Sex-related differences in spontaneous reports on non-selective monoamine reuptake inhibitors

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Background

In Germany, women are affected by depressive and anxiety disorders twice as often as men[1]. Non-selective monoamine reuptake inhibitors (NSMRI) are used to treat depressive disorders and are also used – sometimes off-label – for other indications such as anxiety and sleep disorders. Amitriptyline, doxepin, opipramol and trimipramine are the most frequently prescribed NSMRI in Germany[2]. Previous reports have identified sex-related differences, for example, adverse drug reactions (ADR) of NSMRI that seem to affect female patients more often than male ones[3]. The German summary of product characteristics (SPC), however, does not recommend different dosages for male and female patients[4,5,6,7].

Aim

To analyze spontaneous ADR reports on amitriptyline, doxepin, opipramol and trimipramine with regard to any sex-related differences.

Methods

According to their professional code of conduct German physicians are obliged to report suspected ADR to the Drug Commission of the German Medical Association (DCGMA). For the present evaluation, spontaneous reports on suspected ADR of amitriptyline, doxepin, opipramol and trimipramine (suspect/interacting), reported to the DCGMA from May 1, 2007 to December 31, 2021, are included. Reports on SOC (MedDRA system organ class) “injury, poisoning and procedural complications” were excluded because they contain reports on medication errors and intentional overdose. Furthermore, reports about subjects < 18 years or with missing age information were excluded. The final data set was analyzed for sex differences in patient characteristics, medication details and reported adverse events. Because of the small number of patients, we did not perform statistical tests and the results are presented descriptively.

Results

From May 1, 2007 to December 31, 2021, a total of about 50.000 cases were reported to the DCGMA, of which 95 were included: 32 reports on amitriptyline, 13 on doxepin, 31 on opipramol, 20 on trimipramine (one patient was simultaneously treated with trimipramine and doxepin). Sixty-six (69.5 %) reports were on females, 29 (30.5 %) on males. Mean age was 51.7 years in males and 55.9 years in females. Of 53 “serious” reports containing at least one serious reaction, 38 (57.6 % of a total of 66) were related to women, 15 (51.7 % of 29) to men (table 1, figure 1).

Table 1: Overview of included case reports

Total	Sex		Mean age (years)	Serious		Mean age (years)
95	Male	29 (30.5 %)	51.7	Yes	15 (51.7 %)	50.7
				No	14 (48.3 %)	52.8
	Female	66 (69.5 %)	55.9	Yes	38 (57.6 %)	56.1
				No	28 (42.4 %)	55.5

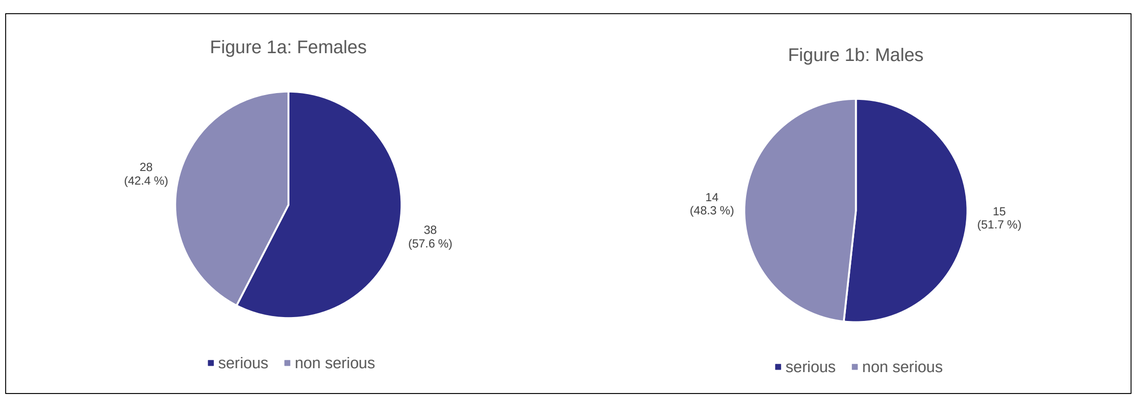

Figure 1: Proportion of serious versus non serious case reports in female (figure 1a) and male patients (figure 1b)

The most frequent ADR, that were reported at least three times were dizziness, jaundice, increased transaminases, disturbances in attention and nausea in female users. In male users the most frequently reported reactions were increased transaminases and increased hepatic enzymes (table 2).

Table 2: Most frequently reported MedDRA preferred terms (at least n = 3 reports)

Females		Males	
Preferred term	**Number**	**Preferred term**	**Number**
Dizziness	6	Transaminases increased	5
Jaundice	5	Hepatic enzyme increased	3
Increased transaminases	4		
Disturbances in attention	3		
Nausea	3		

The most frequently reported indications in female users were depressive disorders (e.g. depression, depressed mood, grief reaction), pain related conditions (e.g. pain, neuralgia, migraine prophylaxis), sleep disorders (e.g. insomnia, initial insomnia, sleep disorder), anxiety related conditions (e.g. anxiety disorder, panic attack, panic disorder) and unspecific somatic symptoms (e.g. somatic symptom disorder, autonomic nervous system imbalance, fatigue). In males, the most frequently reported indications were depressive disorders, sleep disorders, pain and anxiety related conditions (figure 2).

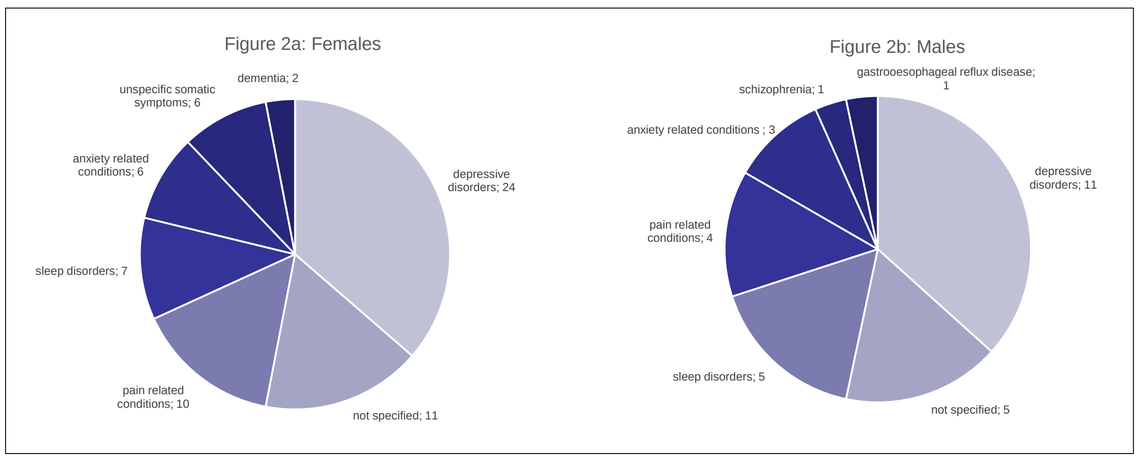

Figure 2: Indications for NSMRI treatment in female (figure 2a) and male patients (figure 1b)

Mean and median dosages are reported in table 3: Overall dosages are reported on the left side. In the right part of the table, dosages for the most frequently reported indication (depressive disorders) in both sexes are reported (table 3).

Table 3: Mean and median dosages overall and for the treatment of depressive disorders in male and female patients

	Overall (mg)				Depressive disorders (mg)			
	Females		Males		Females		Males	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Amitriptyline	40.7	25	64.6	62.5	44.5	25	60	50
Doxepin	57.5	50	125*	125*	75	50	125	125
Opipramol	119.4	100	120.8	112.5	89.3	100	125	125
Trimipramine	101.4	50	75*	50*	100	50	50**	50**

* One male patient was excluded for this analysis because he had taken 7000 mg doxepin and 6000 mg trimpramine for suicide attempt

** n = 1

Discussion

In accordance with the prevalence of depressive and anxiety disorders in the German general population[1], about two thirds of the spontaneous ADR reports on amitriptyline, doxepin, opipramol and trimipramine were in female users. Various hepatic reactions are listed in the SPC of amitriptyline, doxepin, opipramol and trimipramine[4,5,6,7] which is reflected by the spontaneous reports in both sexes in our data set. The most frequently reported indications were depressive disorders in both sexes, followed by pain related conditions and sleep disorders in female users and sleep disorders and pain related conditions in male users, which can be explained by the known drug effects[4,5,6,7]. Interestingly, six female patients were treated for unspecific somatic symptoms, whereas this diagnosis was not reported in males.

Females tend to be treated with lower dosages than males. This is an interesting finding: Given that the overall proportion of case reports reflects the prevalence of depressive and anxiety disorders in the general population and assuming that women are treated with lower dosages, this could indicate a higher sensitivity of female users to NSMRI. In fact, the proportion of serious reports in females was comparable to males although women are presumably treated with lower dosages. This further supports the possible higher ADR sensitivity of female users. Similar observations have been described previously[3]. However, the case numbers in our evaluation were low, so we could not perform robust statistical tests. Furthermore, our data are based on spontaneous reports and no final conclusion can be drawn about the incidence of ADR or about possible differences in dosages and indications in both sexes. In fact, not only sex-related aspects but also gender aspects could influence the reporting of ADR in male and female patients.

Conclusion

Our data suggest a higher ADR sensitivity of female NSMRI users compared to male ones. However, these findings need to be confirmed in larger data sets. As spontaneous reports are not suitable to derive definite conclusions, specifically-designed studies should be initiated to investigate sex- and gender-based differences in perception and reporting of NSMRI-related ADR.

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