of sex related effectiveness nor adverse reaction was found. In our study, we did not find evidence for sex related prescription differences. For the dosage prescription of zolpidem, it is not clear whether sex should be considered. Nevertheless, the results of our 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 about 10 mg per day).

Regarding zopiclone, Gaillot et al. 1983 [39] found that C_{max} is 14% to 24% higher, and AUC is 16% to 20% higher in women than men. In contrast, we found no evidence of sex influencing the decision of dosage prescription.

Overall, we found very old and limited pharmacokinetic literature about the two most prescribed hypnotics/tranquilizers and zolpidem. There is certainly room for research in this field.

Limitations

Several limitations of the study must be noted. First, the diagnosis of depression was established in clinical routine instead of standardised diagnostic procedures. Secondly, no data are available of the clinical condition, possible comorbidity and duration of treatment. Thirdly, the plasma levels of the patients are not present, instead mean values are taken from the literature. Furthermore, the study is based on the assumption that plasma levels are valid parameters for dosage decision. Finally, only hospitalized patients suffering from depression were examined. The strength of the naturalistic study is the large database reflecting clinical reality.

Conclusion

In conclusion, we found that patients' age does influence physician decisions, but to a lower extent than what pharmacological literature would suggest. On the other hand, we found that sex overall does not influence physician decision-making. Further, the plasma level differences found in pharmacokinetic literature between sexes are overall much larger than the prescribed dosages differences. We recall, patients body weight is not present in the dataset we analysed. Therefore, the results are not adjusted for weight. According to the Federal Statistical Office of Germany, males have an average body weight of 85 kg and women of 68.7 kg [41]. Men have in average 23.7% more body mass than women [41]. Hence, not only the sex differences in pharmacokinetics are not taken into account, but also sex differences in body mass do not seem to influence clinical decisions. Overall, the results of our study imply two possibilities: either plasma levels are not as correlated to drug effectiveness and adverse effects as is generally believed, or there is an underestimation of biological sex differences on behalf of physicians. The latter interpretation may also explain the partially disproportional number of adverse reactions in women. Although there is a large overlap in biological parameters between sexes, mean plasma levels differ substantially. However, we do not see these sex differences in the mean dosages. There is an urgent need for studies to examine whether adjusting the dosage in women on the basis of blood levels leads to better efficacy and lower frequency of adverse effects than the "treatment as usual" with similar dosages for both sexes.

Declarations

Ethics approval and consent to participate

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. Hence, all methods (statistical analyses) were carried out in accordance with relevant guidelines and regulations.

(All experimental protocols were approved by the named institutions: Not applicable, since no experiments).

(Confirming that informed consent was obtained from all subjects: Not applicable, since only anonymised data was used,)

Consent for publication:

Not applicable (all authors agreed with the publication).

Availability of data and materials:

Not applicable

Competing interests

ST is a member of the advisory board for Otsuka and Janssen-Cilag and has received speaker's honoraria from Janssen-Cilag, Lundbeck/Otsuka and Servier. All other authors state they have no conflicts of interest to declare.

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Authors' contributions

W.G. and S.T. initiated the study. W.G. and M.de B. wrote the main manuscript text. M.de B. conducted the final statistical analyses and prepared figures and tables. X.B. carried out the preliminary statistical analyses. H.S. designed the database for the evaluation and supervised the statistics. A.W. undertook the literature research. A.W., K.C., M.S., H.S., R.G and S.T. gave suggestions for improvement of the various versions of the manuscript. All authors reviewed and accepted the final version.

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Figures

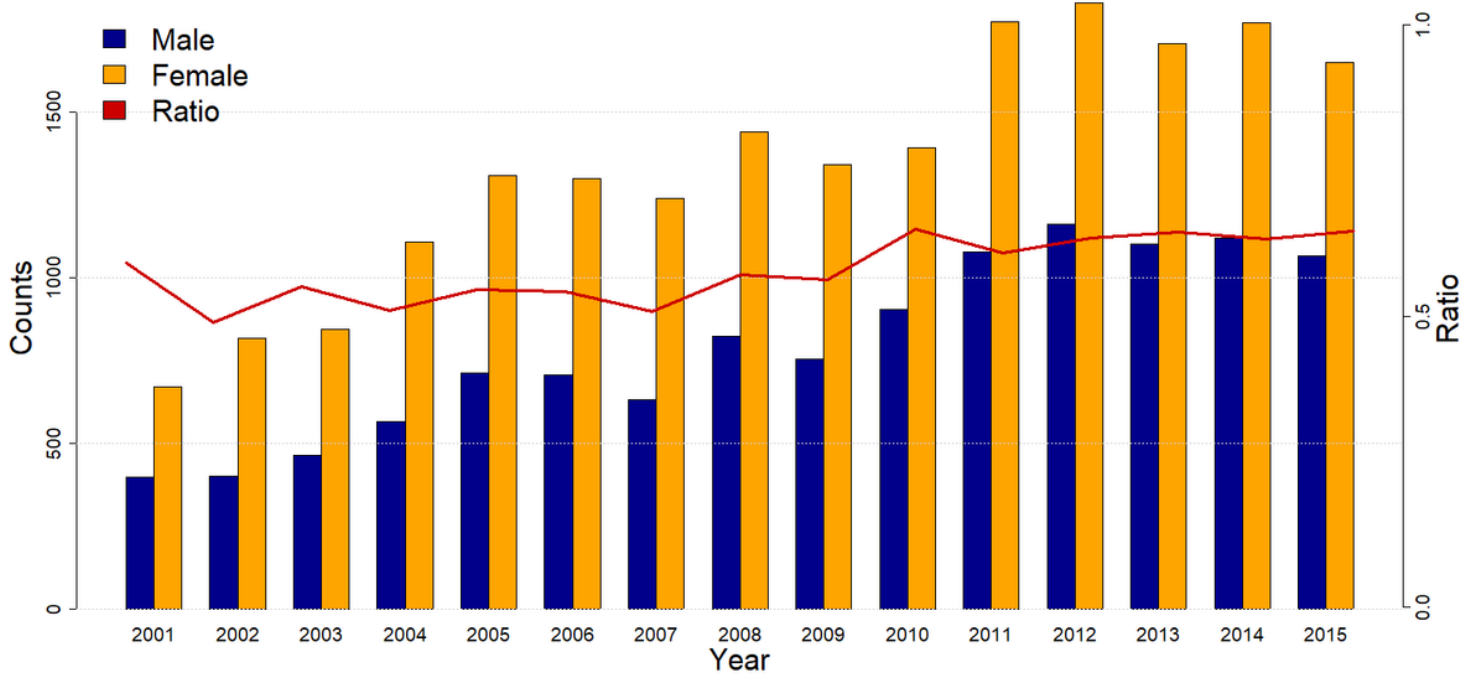


Figure 1

Number of patients with MDD by year Number of male and female patients in our sample by calendar years between 2001 and 2015. Blue: Males. Orange: Females. Red: males divided by females. The ratio between male and female changes only slightly along the years. MDD: Major Depressive Disorders

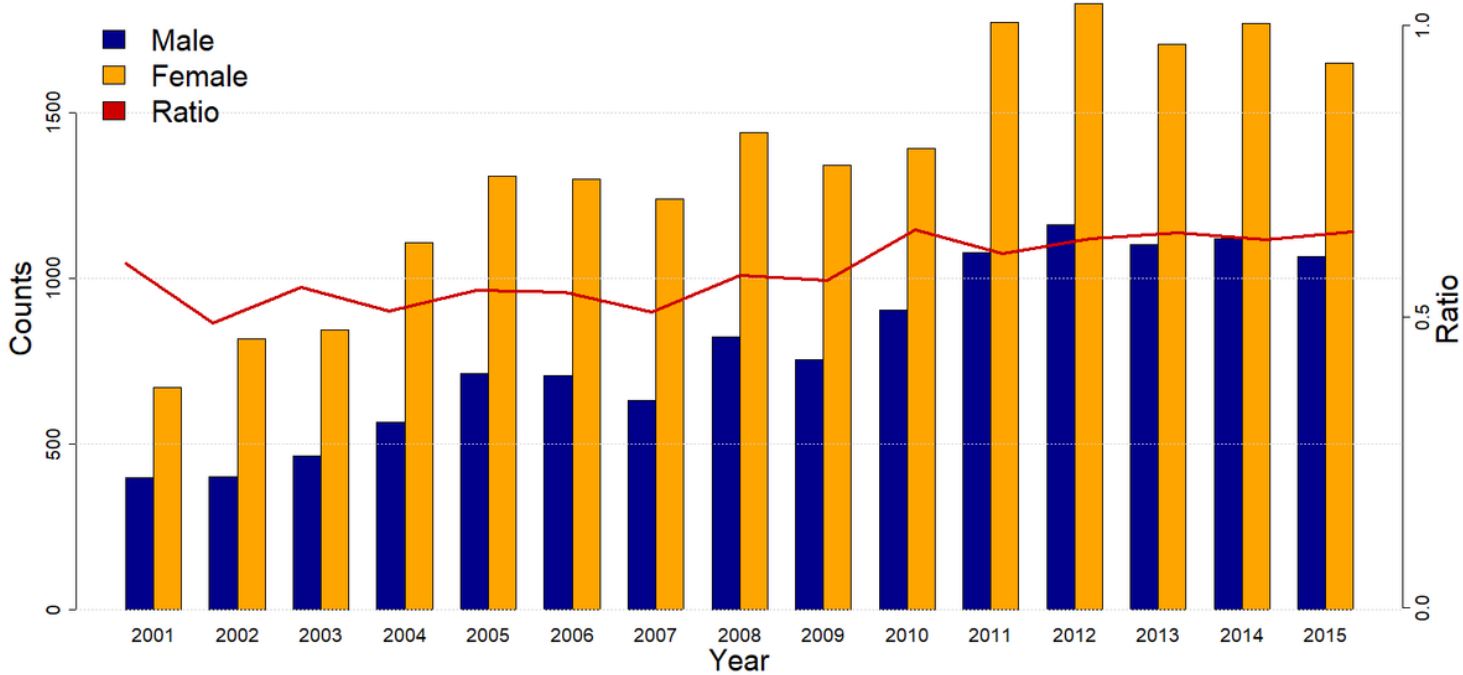


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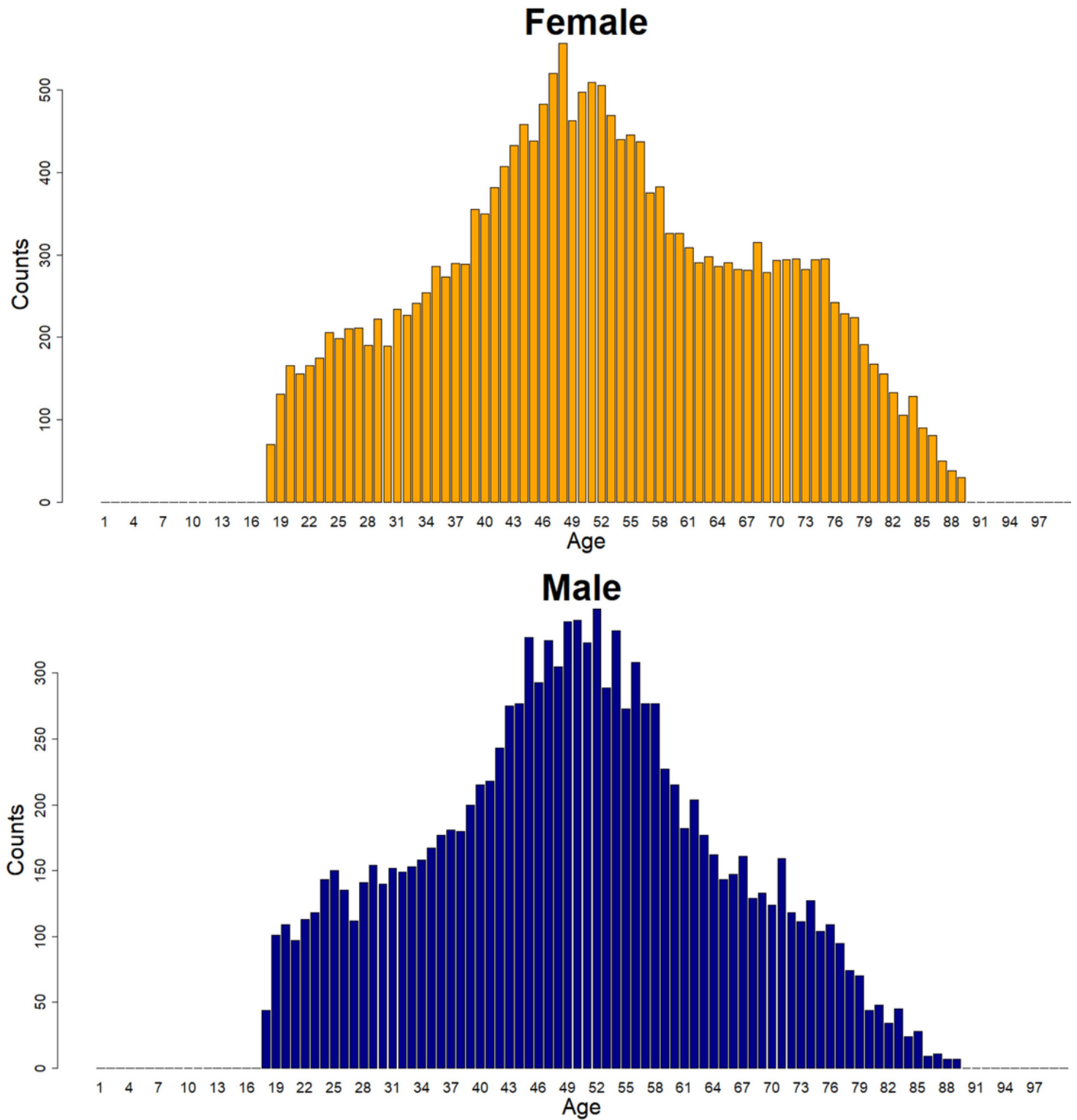


Figure 2

Age distributions On the top the female age distribution, on the bottom the male age distribution. In our sample are proportionately more elderly women then elderly men, and overall more women.

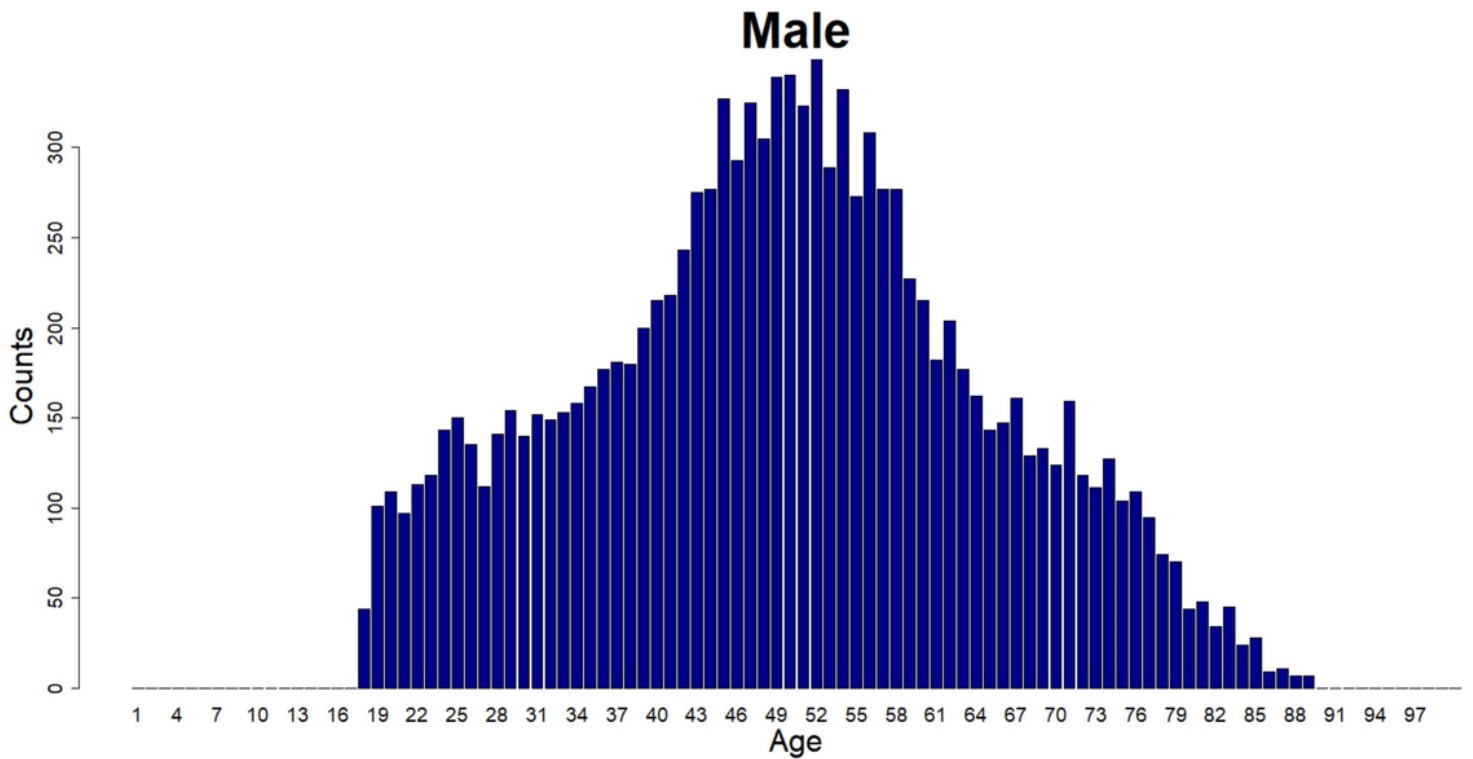
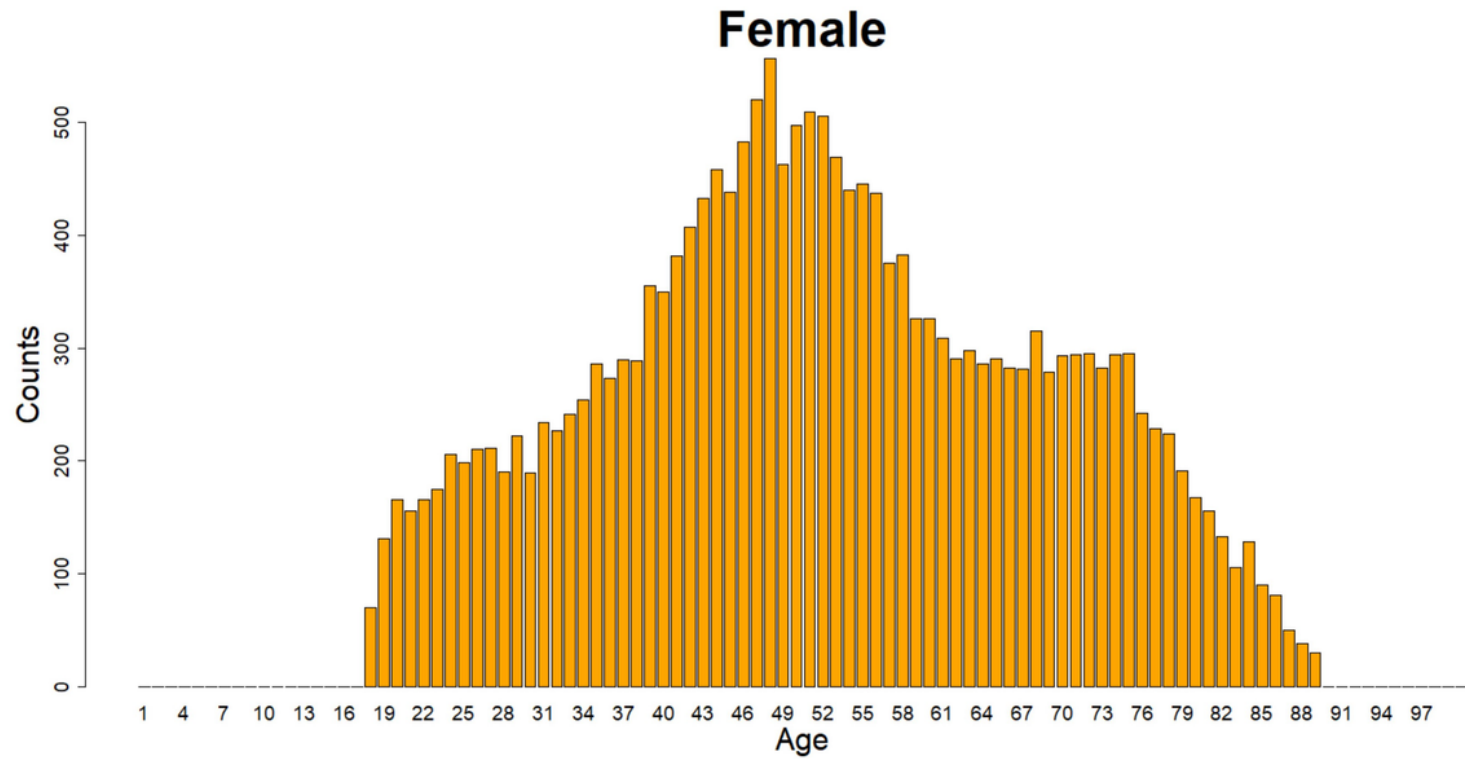


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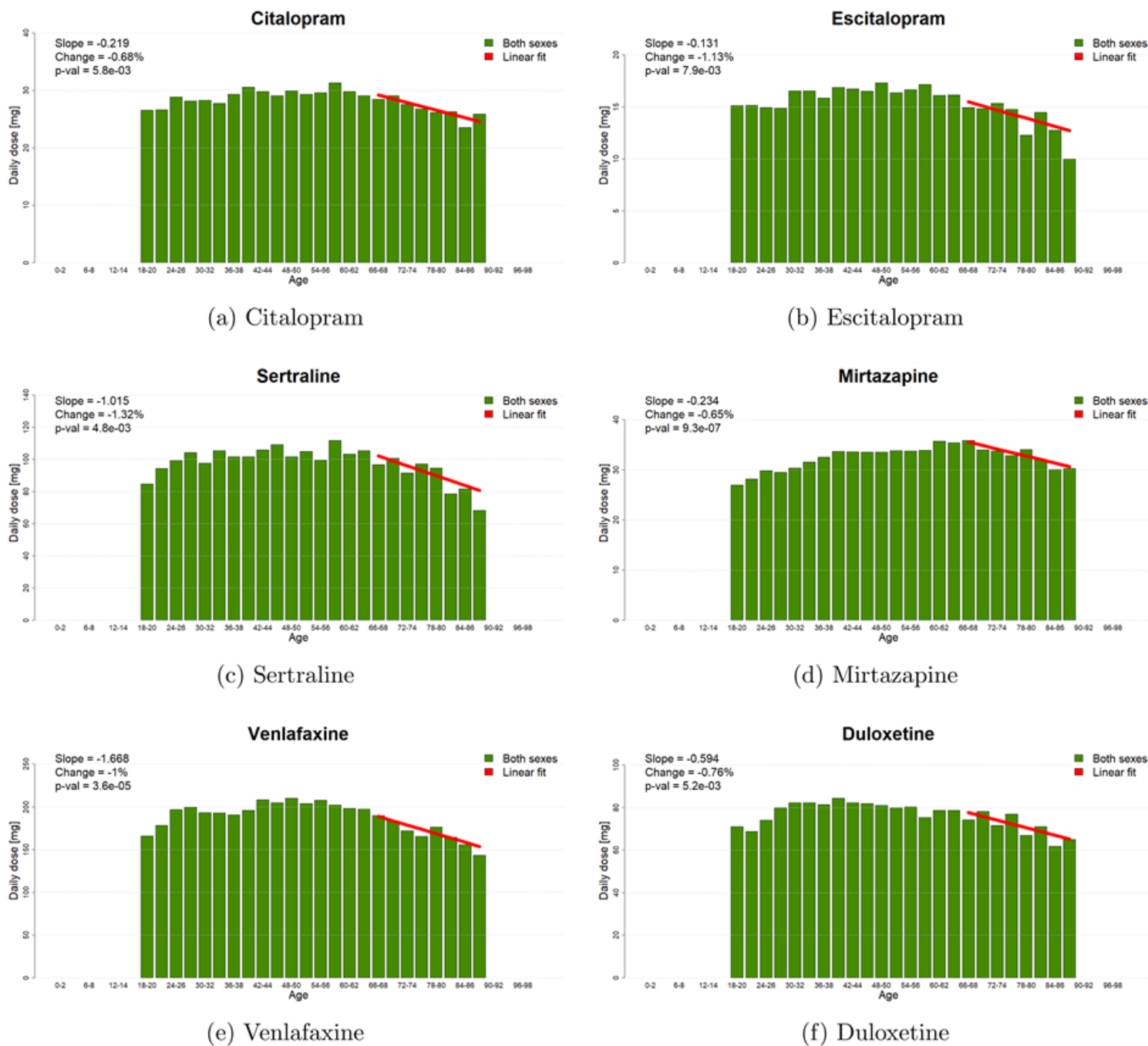
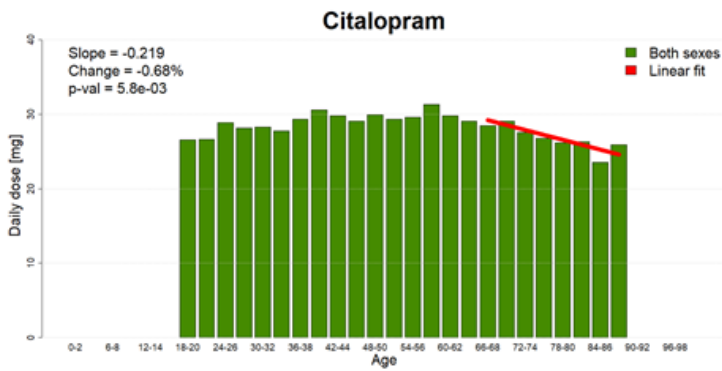
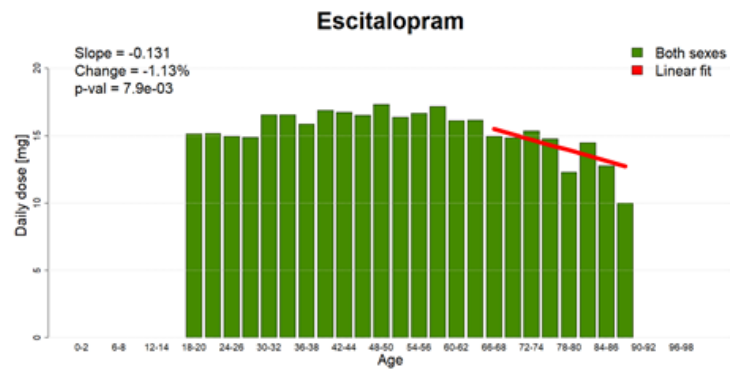


Figure 3

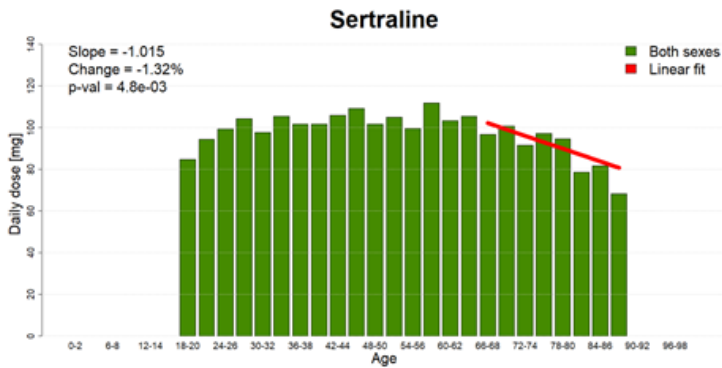
Daily dose by age: Antidepressants Daily prescribed doses (mg) of antidepressants by age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups of three consecutive years. The patients are between 18 and 89 years old. In red, a linear model fitted to patients between 66 and 89 years old is shown. 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, $p < 0.001$ in all cases.



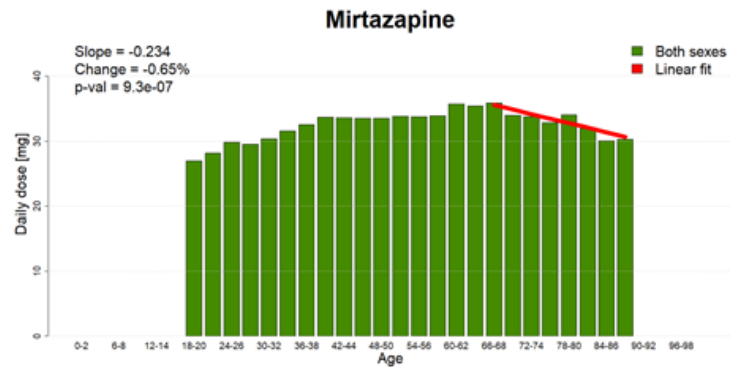
(a) Citalopram



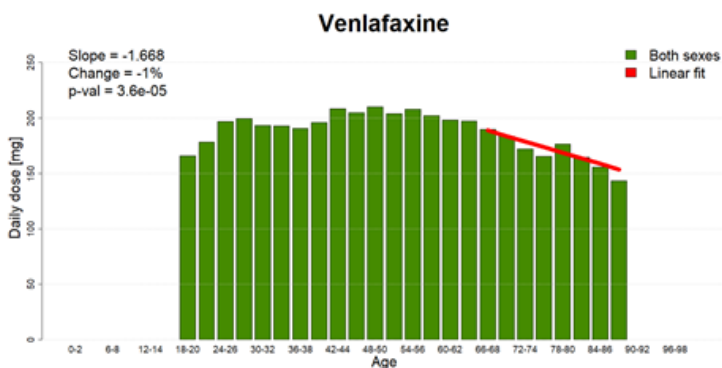
(b) Escitalopram



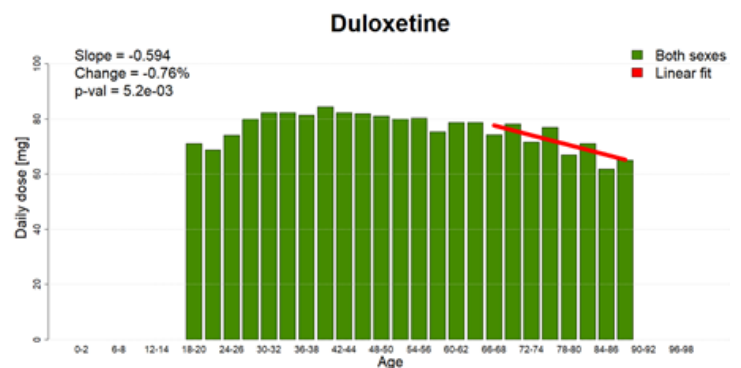
(c) Sertraline



(d) Mirtazapine



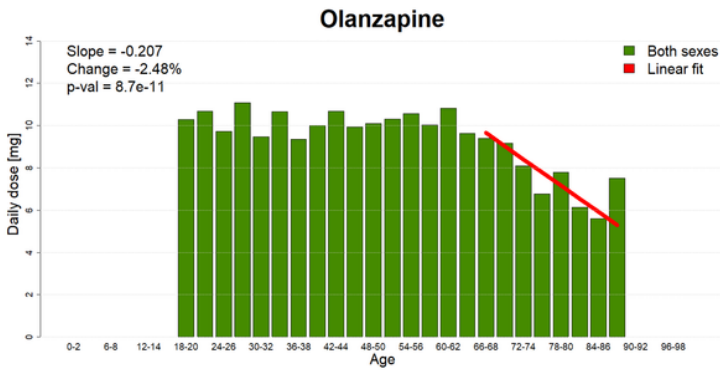
(e) Venlafaxine



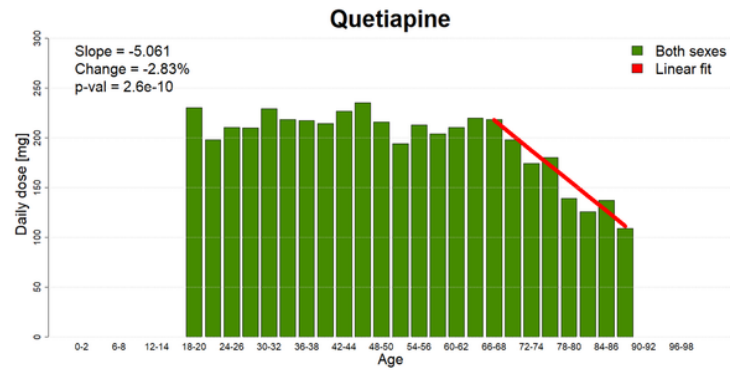
(f) Duloxetine

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Daily dose by age: Antidepressants Daily prescribed doses (mg) of antidepressants by age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups of three consecutive years. The patients are between 18 and 89 years old. In red, a linear model fitted to patients between 66 and 89 years old is shown. 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, $p < 0.001$ in all cases.



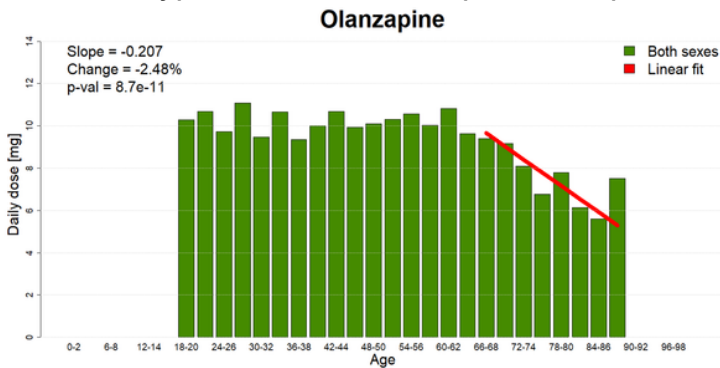
(a) Olanzapine



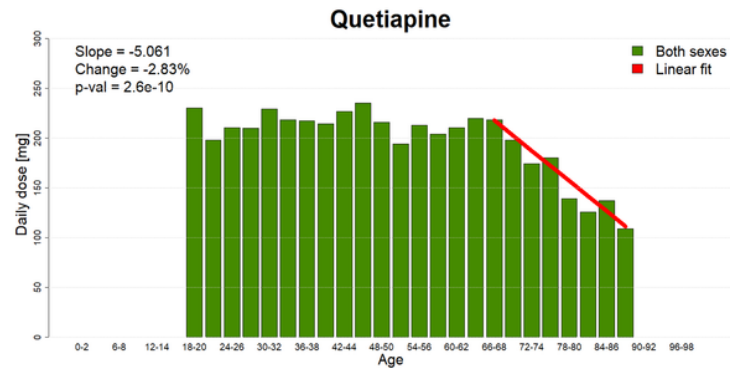
(b) Quetiapine

Figure 4

Daily dose by age: Antipsychotics Daily prescribed doses (mg) of antipsychotics by age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups of three consecutive years. The patients are between 18 and 89 years old. 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, $p < 0.001$ in both cases.



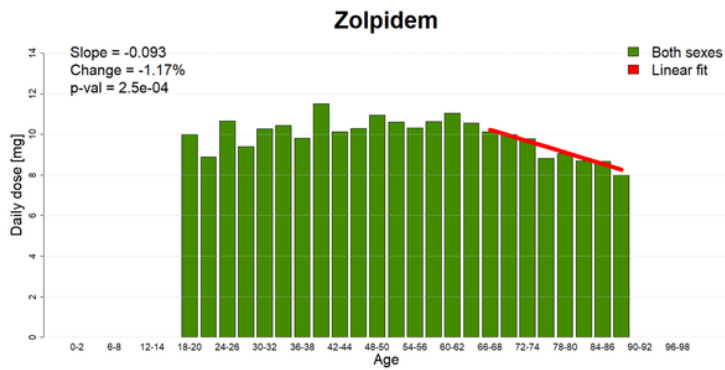
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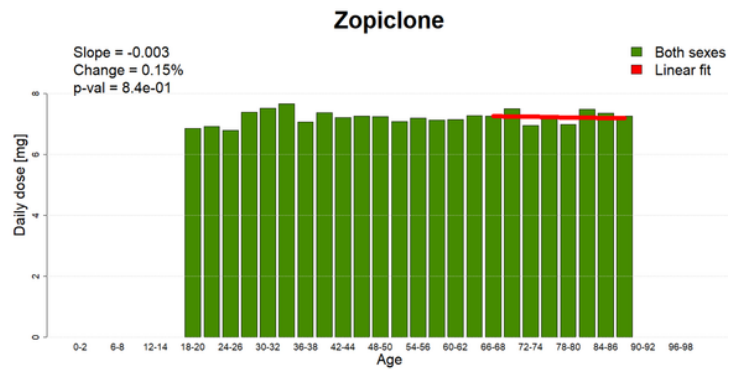
(b) Quetiapine

Figure 4

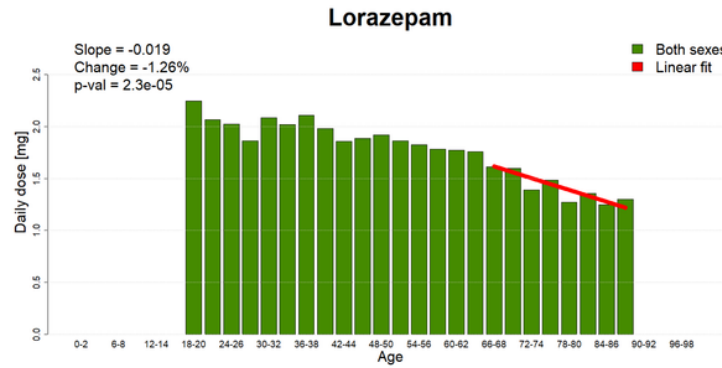
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(a) Zolpidem



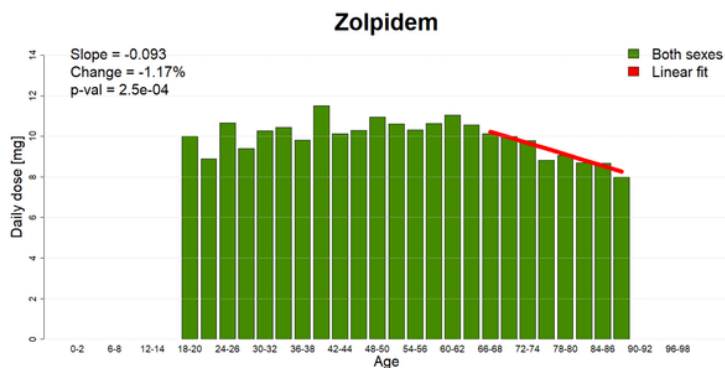
(b) Zopiclone



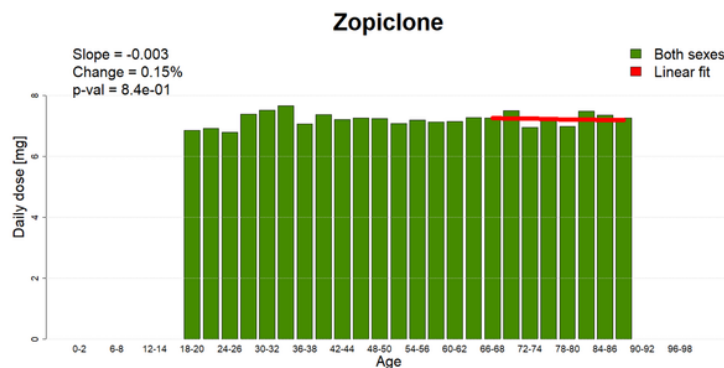
(c) Lorazepam

Figure 5

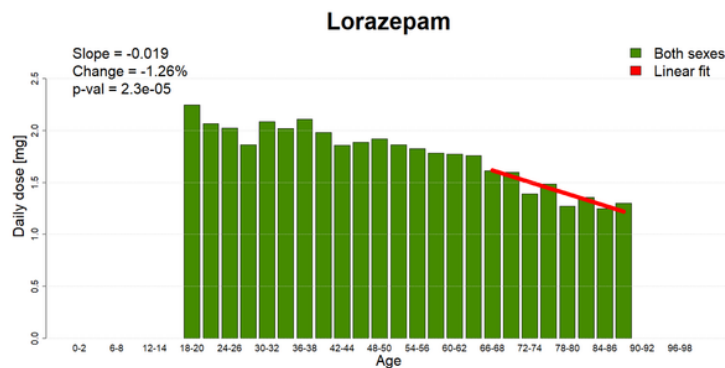
Daily dose by age: Hypnotics and Tranquilizers Daily prescribed doses (mg) of hypnotics and tranquilizers by age including both male and female patients. The height of the bars corresponds to the mean daily dosage for inpatients within age groups of three consecutive years. The patients are between 18 and 89 years old. 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, n.s. (not significant) for zopiclone; $p < 0.001$ in both other cases.



(a) Zolpidem



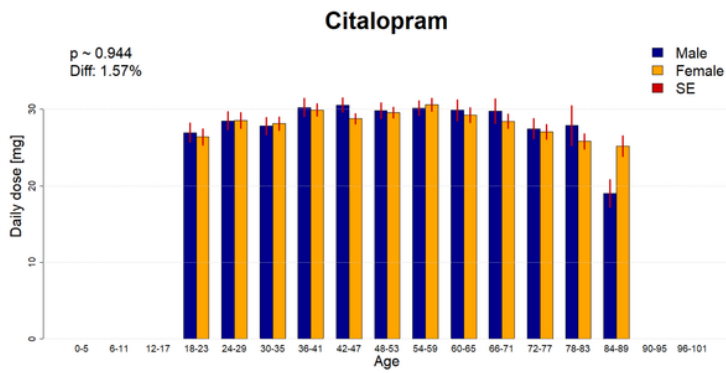
(b) Zopiclone



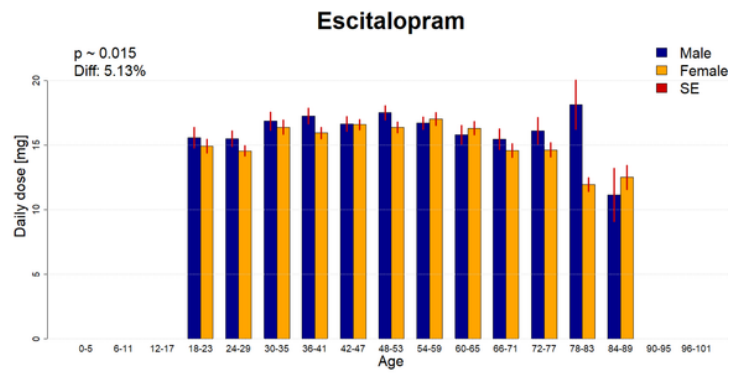
(c) Lorazepam

Figure 5

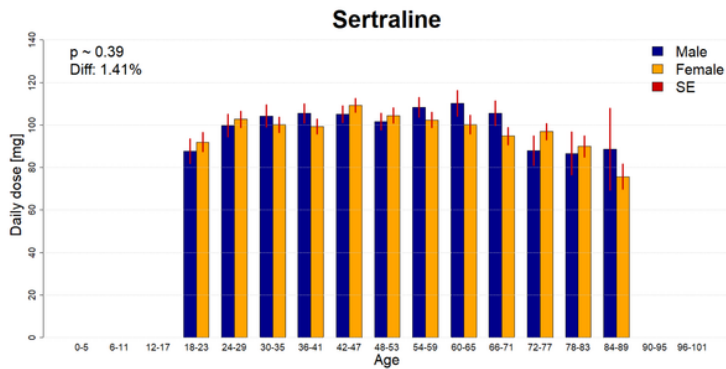
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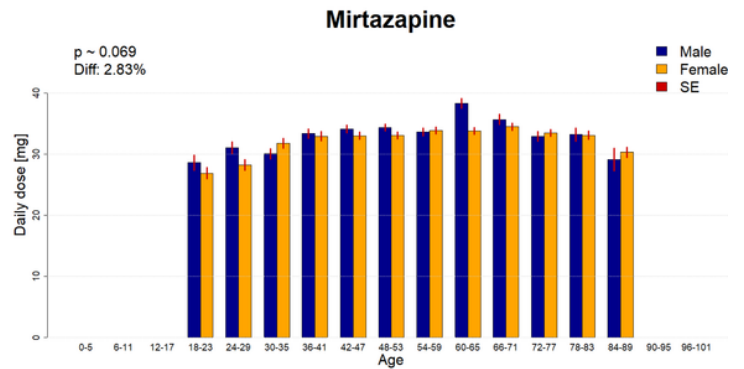
(a) Citalopram



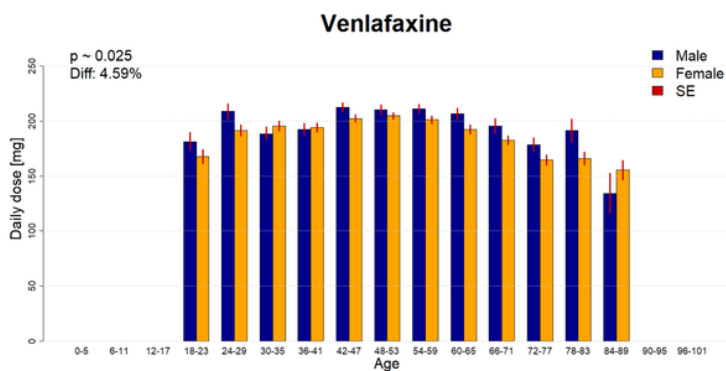
(b) Escitalopram



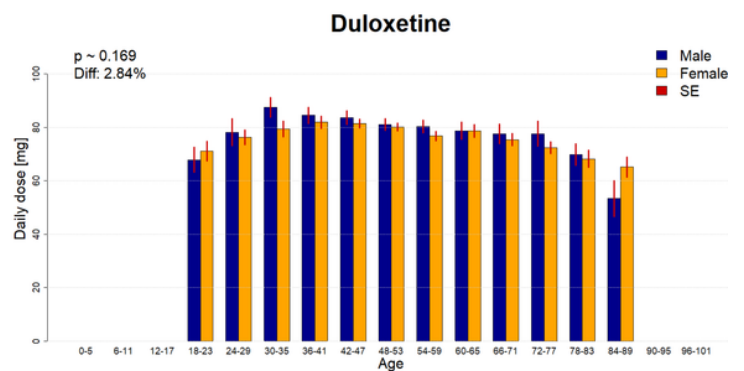
(c) Sertraline



(d) Mirtazapine



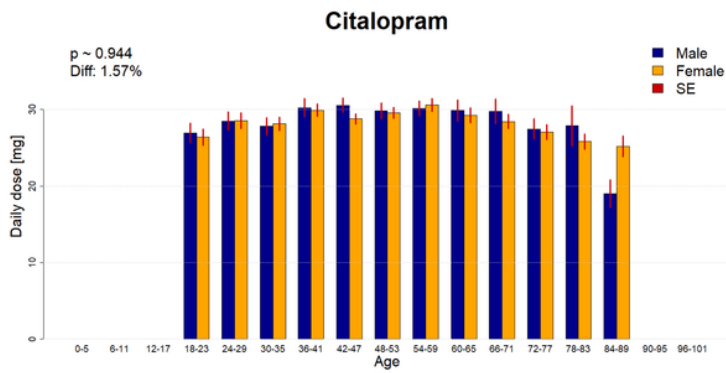
(e) Venlafaxine



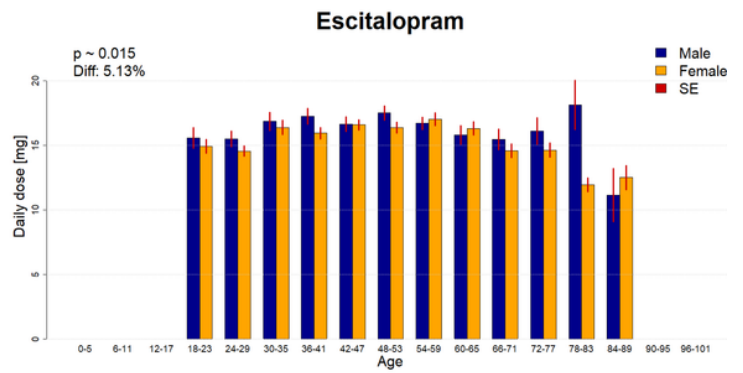
(f) Duloxetine

Figure 6

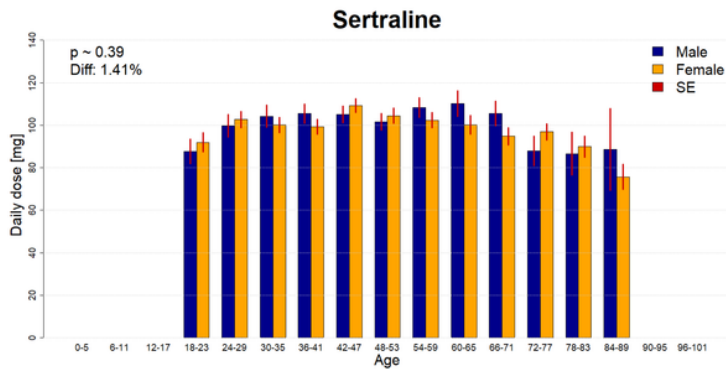
Daily dose by age and sex: Antidepressants Daily prescribed doses (mg) of antidepressants by age: males in blue and female in orange. The standard error is depicted in red. The height of the bars corresponds to the mean daily dosage for inpatients within age groups of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are small. $p < 0.05$ for escitalopram and venlafaxine; n.s in all other cases.



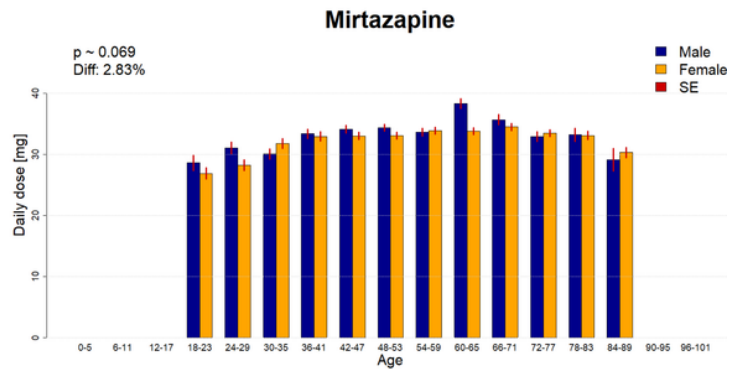
(a) Citalopram



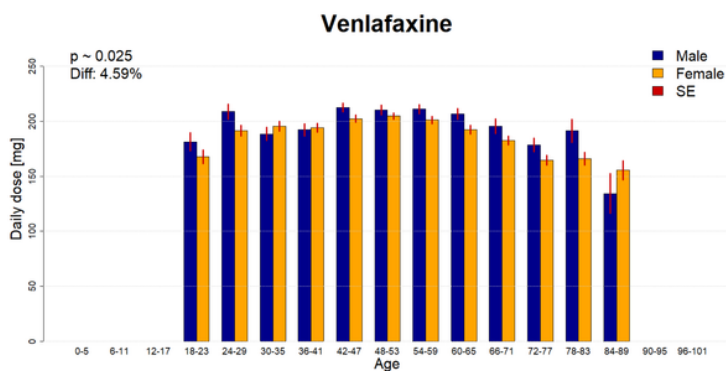
(b) Escitalopram



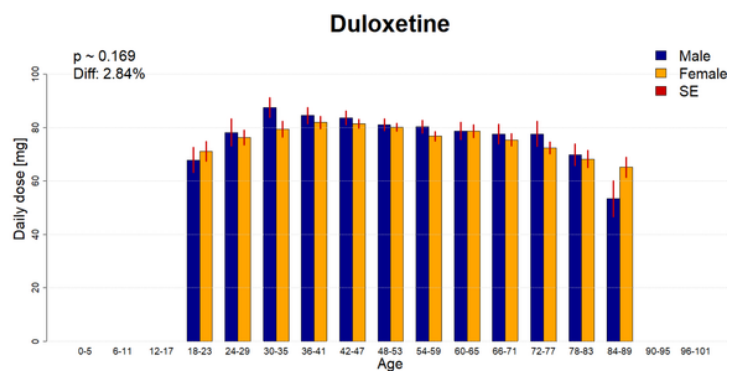
(c) Sertraline



(d) Mirtazapine



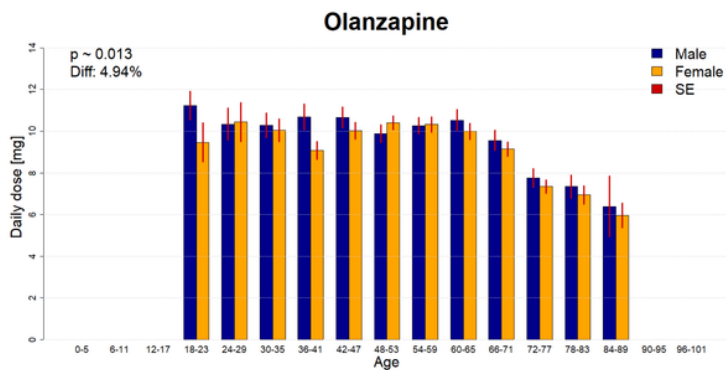
(e) Venlafaxine



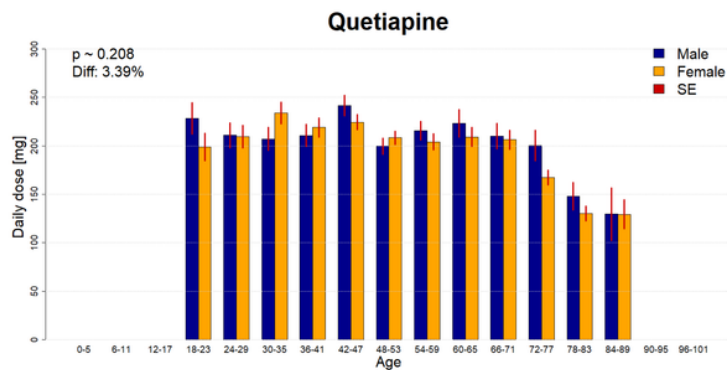
(f) Duloxetine

Figure 6

Daily dose by age and sex: Antidepressants Daily prescribed doses (mg) of antidepressants 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 of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are small. $p < 0.05$ for escitalopram and venlafaxine; n.s in all other cases.



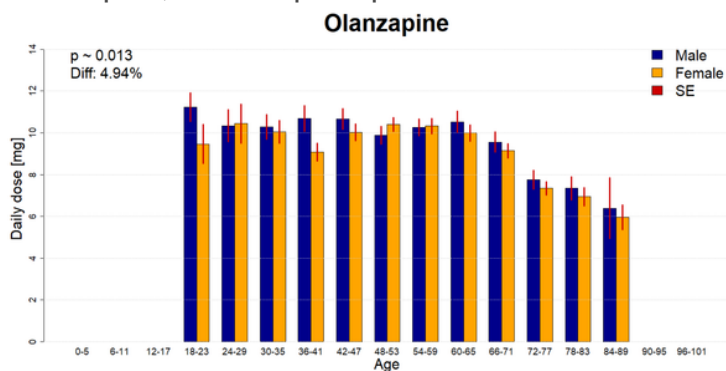
(a) Olanzapine



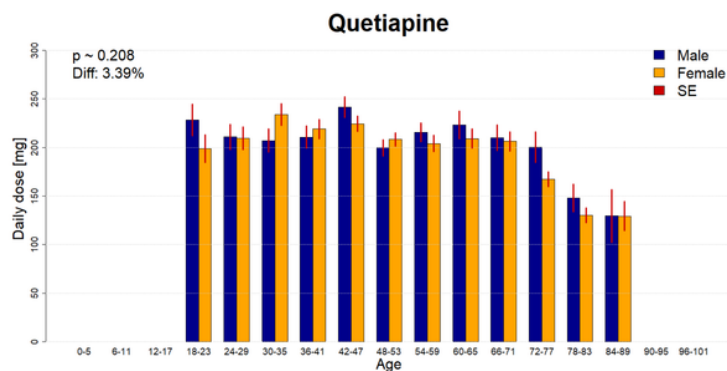
(b) Quetiapine

Figure 7

Daily dose by age and sex: Antipsychotics Daily prescribed doses (mg) of antipsychotics 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 of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are either small or statistically insignificant: $p < 0.05$ for olanzapine, n.s. for quetiapine.



(a) Olanzapine



(b) Quetiapine

Figure 7

Daily dose by age and sex: Antipsychotics Daily prescribed doses (mg) of antipsychotics 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 of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are either small or statistically insignificant: $p < 0.05$ for olanzapine, n.s. for quetiapine.

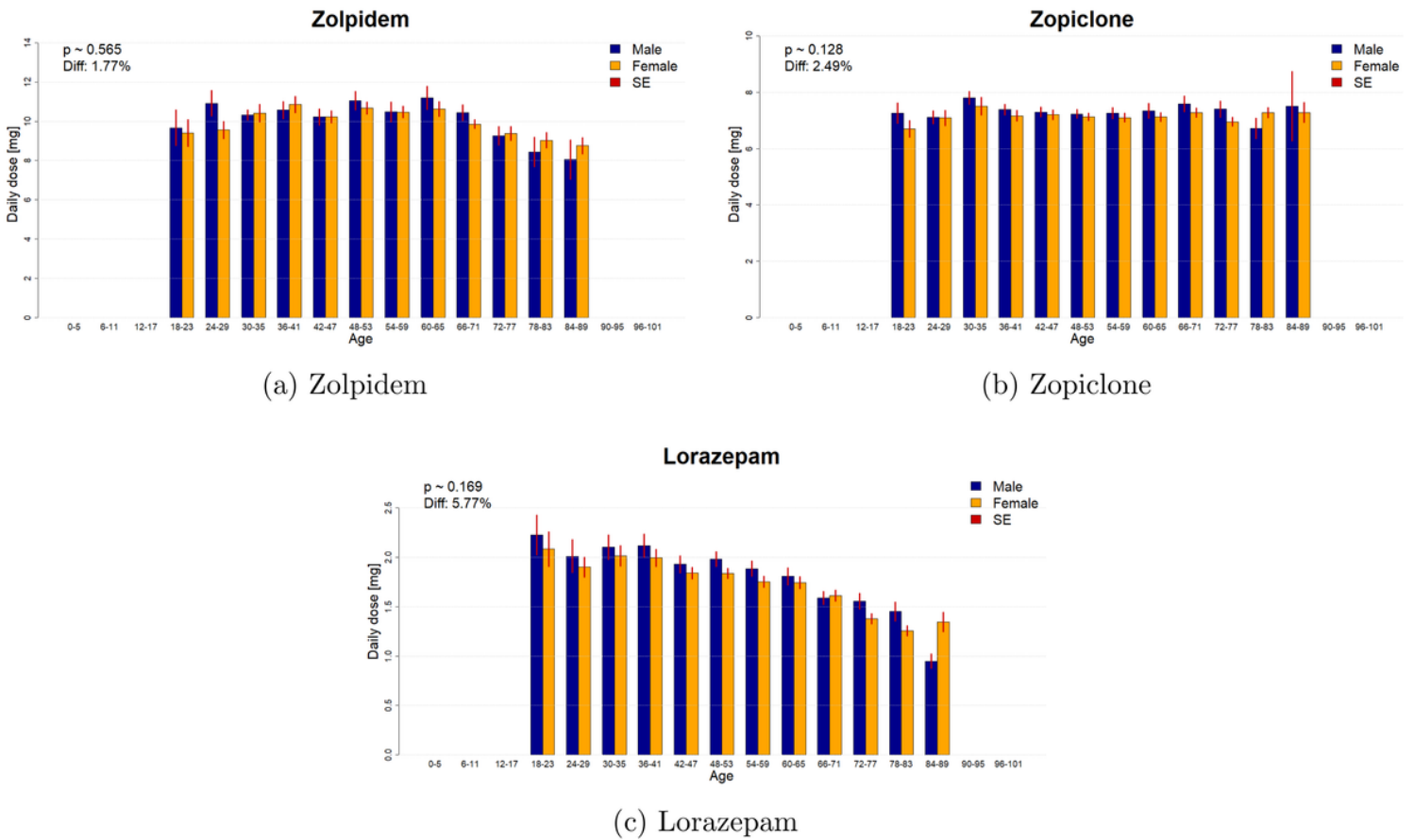


Figure 8

Daily dose by age and sex: Hypnotics and Tranquilizers Daily prescribed doses (mg) of hypnotics and tranquilizers 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 of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are small and statistically insignificant.

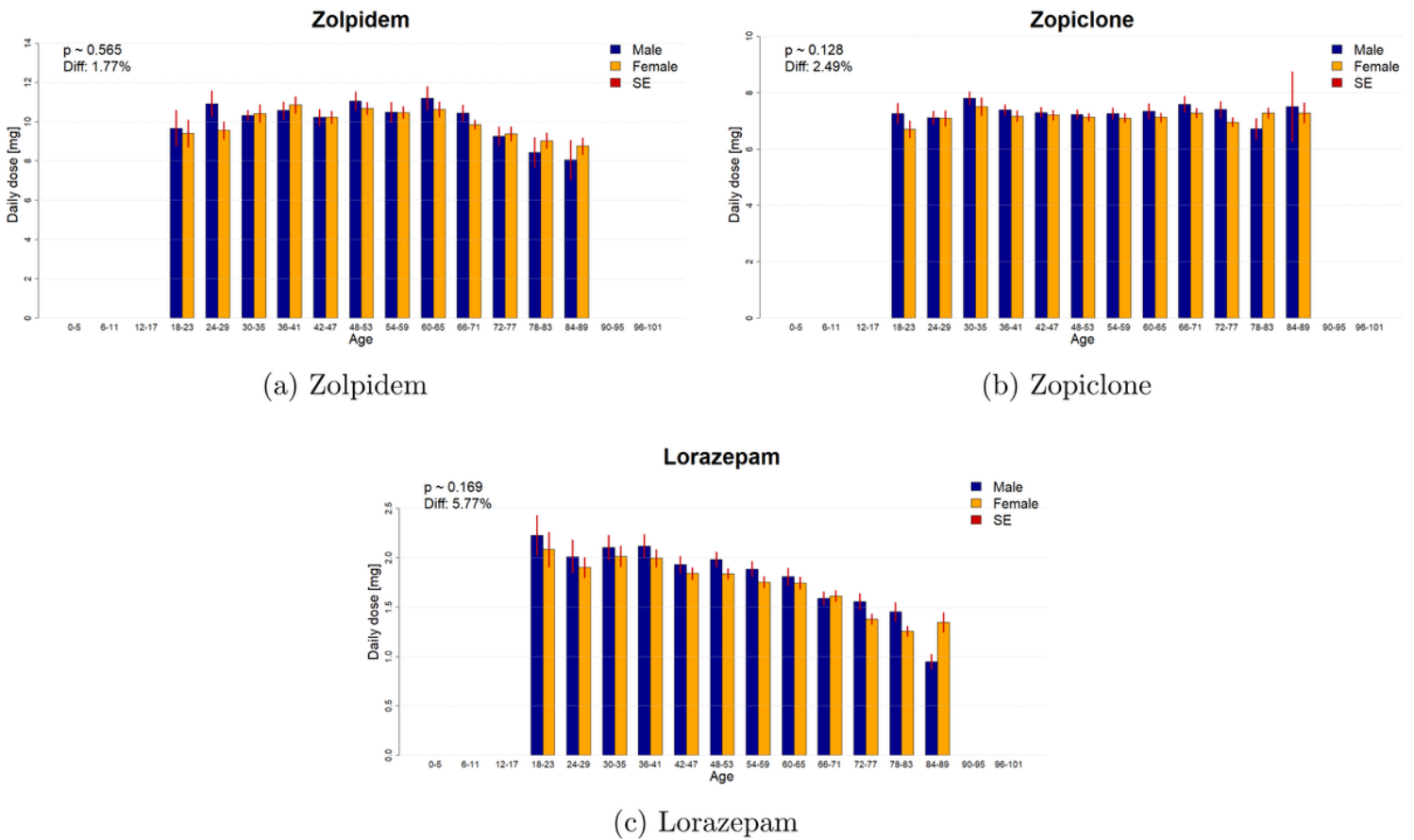


Figure 8

Daily dose by age and sex: Hypnotics and Tranquilizers Daily prescribed doses (mg) of hypnotics and tranquilizers 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 of three consecutive years. The patients are between 18 and 89 years old. P-value: 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 are chosen as reference. From the plots can be seen, that the prescribed dosage differences between men and females are small and statistically insignificant.

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