Effect of Direct Healthcare Professional Communication on Citalopram and Escitalopram

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Background

In 2011, the US Food and Drug Administration informed on the dose dependent QTc-prolonging effect of citalopram[1]. In Germany, direct healthcare professional communication letters (DHPC) were sent out to inform on the cardiac risks associated with citalopram and escitalopram administration. As regulatory measures the maximum daily dose of citalopram and escitalopram was restricted, in the summary of product characteristics QTc-prolonging co-medication was stated as contraindicated[2,3].

Previous studies showed incomplete implementation of the DHPC: Whereas the recommendations on the new maximum daily dose were followed[4-7], the contraindication concerning QTc-prolonging drugs was not[4,6,7]. The effect of the DHPC specifically in patients with anxiety disorders was not yet studied.

Aim

The aim of the study was to analyze the effect of the DHPC on citalopram and escitalopram prescription in inpatients with anxiety disorders by using drug utilization data from the project “Arzneimittelsicherheit in der Psychiatrie e.V.” (AMSP).

Methods

AMSP is a multicenter pharmacovigilance project in which adverse reactions potentially related to psychotropic drugs are documented and assessed. Drug utilization data is also recorded on two so-called reference days per year: On these days, the entire medication of current inpatients is collected in the participating centers[4]. From 1993 to 2017, medication data of 67,000 patients in total were recorded on reference days.

Data from reference days 2004–2010 (pre-DHPC) and 2013–2017 (post-DHPC) were used to examine whether 1) the proportion of patients treated with a higher than newly recommended daily dose of citalopram and escitalopram and 2) the proportion of patients with QTc-prolonging co-medication (according the German SPC) declined post-DHPC. Data from adult inpatients with anxiety disorders treated with citalopram or escitalopram were used. Citalopram and escitalopram were evaluated in a combined category.

Results

In this analysis data of patients with anxiety disorders treated with citalopram or escitalopram were included, 364 pre-DHPC, 262 post-DHPC. Demographic data pre- and post-DHPC did not differ (Table 1).

Table 1: Demographic data pre- and post-DHPC

	Pre-DHPC (2004–2010)	Post-DHPC (2012–2017)
Pharmacologically treated patients with anxiety disorders	**1201**	**1076**
- Patients treated with antidepressants	951 (79.2 %)	846 (78.6 %)
- Patients treated with citalopram	148 (12.3 %)	76 (7.1 %)
- Patients treated with escitalopram	216 (18.0 %)	186 (17.3 %)
Total (citalopram or escitalopram)	**364**	**262**
- female	222 (61.0 %)	155 (59.2 %)
- male	142 (39.0 %)	107 (40.8 %)
- 18–64 years	330 (90.7 %)	229 (87.4 %)
- ≥ 65 years	34 (9.3 %)	33 (12.6 %)
- Mean age (years, range)	42.0 (18–86)	44.4 (19–83)

The proportion of patients exceeding the maximum recommended daily dose decreased from 10.7 to 5.4 % ($\chi^2(1) = 5.543$; $p = 0.019$). The proportion of patients with QTc-prolonging co-medication did not change ($\chi^2(1) = 0.60$; $p = 0.437$, Table 2).

Table 2: Proportion of patients exceeding the new maximum recommended daily dose and proportion of patients with QTc-proloning co-medication: Comparison pre- and post-DHPC

	Pre-DHPC (2004–2010)	Post-DHPC (2012–2017)	p-value
Proportion of patients			
- Exceeding the maximum recommended daily dose	39 (10.7 %)	14* (5.4 %)	p = 0.019
- Within the maximum recommended daily dose	325 (89.3 %)	246* (94.6 %)	
Proportion of patients			
- With QTc-prolonging co-medication	199 (54.7 %)	135 (51.5 %)	p = 0.437
- Without QTc-prolonging co-medication	165 (45.3 %)	127 (48.5 %)	

*The daily dosage of two patients post-DHPC was not given. So data of only 260 patients were included in this analysis.

The proportion of elderly (≥ 65 years) high-dose patients was 29.4 % pre- and 15.2 % post-DHPC, the respective proportions of the younger patients were 8.8 and 4.0 % (Table 3). Elderly patients were more likely to be overdosed post-DHPC than younger patients (OR = 4.33; 95 % CI 1.35–13.83; Fisher‘s exact test: p = 0.021).

Table 3: Patients exceeding the newly recommended maximum dails dose depending on age

		Pre-DHPC (2004–2010)	Post-DHPC (2012–2017)
18–64 years	**Total**	**330**	**227**
	- Proportion exceeding the maximum recommended daily dose	29 (8.8 %)	9 (4.0 %)
	- Proportion within the maximum recommended daily dose	301 (91.2 %)	218 (96.0 %)
≥ 65 years	**Total**	**34**	**33**
	- Proportion exceeding the maximum recommended daily dose	10 (29.4 %)	5 (15.2 %)
	- Proportion within the maximum recommended daily dose	24 (70.6%)	28 (84.8 %)

Both, pre- and post-DHPC, the most frequently used QTc-prolonging co-medications were quetiapine and mirtazapine (pre-DHPC: mirtazapine 47/364 patients (13.0 %), quetiapine 33/364 (9.1 %); post-DHPC: mirtazapine 38/262 (14.5 %); quetiapine 32/262 (12.2 %); Figure 1).

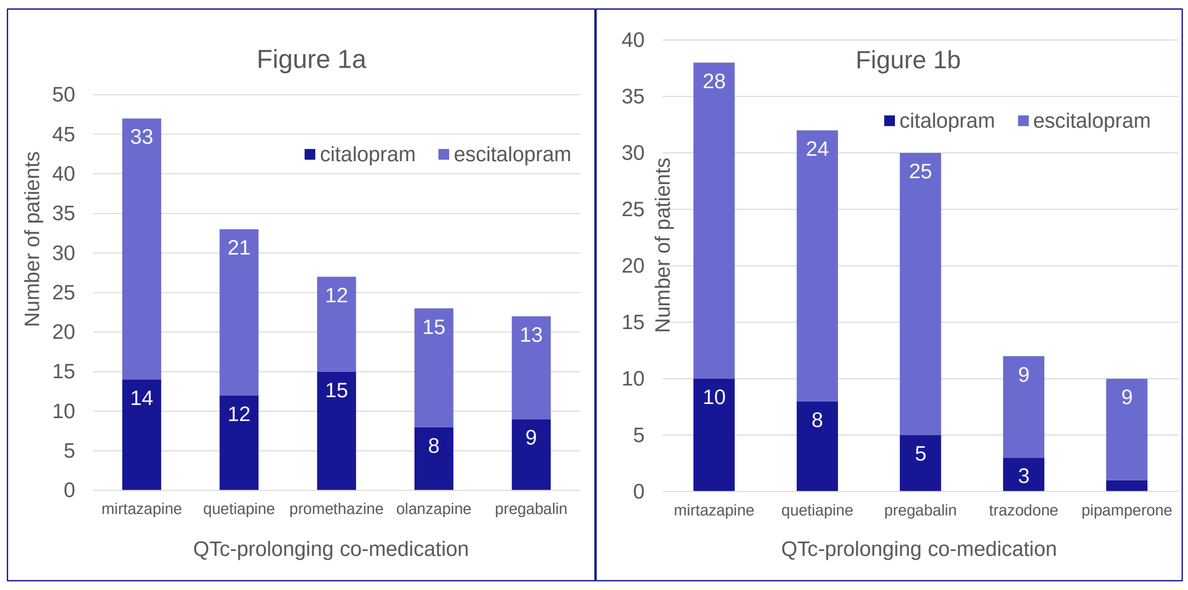

Figure 1: Most frequently used QTc-prolonging co-medication pre-DHPC (1a) and post-DHPC (1b)

The total use of citalopram decreased from 12.3 to 7.1 % ($\chi^2(1) = 17.70$; $p < 0.001$) whereas the use of escitalopram remained virtually unchanged (18.0 vs. 17.3 %, $\chi^2(1) = 0.191$; $p = 0.662$; Table 1).

Discussion

As in previous studies, the proportion of patients exceeding the new maximum daily dose declined significantly post-DHPC whereas the proportion of patients with QTc-prolonging co-medication did not change. This might be partly explained by the fact that precise recommendations such as the newly recommended maximum daily dose might be easier to be followed than complex ones, e.g. the recommendation to avoid any QTc-prolonging co-medication. Furthermore, the clinical significance of the DHPC in healthy patients with normal baseline QTc-interval may be questioned because the DHPC report average values for the QTc-prolongation, not the percentage of patients with a pathological QTc-interval under citalopram or escitalopram[2,3].

The maximum dosage post-DPHC was more frequently exceeded in elderly than in younger patients, probably because the recommended maximum dose in this age group is considered as too low from a clinical point of view. The decrease in citalopram use cannot be attributed to a decline in antidepressant use in general as the proportion of patients treated with antidepressants remained approximately the same post-DHPC. Pre- and post-DHPC, mirtazapine and quetiapine were the most frequently used QTc-prolonging co-medications. This may be explained by their sedative properties, which are advantageous when treating patients with anxiety disorders.

Conclusion

Information on drug risks should be formulated as precisely as possible. Advice in specific clinical situations (e.g. imbalance of electrolytes) and therapeutic alternatives should be given. This could facilitate the implementation of new recommendations.

References/further sources of information: The data presented here are based on the master’s thesis of UK. A manuscript with the full publication is submitted to Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. [1] U.S. Food and Drug Administration (FDA): FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide): https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-abnormal-heart-rhythms-associated-high-doses-celexa-citalopram (last access: 8-10-2022). Silver Spring, August 24, 2011. [2] Lundbeck GmbH: Wichtige Arzneimittelinformation für medizinisches Fachpersonal: Zusammenhang von Cipramil® (Citalopramhydrobromide(Citalopram-hydrochlorid) mit dosisabhängiger QT-Intervall-Verlängerung. Rote-Hand-Brief vom 31.10.2011. [3] Lundbeck GmbH: Wichtige Arzneimittelinformation für medizinisches Fachpersonal: Zusammenhang von Escitalopram (Cipralex®) mit dosisabhängiger QT-Intervall-Verlängerung. Rote-Hand-Brief vom 05.12.2011. [4] Friesen KJ, Bugden SC: The effectiveness and limitations of regulatory warnings for the safe prescribing of citalopram. Drug, healthcare and patient safety 2015; 7: 139-145. [5] Gerlach LB, Kim HM, Yosef M, Sales AE, Stano C, Kales HC et al.: Assessing responsiveness of health systems to drug safety warnings. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry 2018; 26: 476-483. [6] Schächtele S, Tümena T, Gaßmann KG, Fromm MF, Maas R: Implementation of warnings from Dear Doctor Letters (Rote-Hand-Briefe): an analysis of medication data from a large cohort of elderly patients. Dtsch Arztebl Int 2014; 111: 255-263. [7] de Bardeci M, Greil W, Stassen H, Willms J, Koberle U, Bridler R et al.: Dear Doctor Letters regarding citalopram and escitalopram: guidelines vs real-world data. European archives of psychiatry and clinical neuroscience 2022: Epub ahead of print. [8] Grohmann R, Engel RR, Ruther E, Hippius H.: The AMSP drug safety program: methods and global results. Pharmacopsychiatry 2004; 37 (Suppl. 1): 4-11.

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