ORIGINAL ARTICLE

Implementation of Warnings From Dear Doctor Letters (Rote-Hand-Briefe)

An Analysis of Medication Data From a Large Cohort of Elderly Patients

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SUMMARY

Background: Dear Doctor Letters (also known as Direct Healthcare Professional Communications) inform physicians about significant newly discovered drug risks and about measures to take to reduce these risks. How far these warnings actually influence prescribing behavior is unclear.

Methods: The Geriatrics in Bavaria–Database (GiB-DAT, Geriatrie in Bayern Datenbank) collects data from more than 50 centers offering inpatient geriatric health care. Based on GiB-DAT data, the discharge medication of 76 568 patients (81 ± 8 years, 67% women) was recorded in a standardized manner and analyzed for the implementation of information contained in two Dear Doctor Letters about the risks of dose-related or drug interaction–related QT interval prolongation caused by citalopram or escitalopram.

Results: Patients were discharged with a median of 8 drugs. In the four quarters of 2012 following release of the Dear Doctor Letters, in comparison to the four quarters before their publication, a marked drop from 9.8% to 4.1% was seen in prescriptions for >20 mg/day citalopram—a dosage no longer recommended in elderly patients—and a similar drop from 23.6% to 12.8% in prescriptions for >10 mg/day escitalopram ($p < 0.0001$). Co-prescription of either of these two drugs with other QT interval–prolonging drugs, which was now contraindicated, remained almost unchanged (citalopram: 19.3% [95% confidence interval (CI): 17.9–20.9%] versus 18.4% [95% CI: 17.0–19.8%]; escitalopram: 17.6% [95% CI: 15.8–19.6%] versus 17.1% [95% CI: 14.5–19.9%]).

Conclusion: Simple information in Dear Doctor Letters, such as a reduction of the maximum daily dose, was better implemented than complicated information regarding contraindicated co-medication. Quality assurance systems such as the GiB-DAT network make it possible to identify problems of this kind. Licensing authorities and pharmaceutical companies should improve the clinical usability, e.g., by providing official reference lists of drugs with safety warnings.

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When studying the incidence of medication errors, we repeatedly noticed the occurrence of non-adherence to contraindications that were also the subject of recent Dear Doctor Letters (known as *Rote-Hand-Briefe* in Germany or as Direct Healthcare Professional Communications [DHPCs] in other countries) (1). The question therefore naturally arose: how far, and how fast, are the safety-related contents of these letters actually implemented in everyday clinical practice?

In Germany, around 20 to 40 Dear Doctor Letters are issued every year. The purpose of these letters is to inform relevant healthcare professionals (physicians and pharmacists) about significant newly discovered drug risks and measures to reduce them even before the official prescribing information (also known as Summary of Product Characteristics, SmPC) is updated (2).

In October 2011, a Dear Doctor Letter was released in Germany on dose-dependent QT interval prolongation caused by citalopram. Important points were a reduction of the maximum daily dose to 20 mg in patients aged >65 years and those with impaired liver function, and a new contraindication for administration of citalopram in patients with existing prolonged QT interval or in combination with other QT interval–prolonging drugs (3–5) (*eBox*).

Two months later, a similar warning was issued for escitalopram (6–8); again, similar to citalopram, the maximum dose in older patients was limited, to 10 mg. These new instructions for use were included in the official prescribing information for the originator products as early as December 2011 for Cipralex® and in March 2012 for Cipramil®, and for the generics (available only for citalopram) by May 2012.

Both genetic and drug-induced disturbances of heart muscle cell repolarization can show up in the ECG as a prolonged QT interval. Since the length of the QT interval also depends on the heart rate, the QT interval given is usually corrected for rate (QTc). A patient with a prolonged QTc interval is at increased risk of Torsade de pointes (TdP) tachycardia, which can lead to ventricular fibrillation (9, 10).

We took these Dear Doctor Letters as an example to investigate the implementation of the recommendations made in them in older patients, using data from the Geriatrics in Bavaria–Database (Geriatrie in Bayern Datenbank, GiB-DAT). These warnings must be

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TABLE 1

Characteristics of the study population in the nine quarterly periods Q4/2010 to Q4/2012

	All patients receiving at least one drug	All patients receiving citalopram	All patients receiving escitalopram
Total N from Q4/2010 to Q4/2012	76 568	6243	2606
Mean age, years (SD)	81 ± 8	80 ± 7	80 ± 8
Women, n (%)	51 338 (67)	4504 (72)	1814 (70)
Number of drugs at discharge, median (25 th –75 th percentiles)	8 (6–11)	9 (7–12)	9 (7–12)
Number of diagnoses at discharge, median (25 th –75 th percentiles)	11 (9–15)	12 (10–16)	11 (9–15)
Number of patients with main and subsidiary diagnoses, abbreviated ICD codes (% of total population)			
I07 Cardiovascular	65 814 (86)	5300 (85)	2345 (90)
I13 Trauma	37 123 (48)	3026 (49)	1264 (49)
I12 Symptoms not otherwise classified	39 824 (52)	3472 (56)	1571 (60)
I10 Musculoskeletal	37 032 (48)	3004 (48)	1291 (50)
I04 Psychiatric	31 484 (41)	3662 (59)	1711 (66)
I05 Neurologic	26 819 (35)	2397 (38)	1125 (43)
I14 Other	31 073 (41)	2438 (39)	1032 (40)
I03 Endocrinologic	43 452 (57)	3483 (56)	1565 (60)
I11 Urologic	30 946 (40)	2508 (40)	1073 (41)
I08 Pulmonary	19 180 (25)	1565 (25)	689 (26)
I9 Gastroenterologic	19 701 (26)	1571 (25)	698 (27)
I01 Infections	13 034 (17)	1089 (17)	473 (18)
I02 Tumors	21 828 (29)	1736 (28)	774 (30)
Length of hospital stay, days	21 (17–26)	21 (18–28)	21 (19–28)
Barthel score at admission, median (25 th –75 th percentiles)	45 (30–60)	40 (25–55)	40 (25–55)
Barthel score at discharge, median (25 th –75 th percentiles)	75 (50–85)	65 (45–80)	65 (40–85)
Geriatric Depression Scale (GDS) at admission, median (25 th –75 th percentiles)	4 (2–6)	5 (3–7)	6 (3–8)

assumed to have a particular relevance in elderly patients because of the increased multimorbidity and polypharmacy in this patient group.

Methods

GiB-DAT network

This investigation was based on data from the Geriatrics in Bavaria–Database (Geriatric in Bayern Datenbank, GiB-DAT) (11, 12), a network of more than 50 centers offering inpatient geriatric health care. These centers have joined together to continually assess and improve the quality of patient care (13). Participating centers provide, among other things, pseudonymized or anonymized data about discharge medication. The data must be formally regarded as case-based, because a small percentage of repeat admissions cannot be ruled out. GiB-DAT holds standardized data on about 91% of all Bavarian geriatric rehabilitation facilities and about

74% of all Bavarian acute geriatric wards (as of October 2012) (14). The present study was approved by the ethics committee of the Friedrich-Alexander University of Erlangen-Nuremberg. For the analysis of prescription or co-prescription of citalopram and escitalopram with QT interval-prolonging drugs, the complete ATC-coded discharge medication of 76 568 patients was available. For more than 95% of these patients, in addition, it was possible to assess the exact prescribed dosage of the drugs concerned.

The discharge medication data were used to investigate the prescribed dosages of citalopram or escitalopram, and co-prescriptions of citalopram or escitalopram with other QT interval-prolonging drugs—combinations that were contraindicated after the release of the Dear Doctor Letter in the fourth quarter of 2011—in each of the four quarters before and after the publication of the Dear Doctor Letters. The

FIGURE 1a

Daily dose of citalopram (%)

Evolution over time of percentages of patients receiving daily doses of 10 mg, 20 mg, and >20 mg citalopram

In the four quarters after publication of the Dear Doctor Letter (DDL) on citalopram in October 2011, a marked decrease was seen in the numbers of patients on the 20 mg/day dosage, while numbers on the 10 mg/day dosage increased. The dosage of more than 20 mg/day citalopram, contraindicated in patients over 65 years of age after publication of the DDL, declined from 9.8% to 4.1% of all patients treated with citalopram. No relevant changes in dosages occurred following updating of the Summary of Product Characteristics (SmPC) in March 2012.

prescribed dosages were also used as a basis to calculate whether the maximum daily dose of each of these drugs had been adhered to.

The most important contents of the Dear Doctor Letters are summarized in the *eBox*.

QT interval-prolonging drugs

Drugs were classified as prolonging QT interval using the lists published at CredibleMeds.org (formerly azcert.org) of the University of Arizona Centers for Education & Research on Therapeutics (AZCERT), because no officially authorized list of these risky drugs exists for Germany (15). For the analysis, we chose drugs with the following QT risk: “risk of TdP” (proven risk of triggering TdP tachycardia, corresponding to “high-risk QT drug”), “possible risk of TdP” (potential risk based on individual case reports), “conditional risk of TdP” (conditional risk of TdP, only under particular conditions). In the analyses we included either all the groups together (QT drug) or only the “risk of TdP” group (high-risk QT drug).

The analysis used the list of drugs available in Germany as at 17 May 2012 (*eTable*).

Statistical analysis

Data were collected in an MS Visual Fox Pro database, version 9.0, and exported into SPSS version 13.0 (SPSS, Chicago, IL). For the mainly descriptive statistics (mean, median, percentages, standard deviation, quartiles, etc.), SPSS was also used. Exact confidence intervals were calculated using a free online

tool (16). For comparisons of frequencies (categorical data), Fisher’s exact test was employed (17).

Results

The discharge medication of 76 568 geriatric patients (81 ± 8 years, 67% women) 12 months before and after publication of the Dear Doctor Letters on citalopram and escitalopram was studied (*Table 1*). Patients received a median of eight drugs at discharge. The data of 8804 patients in the fourth quarter of 2011—the quarter in which the Dear Doctor Letters were issued—were excluded from further analysis.

Observance of changed maximum doses

Because 98% of all patients studied were in the 65+ age group, the reduced daily maxima valid from the day the Dear Doctor Letters were issued applied. These were: 20 mg for citalopram and 10 mg for escitalopram. Analysis of the prescribed dosages in the four quarters before and after publication of the Dear Doctor Letters showed that only 4.1% (95% CI: 3.4–4.9%) of prescriptions exceeded the maximum dosage after this date, compared to 9.8% (95% CI: 8.7–11.0%) before the safety warning was issued ($p < 0.0001$). In addition, a marked change was observed in the prescription frequency of citalopram from 20 mg to 10 mg (*Figure 1a*). Likewise, for escitalopram, the percentage of patients for whom dosages above 10 mg/day were prescribed went down from 23.6% (95% CI: 21.5–25.7%) to 12.8% (95% CI: 10.6–15.5%) ($p < 0.0001$) (*Figure 1b*).

Evolution over time of percentages of patients receiving daily doses of 5 mg, 10 mg, and >10 mg escitalopram

With escitalopram, a marked decrease was seen in dosages of >10 mg, now contraindicated in patients aged over 65, after publication of the DDL, from 23.6% to 12.8% of all patients treated with escitalopram. Simultaneously, a rise was seen in the number of 10 mg/day dosages. After a delay, in the second quarter of 2012 a further decrease was seen in the number of 10 mg/day dosages, while the number of dosages of half that amount (5 mg/day escitalopram) rose. The Summary of Product Characteristics (SmPC) was updated in December 2011

FIGURE 1b

Daily dose of escitalopram (%)

Co-prescription of citalopram or escitalopram with QT interval-prolonging drugs

In the four quarters before publication of the safety warning (4/2010 to 3/2011), 2710 (8.3%) of 32 677 patients received citalopram (Table 2). In 524 of these patients (19.3% [95% CI: 17.9–20.9%]), citalopram was prescribed in combination with another QT-interval-prolonging drug, and in the case of 135 of these patients (5.0% [95% CI: 4.2–5.9%]) it was prescribed together with drugs carrying a high risk for the occurrence of TdP tachycardia. These numbers did not change much after the publication of the safety warning

($p = 0.37$ and 0.41 , respectively): in the following four quarters of 2012, a total of 2783 (7.9%) of 35 087 patients received citalopram. In 511 patients (18.4% [95% CI: 17.0–19.8%]) the QT-relevant drugs were co-prescribed, and in 125 of these patients (4.5% [95% CI: 3.8–5.3%]) they were prescribed together with drugs carrying a high risk for the occurrence of TdP tachycardia (Figure 2). In terms of QT-relevant co-prescriptions before and after publication of the Dear Doctor Letter, the evolution for escitalopram was practically identical with that for citalopram: 17.6% vs. 17.1% [$p = 0.77$] for the percentage of patients co-prescribed escitalopram and any other QT-interval-prolonging drug(s), and 4.6% vs. 5.3% [$p = 0.53$] for patients co-prescribed high-risk QT interval-prolonging drugs (Figure 2).

In contrast to the picture for citalopram, during the observation period a marked drop in escitalopram prescriptions by over 50% was noted, from a total of 1578 prescriptions among 32 677 patients (4.8%) to 739 among 35 087 (2.1%) (Figure 3).

TABLE 2

Percentage of the whole study population receiving co-medication with other QT-interval-prolonging drugs (QT drugs) in addition to citalopram or escitalopram

Patients	Before DDL	After DDL
Total number	32 677	35 087
Citalopram (%)	2710 (8.3)	2783 (7.9)
Citalopram + any QT drug (%)	524 (1.6)	511 (1.5)
Citalopram + high-risk QT drug (%)	135 (0.4)	125 (0.4)
Escitalopram (%)	1578 (4.8)	739 (2.1)
Escitalopram + any QT drug (%)	278 (0.9)	126 (0.4)
Escitalopram + high-risk QT drug (%)	73 (0.2)	39 (0.1)

Medication data from Q4/2011 (date of publication of release of the Dear Doctor Letters [DDLs]) are not included

Top 20 most frequent combinations with other QT-risk drugs

In the analysis of the most frequent combinations of QT interval-prolonging drugs with citalopram and escitalopram, just 20 drugs were responsible for more than 90% of all co-prescriptions. For both citalopram and escitalopram, the most frequently used QT interval-prolonging drugs were quetiapine and resperidone, followed by domperidone and amitriptyline or amiodarone and domperidone (Table 3).

FIGURE 2

Co-prescription with other QT interval-prolonging drugs (%)

Number of patients in whom citalopram or escitalopram was co-prescribed alongside other QT interval-prolonging drugs.

Figure shows the number of patients in whom citalopram or escitalopram was co-prescribed alongside other QT interval-prolonging drugs (QT drug) as a percentage of all citalopram or escitalopram prescriptions before and after publication of the Dear Doctor Letter (DDL). Combinations with QT interval-prolonging drugs in risk groups 1 to 3 (according to CredibleMeds.org) changed overall for both drugs only slightly, from 19.3% to 18.4% for citalopram and from 17.6% to 17.1% for escitalopram. The percentages of combined prescriptions of citalopram and escitalopram with high-risk QT drugs, corresponding to risk group 1, also changed only slightly after publication of the DDLs

Discussion

In our analysis of the discharge medications of a large cohort of elderly patients, we found that simple instructions in Dear Doctor Letters, such as new dosage maxima, were better observed than more complicated warnings such as that co-prescription of QT interval-prolonging drugs was now contraindicated—warnings that remained largely unobserved. The primary aim of the study was to investigate to what extent instructions in Dear Doctor Letters were implemented in clinical practice after publication of the warnings. The question that almost automatically follows on from this, about the clinical relevance of such warnings, has been the object of other studies. A purely temporal association between events is naturally no proof of causality. However, the observed divergent evolution of the co-prescription of contraindicated drugs, their dosages, and the absolute prescription rates does make certain interpretations particularly plausible.

The original trigger for the Dear Doctor Letter under investigation was a warning issued by the US Food and Drug Administration (FDA) on 24 August 2011. The

study underlying this warning was the first prospective study to show a dose-dependent prolongation of the QT interval by citalopram at therapeutic doses (18, 19). Although this prolongation effect was not so strong in the studies on which the escitalopram analysis was based, and in the USA (unlike in Europe) the warning remained restricted to citalopram, several authors do not believe this means that any assumption can be drawn about greater cardiac safety of escitalopram (20). The clinical usefulness of the specific warnings relating to QT risks remain under debate in the current literature, however (21–23). After one study of more than 3.4 million patients found no evidence of increased risk of ventricular arrhythmias and sudden cardiac death from citalopram (24), a Danish study found that citalopram increased the risk of preclinical cardiac arrest by just under 30% (odds ratio 1.29, 95% CI: 1.02–1.63) (25). Against this background, a very critical statement by the German Association of Psychiatry, Psychotherapy and Psychosomatics (DGPPN, Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde)

Evolution over time of the prescriptions for citalopram and escitalopram after introduction of the reimbursement limit (RL) in the German statutory health insurance system and after publication of the Dear Doctor Letters (DDLs). After a reimbursement limit was introduced for escitalopram in the third quarter of 2011, prescriptions dropped markedly

FIGURE 3

is interesting; it was sent to doctors by one of the pharmaceutical companies concerned. This statement recommends reacting “rationally” to the Dear Doctor Letters (without disclosing any possible conflicts of interest on the part of the authors of the statement). Irrespective of the content, the promulgation of “softening” statements by manufacturers of the drugs in question is distinctly problematic (26, 27).

On the basis of a recently published study, there is renewed discussion about the information available on risk due to increased dosages in terms of possibly reduced clinical effectiveness in depression after dose reduction. The warnings emanating from the licensing authorities are being challenged even more (28). In this US study which investigated over 600 000 patients who received citalopram between 2004 and 2009, no increased risk of ventricular arrhythmias or mortality was shown for dosages higher than 40 mg/day.

In the case of citalopram, and, even more, escitalopram, it could also be argued that the warnings were not implemented because doctors knew that there was a great deal of criticism of the safety warnings in the current literature. Closer inspection shows that this is unlikely to be the case, however. For although it is precisely the association with the dosage that is under attack in the literature, and that the dosage acts as only one risk factor among others such as sex and electrolyte status (29), German doctors have been relatively consistent in implementing the recommendation about

reducing dosages, but not the warning regarding contraindicated combinations.

One explanation could be that for the doctor prescribing a new drug in addition to existing medication, reconciling all the prescribing information (SmPCs) and published Dear Doctor Letters is virtually impossible, because, contrary to the common assumption, drug safety warnings in the prescribing information are often inconsistent with each other (Pfistermeister B, Fromm MF, Maas R. Gleicher Wirkstoff – unterschiedliche Indikationen, Kontraindikationen und Nebenwirkungen. Ein Vergleich von Fachinformationen verschiedener Generika. *Arzneiverordnung in der Praxis* 2013; 40: 88 [Abstract]). A general influence of safety warnings on prescription numbers has already been observed in a Dutch study (30). The reduction in prescriptions for escitalopram, which has not been seen for citalopram, is notable (Figure 3) and argues against an association with the Dear Doctor Letters. The reason for it is probably to do with drug reimbursement: escitalopram has been included in the fixed-amount group of “selective serotonin reuptake inhibitors” in a decision of the Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss) that came into effect on 1 July 2011 (31, 32).

Many authors assume that combining QT interval-prolonging drugs further increases the overall risk of the occurrence of TdP (33, 34). The results of a Dutch study suggest that checking QT interval by ECG

TABLE 3

Top 20 QT interval-prolonging drugs prescribed in combination with citalopram or escitalopram

	Citalopram			Escitalopram		
	ATC code	Drug	Percentage of all co-prescriptions (%) [*]	ATC code	Drug	Percentage of all co-prescriptions (%) [*]
1	N05AH04	Quetiapine	15.0	N05AH04	Quetiapine	15.5
2	N05AX08	Risperidone	14.1	N05AX08	Risperidone	11.8
3	A03FA03	Domperidone	7.9	C01BD01	Amiodarone	9.8
4	N06AA09	Amitriptyline	7.7	A03FA03	Domperidone	9.5
5	C01BD01	Amiodarone	7.3	J01MA02	Ciprofloxacin	6.4
6	N06DA04	Galantamine	5.8	N04BB01	Amantadine	5.8
7	J01MA02	Ciprofloxacin	4.5	N06AA09	Amitriptyline	5.4
8	N06AA12	Doxepin	4.2	J01EE01	Trimethoprim	4.0
9	N04BB01	Amantadine	4.2	N06AA06	Trimipramine	3.7
10	N06AA06	Trimipramine	2.7	N06AA12	Doxepin	3.4
11	J01EE01	Trimethoprim/sulfamethoxazole	2.5	N06DA04	Galantamine	3.3
12	N05AD01	Haloperidol	2.4	N05AH03	Olanzapine	3.2
13	J01MA12	Levofloxacin	2.1	N05AD01	Haloperidol	2.3
14	N05AH03	Olanzapine	2.0	N05AN01	Lithium	1.7
15	G04BD08	Solifenacin	1.8	L02BA01	Tamoxifen	1.5
16	J01MA14	Moxifloxacin	1.5	N05AH02	Clozapine	1.3
17	L02BA01	Tamoxifen	1.5	G04BD08	Solifenacin	1.1
18	N06AX16	Venlafaxine	1.5	J01MA12	Levofloxacin	1.1
19	C07AA07	Sotalol	1.0	J02AC01	Fluconazole	0.8
20	N05AN01	Lithium	1	C01EB18	Ranolazine	0.7
	Subtotal (%)		90.7			92.3
	Other		9.3	Other		7.7
	Total		100	Total		100

^{*}Percentages relate to the total number of prescriptions pairing citalopram or escitalopram with any other QT interval-prolonging drug.
ATC, anatomical therapeutic chemical classification system

at the start of co-medication should be more widely practiced (35). The study also investigated the practical implementation of electronic drug–drug interaction (DDI) alerts about QTc interval-prolongation when problematic drug combinations are prescribed. In only about one third of all cases in which doctors prescribed the problematic drug combinations despite the DDIs was an ECG performed before and after the start of treatment. In 51% of these patients, QTc interval-prolongation was diagnosed; in 31% of cases, even, an increased risk of TdP tachycardia (defined by a QTc interval >500 ms or prolongation of the QTc interval >60 ms) had to be assumed.

However, data by which specific contents of Dear Doctor Letters can be checked—as, in the present case, individual QT intervals before the start of treatment to rule out pre-existing QT prolongation—often do not exist. But even in this case where they do, it would still

be difficult to check for risky QT prolongation, since there are no clear threshold values for QT or QTc intervals in the warnings. This problem also exists in the updated prescribing information on citalopram and escitalopram, according to which ECG recordings before treatment should be considered only in patients with clinically stable heart disease (36, 37).

As an alternative, studies have shown that the serum concentration of citalopram can give an indication of QT risk (38). However, again, no conclusion can be drawn from this about the combined effect of several QT interval-prolonging drugs. Another relevant risk of QT interval-prolongation relates to CYP2C19 interactions, which can lead to increased plasma concentrations, but this topic has not yet been addressed in Dear Doctor Letters. Because of the large number of drugs being prescribed per patient (the median is 8) in the present study, it must be assumed that many older

patients have an overall side effect profile that is very difficult to gauge. In our view, manufacturers and licensing authorities have a duty to give medically unambiguous information that can—above all—be acted on in clinical practice. New Zealand offers an example in the form of a helpful statement issued by the licensing authority that evaluates many relevant drug substances (39). Given the large number of combinations involved, it becomes clear that when dealing with warnings of this kind, more computer support in prescribing would be helpful. Even just the “top 20” list of most common co-medications presented in this article (Table 3) would allow over 90% of all doubtful pair combinations to be recognized.

It should also be remembered that the CredibleMed lists used in the present study do not contain drugs such as pipamperone and melperone which are frequently prescribed for elderly people in Germany and are also regarded as carrying QT interval-prolonging risk (9). This makes particularly clear the need for a national-level list containing binding information.

A limitation of this study is that it did not have access to outpatient data. Still, outpatient prescriptions may have affected our findings in the inpatient setting. It should also be borne in mind that this study focused on Dear Doctor Letters about citalopram and escitalopram; further studies would be needed to establish how far its findings can be extrapolated to other Dear Doctor Letters.

Conclusion

In the study presented here, simple instructions in two Dear Doctor Letters for citalopram and escitalopram, to change the permitted maximum dosage in elderly patients, were much better implemented than the warnings about newly contraindicated combinations with other QT interval-prolonging drugs.

KEY MESSAGES

- For the prescribing physician, Dear Doctor Letters are important, binding sources of information about current drug-related risks.
- Simple warnings (such as new maximum doses) are much more consistently implemented than complex warnings, which often require further research (e.g., a blanket contraindication for all drug substances with a particular property such as “QT interval-prolonging”).
- Pharmaceutical companies and licensing authorities should word the information in Dear Doctor Letters more precisely and, above all, in a way that makes this information easier to put into clinical practice, including integration into clinical decision support systems (CDSS).
- Additional quality assurance systems are needed for the identification and implementation of safety warnings.

Pharmaceutical companies and licensing authorities should word the information in Dear Doctor Letters more precisely and, above all, in a way that allows the information to be put into practice by clinicians. Officially authorized, national-level prescribing lists would be helpful. With quality assurance systems such as the GiB-DAT network, it is possible to uncover problems and undertake measures such as ECG monitoring or documentation of other risk factors to improve the safety of drug therapy.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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ORIGINAL ARTICLE

Implementation of Warnings From Dear Doctor Letters (Rote-Hand-Briefe)

An Analysis of Medication Data From a Large Cohort of Elderly Patients

Simone Schächtele, Thomas Tümena, Karl-Günter Gaßmann, Martin F. Fromm, Renke Maas

eBOX

Main contents of the Dear Doctor Letters relating to citalopram (dated 31 October 2011) and escitalopram (dated 5 December 2011)

- Citalopram and escitalopram have been associated with dose-dependent QT-interval prolongation.
- The recommended maximum dose is limited to 40 mg for citalopram; for escitalopram it remains at 20 mg. For older patients (>65 years) and for patients with impaired liver function, these maxima are reduced to 20 mg and 10 mg, respectively, even in the absence of other risk factors.
- Use of either or these substances with any other drug known to prolong QT interval is from this date regarded as contraindicated. Examples are:
 - Class IA and III antiarrhythmics
 - Tricyclic antidepressants
 - Antipsychotics (e.g., phenothiazine derivatives, pimocide, haloperidol)
 - Certain antibiotics (e.g., moxifloxacin, sparfloxacin, erythromycin IV, pentamidine, and antimalarials, especially halofantrin)
 - Certain antihistamines (e.g., astemizole, mizolastine)
- Administration of both these drugs is also contraindicated in patients with existing known QT interval-prolongation or congenital long-QT syndrome.
- In addition to hypokalemia and pre-existing QT interval-prolongation, female sex is also named as a risk factor.
- In patients at increased risk of torsade-de-pointes tachycardia, e.g., those with heart failure, recent myocardial infarction, bradyarrhythmia, or a tendency to hypokalemia or hypomagnesemia related to other accompanying diseases or medications, caution is indicated.

eTABLE

Summary list of QT interval-prolonging drugs available in Germany (modified from CredibleMeds.org)

Substance	Risk group	Substance	Risk group
Alfuzosin	2	Isradipine	2
Amantadine	2	Itraconazole	3
Amiodarone	1	Ketoconazole	3
Amisulpride	3	Lapatinib	2
Amitriptyline	3	Levofloxacin	2
Arsenic trioxide	1	Levomethadone	1
Astemizole	1	Lithium	2
Atazanavir	2	Methadone	1
Azithromycin	1	Moxifloxacin	1
Quinidine	1	Nicardipine	2
Chloral hydrate	2	Nilotinib	2
Chloroquine	1	Nortriptyline	3
Chlorpromazine	1	Octreotide	2
Ciprofloxacin	3	Ofloxacin	2
Cisapride	1	Ondansetron	2
Citalopram	1	Paliperidone	2
Clarithromycin	1	Paroxetine	3
Clomipramine	3	Pentamidine	1
Clozapine	2	Pimozide	1
Cotrimoxazole	3	Quetiapine	2
Desipramine	3	Ranolazine	2
Diphenhydramine	3	Risperidone	2
Domperidone	1	Ritonavir	3
Doxepin	3	Roxithromycin	2
Dronedarone	2	Sertindole	2
Droperidol	1	Sertraline	3
Eribulin	2	Solifenacin	3
Erythromycin	1	Sotalol	1
Escitalopram	1	Sunitinib	2
Famotidine	2	Tacrolimus	2
Felbamate	2	Tamoxifen	2
Fingolimod	2	Telithromycin	2
Flecainide	1	Terfenadine	1
Fluconazole	3	Thioridazine	1
Fluoxetine	3	Tizanidine	2
Foscarnet	2	Trazodone	3
Galantamine	3	Trimipramine	3
Granisetron	3	Vandetanib	1
Halofantrine	1	Vardenafil	2
Haloperidol	1	Venlafaxine	2
Imipramine	3	Voriconazole	2
Indapamide	2	Ziprasidone	2

Grading of torsade de pointes (TdP) risk (as at 17 May 2012):

1 = proven TdP risk (= high-risk QT drug, printed in bold)

2 = TdP case reports exist, potential risk

3 = Risk of TdP only under particular conditions such as high dosage or interactions

Sulpiride, melperone, and pipamperone, which also prolong QT interval and are available in Germany, were not AZCERT-classified at the time of the study and are therefore not listed here